

effectiveness of adjunctive low frequency repetitive transcranial magnetic stimulation therapy over the left dorsolateral prefrontal cortex in refractory to medical treatment patients with obsessive-compulsive disorder: a double blind ,randomized clinical trial

Ghazal Jahanbakhsh¹, Alireza Hajseyed javadi¹, Mahnaz Majidi¹

Abstract

Background: Obsessive-compulsive disorder (OCD) is a common neurotic disorder, In 2018 Application of repetitive transcranial magnetic stimulation (rTMS) for treating obsessive-compulsive disorder (OCD) has been approved by the Food and Drug Administration (28), since 2020 different methods has been tested, this study was designed to evaluate the effectiveness of adjunctive low frequency repetitive transcranial magnetic stimulation over the left dorsolateral prefrontal cortex in refractory to treatment patients suffering from obsessive compulsive disorder (OCD)

Methods: This clinical trial was performed on 30 patients with OCD referred from the psychiatry clinic of 22 Bahman Hospital in Qazvin province from 2018 to 2020. Patients were randomly assigned to two groups. Intervention group received rTMS treatment at 1 Hz for 20 min (1200 (pulses / day) over the left DLPFC region as adjunctive to their medical treatment for 3 times a week and for 5 weeks while the control group received only sham condition in addition to their medical treatment. All the patients filled out the Yale Brown Questionnaire (YBOCS) Before the study, after sessions 5 and 10 during treatment, at the end of the treatment and 3 to 6 months after the treatment. The results were compared between the two groups using SPSS software version 16.

Results: The mean score of post-intervention Yale Brown score was significantly lower in the intervention group. ($P < 0.05$), it was also significant by gender (females), marital status ,taking antipsychotic agents in addition to the serotonergic agents and with more treatment sessions, within 3 to 6 months after intervention.

Conclusion: adjunctive low frequency (1 Hz)rtms over the left DLPFC can be effective in reducing Yale Brown score in refractory to treatment patients suffering from OCD after 15 sessions. Gender, treatment sessions, usage of antipsychotic agents as adjuvant with standard treatment regiments, and marital status were identified as predictors for response to adjunctive rTMS therapy.

¹ Department of psychiatry, Qazvin University of Medical science, Qazvin, Iran

Keywords: Repetitive transcranial Magnetic Stimulation (rtms), Obsessive Compulsive disorder(OCD), Yale Brown Questionnaire, sham condition

Introduction:

Obsessive-compulsive disorder (OCD) is a common disabling psychiatric disorder, which causes significant issues in one's social life and function. (1) Since ages, it has been classified as a neurotic disorder. (2) The main feature of it is the constant presence of a mental or practical obsessions that cause a certain compulsion which affects the quality of life, job performance, social activities and relationships. The prevalence of OCD in the world was estimated in 2-3%. (5-3) The prevalence was estimated about 1.9% to 2.5% in Iran in 2004 and The average age of onset of OCD was 21.27 years. (6) A definite and complete response to the medical treatment or full remission is not seen in 60-70% of patients, due to the chronic nature of OCD. (7) Although It manifests earlier in males, (before the age of 10 is 25%), it is more common in females. (8, 9) Genetic and familial factors are the main predisposing factors. (10,11) Today, cognitive-behavioral therapy with exposure and response prevention (ERP) can be the first-line treatment for OCD in children and adults (12) and Meta-analysis studies have reported a high efficacy for it (CBT). (13) However it is not beneficial for all the patients, in particular those who cannot cope with the stress and anxiety of exposure. (14) Despite the relative success in the standard treatments, especially for CBT, the symptoms are remained or relapsed in the patients. [15] On the other hand, only 30-60 % of patients respond to standard medical treatment and completely or partially abandon treatment due to the side effects and the weak respond. (16) In recent years, repetitive transcranial magnetic stimulation (rTMS) has been proposed as a non-invasive adjuvant treatment for OCD. (17) Some studies have shown the therapeutic effect of rTMS in OCD and these studies varied in method and protocols . (25-25) In Iran few studies have been performed which were mostly case reports. (22-25) Although most of these studies reported the positive therapeutic effect of rTMS and symptoms reduction in OCD patients, none of them compared the effectiveness of low

frequency rtms (1Hz) over the left DLPFC with medical therapy alone.. It seems necessary to try this treatment that has the least side effects with the most acceptance among patients and also effectively improves the patient’s symptoms. Therefore, this study aimed to evaluate the effectiveness of rTMS as an adjunctive therapy in combination with medical therapy in patients who were resistant to standard drug therapy.

Methods:

This double-blind, clinical trial study was performed on outpatients with OCD referred from the psychiatry clinic of 22 Bahman Hospital of Qazvin from 2018 to 2020. Patients were entered to the study according to the inclusion criteria and after completing the informed consent form. Sampling was performed using convenient sampling method in refractory to treatment patients suffering from OCD. Considering the ratio of patients with severe OCD and refractory to treatment before and after rTMS based on Seo study (26) and ,P1 = 0.069 and P0 = 0.031 respectively, and regarding the power of 80% and the type one error of 5%, precision 5%, the sample size was estimated 15 cases in each group..

$$n = \frac{(z_{1-\frac{\alpha}{2}}\sqrt{2P(1-P)}z_{1-\beta}\sqrt{P_0(1-P_0) + P_1(1-P_1)})^2}{(P_1 - P_0)^2}$$

Inclusion criteria: age 18-60 year, suffering from moderate to severe OCD, history of OCD for at least one year, no improvement despite treatment with two first line agents approved by FDA for OCD treatment with adequate dosage and duration , YBOCS score of at least 16 and Beck score less than 17.

Exclusion criteria: having another psychiatric comorbidity, history of seizures or epilepsy, pregnancy, history of substance abuse, history of severe head trauma or severe complications of brain surgery, metal implant or pace maker.

Intervention and randomization method:

Before the intervention, all the patients filled out the Yale Brown (YBOCS) and Beck questionnaire. Those with the score of at least 16 in (YBOCS) and without the criteria of depression based on Beck Depression Inventory were entered the study. Many studies have examined the validity and reliability of the Yale Brown (YBOCS) questionnaire. According

to a study by Nakajima et al., This questionnaire has a good internal correlation (ICC = 0.966) and its validity and reliability was reported respectively 0.94 and 0.88 using Cronbach's alpha. (27) Eligible patients were divided in two groups of A or B using the randomized block method with the size of 4. Regarding the results of the study by Elbeh et al., (19) and the study by KUMAR et al., in 2016 for obtaining the better efficacy we performed rtms over the left DLPFC region at the frequency of 1 Hz, and for reaching the better results each patient had more than 10 sessions (21); in this study, the intervention group received rtms at the frequency of 1 Hz for 20 minutes in the left DLPFC region (total 1200 (pulses / day)) for 5 weeks and 3 times per week, simultaneously continuing their medical treatment. The control group received medical treatment along with sham condition (without magnetic stimulation). This was performed by a professionally trained nurse. The main collaborators of the project and the patients were unaware of how patients were assigned in to the intervention or sham groups. The Yale Brown Questionnaire (YBOCS) was filled out by patients before the study, during the treatment sessions 5 and 10, at the end of treatment, and 3to 6 months after the intervention. The results were compared between the two groups. Besides, the scores of the questionnaire were compared between the two groups in terms of demographic factors such as gender, marital status, duration of the disorder and the medication they currently take and the number of treatment sessions.

Statistical analysis:

Quantitative data were reported as mean with standard deviation and qualitative data were reported as frequency with percentage. The normality distribution was evaluated using the Shapiro-Wilk test and its results were confirmed. To compare the scores between the two groups, T-test and to measure score changes during the study repeated measurement analysis were used in SPSS software version 16.

Results:

Data from 30 patients with OCD in two groups were evaluated. The mean age of patients in the control group was 33.1 ± 10.3 years and in the intervention group was 34.1 ± 8.3 years. There was no difference in age distribution between the two groups. ($p=0.787$). The mean duration of disorder in the control group was 13.3 ± 8.5 years and in the intervention group was 13.5 ± 8.4 years ($p = 0.949$). There was a significant difference between the two groups

in terms of the number of the treatment sessions , the average number of sessions in the intervention group (12.6 ± 2.6) was higher than the control group (14.5 ± 1.1) ($p = 0.019$). Other characteristics of patients in the two groups are displayed in Table (1). In terms of other characteristics, there was no difference between the two groups. ($P < 0.05$) (Table 1)

Table 1- Demographic information of OCD patients by two groups

variable	Category	Intervention		sham		Test-statistic	P-value
		n	%	n	%		
Gender	Male	6	40	4	26.7	0.6	0.71
	Female	9	60	11	73.3		
Marital status	Single	5	33.3	6	40	0.144	0.705
	Married	10	66.7	9	60		
Physical issues	yes	1	6.7	1	6.7	-	0.988
	no	14	93.3	14	93.3		
History of ECT administration	yes	1	6.7	2	13.3	0.37	0.988
	no	14	93.9	13	86.7		
Type of current medication	SNRI	0	0	1	6.7	3.039	0.763
	SSRI	1	6.7	3	20		
	TCA	1	6.7	0	0		
	Anti-psychotic adjuvant	5	33.3	4	26.7		
	Combined	8	53.3	7	46.7		

The results of Pearson correlation test did not show any significant relationship between Beck score and Yale Brown score in the two treatment groups before treatment. ($P < 0.05$) In comparison within and between groups, the results in table (2) were obtained. According to the results in the table 2, Yale Brown scores were different between two groups after the treatment. The mean scores were lower in the intervention group. Meanwhile the changes in scores were also significant within each group. (Table 2) (Figure 1)

Table 2- Comparing mean score between and within two groups

variable	Intervention		control		T-test	P-value
	Mean	SD	Mean	SD		
Beck score before	14.2	3.2	14.8	2.3	0.585	0.563
Yale Brown score before	25.4	4.1	29.1	6.2	1.91	0.068
YBOCS after 5 sessions	21	4.3	27.1	5.7	3.33	0.002 *
YBOCS after - 10 sessions	19.3	4.6	26.2	4.7	4.1	0.000 *
YBOCS at the end	16.3	5.04	25.2	4.4	4.7	0.000 *
YBOCS 3to6 months after	19.1	4.5	26.7	5.4	3.9	0.001 *
Trend within groups **	F: 102.1 P: 0.000 *		F :11.01 P: 0.008 *			

*significant at level of 0.05; ** using Repeated measurements test

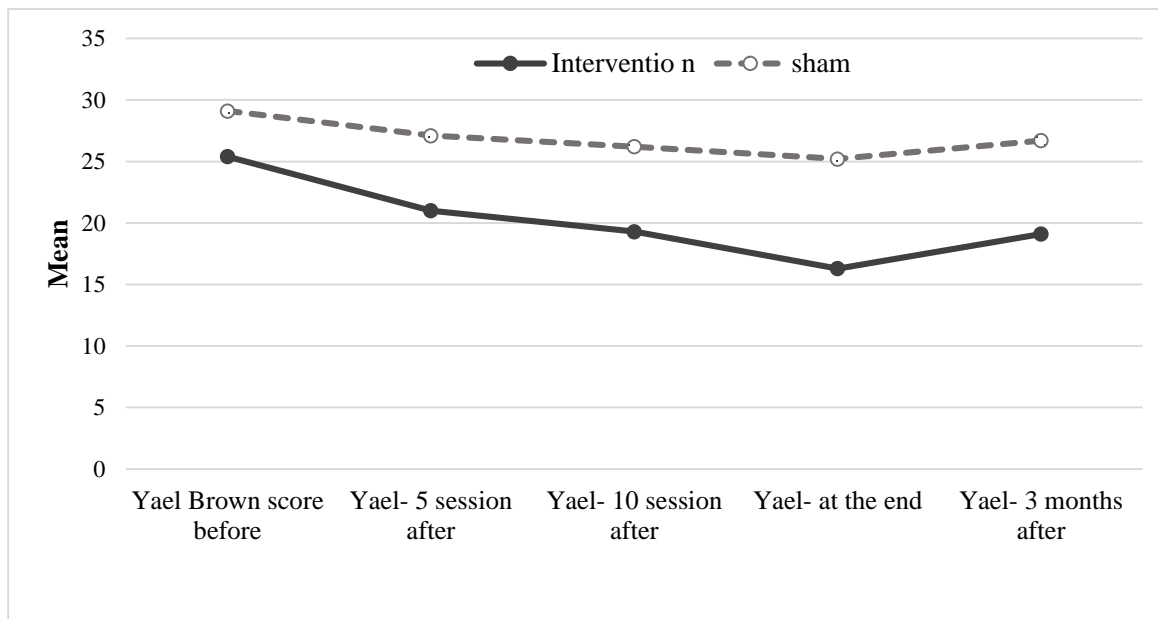


Figure 1- Comparing trend in Yale Brown score between two groups

According to the results in table (3), the decrease in the Yale Brown score was significant both at the end of the intervention and 3to 6 months after the treatment, particularly in female

patients, and it was less in the intervention group. (P <0.05) The decrease in the Yale Brown score in married patients was significant, and it was less in the intervention group. (P <0.05)

Table 3- Comparing mean of Yael Brown score between two groups by demographic factors

Variable	Category	Group	Before intervention	5-session after	10-session after	At the end of study	3 months after
Gender	Male	Intervention	24 ±3.7	19.6 ±3.7	18±5.5	143±5.9	18±4.5
		control	28.2 ±7.1	28±6.9	24.7±4.6	22±5.2	26.7±4.6
	<i>P-value</i>		0.245	0.038 *	0.077	0.102	0.077
	Female	Intervention	26.3±4.3	21.8±4.6	20.2±3.9	17.6±4.1	19.8±4.5
		control	29.3±6.2	26.8±5.5	26.7±4.8	26.5±3.8	27.3±5.7
	<i>P-value</i>		0.231	0.046 *	0.004*	0.000*	0.007*
Marital status	Single	Intervention	25.2±4.8	20±3.4	17.8±5.8	14.8±6.4	18.4±4.9
		control	26±4.7	24.2±4.7	24.5±4.3	22.3±5.5	24±4
	<i>P-value</i>		0.788	0.161	0.057	0.142	0.109
	Married	Intervention	25.5±3.9	21.5±4.4	20.1±3.9	17.1±4.4	19.5±4.4
		control	31.1±6.5	29.1±5.6	27.3±4.8	26.4±3.8	28±5.7
	<i>P-value</i>		0.034 *	0.004*	0.002*	0.000*	0.003*
Disorder duration	Less than 13 year	Intervention	25±4.7	20.7±5	18.8±5.4	15.1±6.1	18.5±5.2
		control	27.7±6.7	26±6.3	25.4±4.9	24.3±4.8	25.6±5.2
	<i>P-value</i>		0.324	0.065	0.016*	0.008*	0.019*
	More than 13 year	Intervention	26±3.4	21.5±3.4	20±3.2	18.2±2.5	20±3.2
		control	31±5.3	28.8±4.4	27.3±4.5	26.4±4.1	28.2±5.8
	<i>P-value</i>		0.082	0.009*	0.009*	0.003*	0.015*
Number of sessions	Less than 13	Intervention	31.5±2.1	25±7.1	23.5±4.9	19.5±4.9	23.5±4.9
		control	30±6.3	27.4±6.5	26.7±4.1	27.7±2.6	29.8±4.8
	<i>P-value</i>		0.759	0.662	0.361	0.223	0.181
	More than 13	Intervention	24.5±5.3	20.4±3.8	18.7±4.3	15.8±5.1	18.5±4.2
		control	28±6.4	26.8±4.9	25.6±5.5	23.8±4.8	24.4±4.8
	<i>P-value</i>		0.211	0.004*	0.007*	0.003*	0.011*

*significant at level of 0.05

In patients with more than 13 treatment sessions, the decrease in Yale Brown score both at the end of the treatment and 3 to 6 months after treatment, was significant between two groups, and it was less in the intervention group. ($P < 0.05$) (Table 3) According to the results in table (4), in patients who were taking antipsychotic agents as adjuvant, the decrease in Yale Brown score at the end of the treatment and 3 to 6 months after the treatment was also significant between two groups, and it was less in the intervention group. ($P < 0.05$) (Table 4)

Table 4- Comparing mean of Yale Brown score between two groups by type of used drug

variable	Group	TCA	SSRI	SNRI	Combined	Antipsychotic with adjuvant
Yale Brown score before	Intervention	-	30.3±7	37	27.3±5.3	29.2±7.8
	control	20	28	-	27.1±3.8	23.2±3.6
	<i>P-value</i>	-	0.801	-	0.947	0.164
YBOCS after 5 session	Intervention	-	30±7	26	26±5.1	27.2±7.4
	control	17	25	-	21.6±4.2	20±4.8
	<i>P-value</i>	-	0.599	-	0.092	0.118
YBOCS after 10 session	Intervention	-	25.6±5.1	30	25.4±5.2	27±4.8
	control	15	25	-	20.2±3.2	17.6±6
	<i>P-value</i>	-	0.921	-	0.048 *	0.039 *
YBOCS at the end	Intervention	-	22±5.2	30	24.2±2.7	30.5±0.71
	control	15	23	-	17.4±3.9	13.6±6.2
	<i>P-value</i>	-	0.883	-	0.006*	0.003*
YBOCS 3 to 6 months after	Intervention	-	24.6±4.6	35	24.3±4.3	32.5±0.71
	control	15	25	-	20±4.2	17.4±4.6
	<i>P-value</i>	-	0.956	-	0.081	0.007*

*significant at level of 0.05

Discussion:

This study aimed to evaluate the efficacy of rTMS as adjuvant in combination with medical treatment in refractory to treatment patients suffering from OCD (treated with at least two first line FDA approved agents for OCD treatment with adequate dosage and duration) .

According to the results of this study, there was no significant relationship between Beck score and Yale Brown score in each group before the treatment. Beck score also did not differ between two groups. Reduction of Yale Brown score was significant in the intervention group at the end of the treatment and 3 to 6 months after the treatment also in female, married patients, in those taking antipsychotic as an adjuvant, and in patients with more treatment sessions, meanwhile the mean score was less in the intervention group than control group. Yale Brown score was also significantly different between two groups in terms of disorder duration. The results of this study also showed that the reduction in the Yale Brown score was significantly higher in the intervention group than control group, which is consistent with the results of study by Rostami et al., in 2020 which indicated the effectiveness of low frequency (1 Hz) rTMS over the DLPFC region on 27 pharmaco-resistant patients suffering from OCD, although the length of each session, the number of pulses received per session and the number of sessions overall were more than our study (30 minutes, 20 sessions and 1800 pulses per session) and they applied rTMS over DLPFC region bilaterally.

According to the present study, gender had effect on patients' improvement in intervention group particularly 3 to 6 months after the treatment the results were significant in females, and YBOCS was significantly less in the intervention group. Nevertheless it was not consistent with Rostami's study that no significant relationship was found between demographic factors and response to rTMS treatment. (28) The results of our study were consistent with a similar study conducted by SEO et al., in 2016. In their study, 14 patients with OCD received low frequency (1 Hz) over the right or left DLPFC region, which indicated the positive effect of rTMS in reducing Yale Brown scores specially in patients who received rTMS over the left DLPFC. In their study session duration and number of pulses received per session were similar to our study, but the number of treatment sessions per week was more than our study (5 sessions) (18) Also, the result of our study on the positive effect of rTMS in refractory to treatment patient suffering from OCD was similar to the study of Dr. Haghighi et al., in 2015, in which 21 patients suffering from treatment-resistant OCD were evaluated (22) however, they applied rTMS treatment over the DLPFC region bilaterally with high frequency at 20 Hz.

Also in a similar study conducted by Pallanti et al., in 2016, 50 patients suffering from treatment-resistant OCD were divided in control and intervention groups. The intervention

group received rTMS at 1Hz in addition to medical treatment for 3weeks and both groups were evaluated at the end of intervention and the main result of their study were consistent with the present study that showed the positive effect of rTMS in patients suffering from treatment-resistant OCD. In their study antipsychotic were augmented to their previous medication which also indicated positive therapeutic effects. However they performed rTMS over the SMA region bilaterally (supplementary motor area). (20)

The current study indicated the positive therapeutic effect of augmenting antipsychotic agents on patients suffering from refractory to treatment OCD in addition to low frequency rTMS treatment over the left DLPFC region and the reduction of Yale Brown scores, was investigated for the first time. Also it is the first study that followed up patients 3 to 6 months after the treatment and compared the effects of factors such as taking antipsychotic agents, gender and marital status in both groups and introduced them as predictors for responding to rtms treatment in patients suffering from treatment-resistant OCD. In our study, the reduction in scores and the differences between two groups were more obvious after 10 sessions of rtms treatments (sessions10-15), which is depicted in figure 1. In this study Yale Brown's score decreased significantly in patients with more treatment sessions, which was consistant with the study by Kumar et al in 2016. (21)

Conclusion:

Based on the findings of our current study and the previous studies, adjunctive low frequency(1 Hz) rTMS treatment over the left DLPFC region can be effective on patients suffering from treatment-resistant OCD and it can improve their condition significantly. Factors such as gender (female), marital status, number of treatment sessions, taking antipsychotic agents as adjuvant with standard medication may be considered as predictors for responding to rTMS treatment in patients suffering from OCD. More interventional studies with long-term follow up and larger sample size are suggested to identify effective predictor factors. The findings of our current study can be helpful for psychiatrists for choosing the effective treatment plan for patients suffering from refractory to treatment OCD.

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