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

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Research Article

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

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Abstract

Background: Obsessive-compulsive disorder (OCD) is a common mental illness. The Food and Drug Administration (FDA) approved repetitive transcranial magnetic stimulation (rMS) to treat OCD in 2018. So far, various approaches have been evaluated. We evaluated the effect of adjunctive low-frequency rMS over the left dorsolateral prefrontal cortex in patients with OCD refractory to treatment.

Methods: The present clinical trial was done on 30 patients with OCD referring from the psychiatry clinic, 22 Bahman Hospital, Qazvin province, between 2018 and 2020 and patients were randomly divided into two groups. The intervention group received rTMS treatment at 1 Hz for 20 min (1200 pulses/day) over the left DLPFC area as adjunctive to the medical treatment three times a week and for five weeks, whereas those in the control group were subjected to only the sham condition plus their medical treatment.

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The Yale-Brown Obsessive-Compulsive Scale (y-BOC.S) was completed by patients before the study, following sessions 5 and 10 during the intervention, at the end of the intervention, and three to six months after the intervention under the direct supervision of a psychiatrist. SPSS software version 26 was used to compare the results between the two groups.

Results: The intervention group showed significantly lower mean Y-BOCS scores after the intervention and at follow-up ($P < 0.05$) and all patients of the intervention group showed significantly lower Y-BOCS scores than their own baseline scores ($P < 0.05$). Also, using antipsychotic agents along with the serotonergic agents caused significantly lower scores in the intervention group at the end of the intervention ($P < 0.05$). All the patients were found with higher follow-up scores than their scores at the end of the intervention; however, this difference was not significant ($p > 0.05$).

Conclusion: Adjunctive low-frequency (1 Hz) rTMS over the left DLPFC is able to effectively reduce Y-BOCS score in OCD patients refractory to treatment following 15 sessions, and the reduction was durable even after three to six months. Using antipsychotic agents as an adjuvant with serotonergic agents was identified as a possible predictor for response to adjunctive rTMS therapy.

Keywords: Repetitive transcranial Magnetic Simulation (rTMS), Obsessive-Compulsive Disorder (OCD), Yale-Brown Obsessive-Compulsive Scale(Y-BOCS score), sham condition

Introduction:

Obsessive-compulsive disorder (OCD) is a common disabling psychiatric disorder, which causes significant problems in a patient's social life and function. (1) It has long been classified as a neurotic disorder. (2) The main feature of OCD is the constant presence of mental or practical obsessions that cause a certain compulsion, which affects the quality of life, job performance, social activities, and relationships. OCD affects 2-3% of the world's population. (3,4,5) Its prevalence was estimated to be about 1.9% to 2.5% in Iran in 2004 and with an average age of onset of 21.27 years. (6) A definite and complete response to the medical treatment or full remission is not seen in %60 of patients due to the chronic nature of OCD. (7) Although it manifests earlier in males (before 10: 25%), it is more common in females. (8, 9) Also, genetic and familial factors are the main predisposing factors for OCD (10,11).

On the other hand, only 30-60 % of patients respond to standard medical treatment and entirely or partially abandon treatment due to the side effects and the weak response. (16) The repetitive transcranial magnetic stimulation (rTMS) is a non-invasive adjuvant treatment for OCD. (17) Some studies have shown the therapeutic effect of rTMS in OCD, and these studies are different regarding methods, protocols, and brain sites. (12-27) A few studies have been performed on the effectiveness of rTMS on patients suffering from OCD in Iran (22,23,24,25,27). Most of these studies have reported the positive therapeutic effect of rTMS and improvement in symptoms in OCD patients, and some have declared that it was not better than the placebo effect; however, they vary in terms of the used method and brain sites. Although the results of the studies performed worldwide are mixed and inconsistent, a large study conducted

by Carmi indicated that high-frequency rTMS over the anterior cingulate cortex and medial prefrontal cortex markedly improved OCD symptoms and can be used in patients refractory to pharmacological and psychological interventions (12). Also, the application of rTMS for treating OCD was approved by the American Food and Drug Administration in 2018 (28).

The rationale for choosing the dorsolateral prefrontal cortex (DLPFC) is that the OCD pathophysiology is associated with hyperactivity in specific cortical-subcortical loops, such as DLPFC, possibly representing a starting point to induce remote stimulation in connected cortico-subcortical circuits, and rTMS directly influences the prefrontal cortical activity, and also can be regarded as the most accessible area to rTMS stimulation because of the superficial location (18,17)

Many studies have administered low- or high-frequency rTMS (1Hz) over the right DLPFC or bilateral DLPFC with medical therapy (18,19,27,22,15). Sarkhel (2010) concluded that adjunctive high-frequency right prefrontal rTMS is not effective for the treatment of OCD (15). Elbeh et al. administrated rTMS over the right DLPFC for ten sessions in their studied three groups, and 1Hz rTMS had a greater clinical benefit than 10Hz rTMS or Sham rTMS (19). Ho-Jun Seo (2016) declared that low-frequency rTMS over the right DLPFC was superior to the Sham rTMS to relieve depression and OCD symptoms in OCD patients refractory to treatment (18).

Only a few studies have administered rTMS over the left DLPFC unilaterally; for example, Sakhdev (2007) tried rTMS over the left DLPFC and indicated two weeks of treatment with rTMS over the left DLPFC was not effective in OCD patients resistant to treatment (14). Also, Prasko concluded that low-frequency rTMS using over the left

DLPFC for ten daily sessions showed no difference from the Sham rTMS to facilitate the impact of serotonin reuptake inhibitors in OCD patients (13).

According to Kumar et al. (2016), for obtaining a better efficacy, we performed rTMS over the DLPFC region at the frequency of 1 Hz, and for reaching better results, each patient had more than ten sessions (21). Since DLPFC is an important part of the cortico-subcortical circuits and regarding its role in OCD pathophysiology and also because a few numbers of the studies have been considered over the left DLPFC unilaterally for the treatment of OCD, we decided to examine a new protocol inspired by Prasko's method (low-frequency over the left DLPFC); however, fewer sessions weekly and more sessions overall were regarded.

Therefore, we evaluated the effectiveness of a new rTMS method as adjunctive therapy in combination with standard medical treatment in pharmaco-resistant patients. It seems necessary to try different therapeutic approaches to establish new protocols for patients suffering from OCD since this treatment is a non-invasive technique and has the fewer side effects with high acceptance among the patients.(18,27,12,17)

Methods:

The current double-blind clinical trial was designed preliminarily in 2016 and was conducted on outpatients with OCD referring from the psychiatry clinic, 22 Bahman Hospital, Qazvin Province, between 2018 and 2020. The subjects were enrolled in the study according to the inclusion criteria and after completing the informed consent form. Sampling was performed using a convenient sampling method, and OCD patients refractory to treatment were included. Considering the population of Qazvin

Province and the ratio of patients with severe OCD who were also refractory to medical therapy and based on previous studies with similar methods (13,18), we estimated 15 patients in each group to receive at least ten sessions of treatment. Overall, 37 patientis were enrolled, but three cases in the intervention group and four in the control group dropped out due to personal issues (mostly difficulty in transportation because of Covoid19 pandemic and the obligation to change the medication), and their data were not included.

Inclusion criteria: The age of 18-60 years, suffering from moderate to severe OCD according to DSM_5, a 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, and Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score of at least 16 and Beck Depression Inventory (BDI) score of less than 17.

Exclusion criteria: Having another psychiatric comorbidity (except nicotine use disorder), a history of seizures or epilepsy, pregnancy or lactation, current record of substance abuse, a history of severe head trauma or severe complications of brain surgery and severe or unstable medical conditions, metal implant or pacemaker, and right hemisphere dominancy.

Intervention and randomization method:

Before the intervention, all patients were visited by a psychiatrist at least twice, and other psychiatric disorders were ruled out (except nicotine use disorder). They were stabilized in their medication for at least three months, and then they filled out the Y-

BOCS and BDI under a psychiatrist's direct supervision. Many studies have examined the validity and reliability of the Y-BOCS. According to Nakajima et al., this questionnaire has an excellent internal correlation (ICC = 0.966), and its validity and reliability have been reported to be 0.94 and 0.88, respectively, Using Cronbach's alpha (26). We used the Persian version of the Y-BOCS, which also has good validity (0.83) and reliability (0.93), respectively, using Cronbach's alpha (29).

Overall, 45 patients were referred from the psychiatry clinic. Those with the score of at least 16 on the Y-BOCS and without depression based on BDI were included in the study. After filling the questionnaires and screening for excluding criteria, 37 entered the study. Eligible subjects were assigned to two groups of A or B using the randomized block method with the size of 4. None of the patients had ever received rTMS treatment.

In our study, the stimulation was administrated with a MAG PRO X100 stimulator (MagVenture Company, Denmark) through a 70-mm figure-of-eight-shaped coil (air film coil).

For both groups, we determined active motor threshold (AMT) as the minimum stimulus intensity causing a liminal motor evoked response while the right abductor policies Brevis (APB) muscle is actively contracted. The motor threshold was determined by visible movements of the right APB in accordance with the traditional International Federation of Clinical Neurophysiology approach to define the motor area. The left DLPFC can be found 5 cm anterior from the motor region along a parasagittal line from the site of optimum APB stimulation (22,27).

The intervention group was subjected to rTMS at 1 Hz for 20 minutes over the left

DLPFC region (a total of 1200 pulses/day) for five weeks and three times per week, simultaneously with their medical treatment and the coil was placed directly on the scalp with no space between.

The control group received medical treatment along with the Sham condition (they were going through a similar process, only they did not receive magnetic stimulation (only the inactive coil was resting on the scalp). This was performed by a professionally trained nurse. The main collaborators of the project and the patients were unaware of how patients were assigned to the intervention or Sham groups. The Y-BOCS was answered by patients under the direct supervision and help of a blind psychiatrist before the study, during the treatment sessions of 5 and 10, when the treatment was finished, and three to six months following the intervention. The two groups were compared and also the score of each patient in each group was compared to his baseline score. Besides, we compared the scores of the questionnaire

between the two groups regarding demographic factors, such as gender, marital status, duration of the disorder, the medication they were currently taking, and the number of treatment sessions.

Also, the medication was kept stable during the study and follow-up. During the investigation, all patients, all the psychiatrists, and the analyst were blind, and the fidelity of blinding was assessed. Most patients were reporting a reduction in symptoms and believed that they were in the intervention group. The preprint of this study was peer-reviewed in 2021, and the study was reanalyzed and revised based on the comments.

Results:

For data analysis, both descriptive and inferential tests were performed. To represent descriptive data, frequenc, frequency percentage, mean, and standard deviation (SD) were measured. The normal distribution of data was also investigated based on skewness and kurtosis measures. For inferential statistics, analysis of covariance, repeated measures analysis of variance (ANOVA), independent *t*-test, and paired sample *t*-test were performed. The significance level (alpha) was set at 0.05 ($P \geq 0.05$) to test the hypotheses. Data analysis was performed in SPSS version 26. The frequencies of qualitative demographic variables, including sex, marital status, medication use, and physical problems, are presented in Table 1. Chi-square test of homogeneity and Fisher's exact test were also used to assess the homogeneity of demographic characteristics in the control and treatment groups (15 participants per group).

Table 1. Qualitative demographic variables and homogeneity test of the study groups

Demographic Variables	**Categories**	**Control group**		**Treatment group**		**Homogeneity test**
		n	%	n	%	P-value
Sex	Female	11	73.3	9	60	0.700
	Male	4	26.7	6	40	
Marital status	Married	10	66.7	10	66.7	1
	Single	5	33.3	5	33.3	
Medication use	Two serotonergic drugs	9	60	6	40	0.262
	Antipsychotic agents	6	40	7	46.7	
	One serotonergic drug	0	0	2	13.3	
Physical problems	No	14	93.3	14	93.3	1
	Yes	1	6.7	1	6.7	

The investigation of the demographic characteristics revealed that most of the participants in the control and treatment groups were female and married. Also, most participants (14 participants per group) had no diseases or physical problems. The results of Chi-square test

and Fisher's exact test (for binary variables) indicated the homogeneity of demographic characteristics in both groups (P>0.05). The mean and SD of quantitative demographic variables, including age, duration of disease, and frequency of treatment sessions, are presented in Table 2.

Table 2. Data related to the underlying quantitative variables based on the homogeneity *t*-test in the study groups

Variables	**Control group**		**Treatment group**		**P-value**
	Mean	SD	Mean	SD	
Age	34.53	9.75	34.07	8.34	0.889
Duration of disease	13.87	6.99	13.53	8.44	0.907
Number of treatment sessions	13.67	2.29	14.47	1.06	0.234

As shown in Table 2, the two groups were homogeneous in terms of age, duration of disease, and number of treatment sessions (P<0.05). The mean (±SD) values of the main study variables, including the Beck's Depression Inventory (BDI) and Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) scores, for each study group, are presented in Table 3.

Table 3. A description of primary variables, including depression and obsessive-compulsive disorder (OCD) based on the homogeneity test of variance and mean comparisons between the groups

Variables	**Control group**	**Treatment group**		

	M	SD	Skewness	Kurtosis	M	SD	Skewness	Kurtosis	**P-value**	**P-value**
Depression	14.4	2.17	-1.18	1.87	14.2	3.2	-1.10	-0.17	0.058	0.844
OCD–pretest	27.4	4.91	0.22	-0.079	27.5	4.6	0.02	0.24	0.501	0.939
OCD–during treatment 1	27.20	5.24	0.18	-0.094	26.87	5.04	0.17	0.59	0.402	0.860
OCD–during treatment 2	26.93	5.51	0.15	-0.65	25.40	4.29	0.15	1.16	0.139	0.402
OCD–posttest	27.3	4.15	0.09	-0.02	24.0	4.3	-0.27	-0.32	0.867	0.044
OCD–follow-up	27.8	4.72	0.07	-0.64	24.2	4.5	0.10	-0.47	0.644	0.042

According to the results, the mean scores of BDI were 14.40 and 14.20 in the control and treatment groups, respectively. The results of Levene's test confirmed the homogeneity of variance, and the results of independent sample *t*-test showed that both groups were similar regarding the BDI score (P>0.05). Moreover, the Y-BOCS score was 27.40 at baseline in the control group, which decreased to 27.33 after the study; the homogeneity of variance and lack of mean differences were statistically confirmed in the two groups (P>0.05). There was no significant difference regarding the score of Y-BOCS before and during the intervention (P>0.05). In the final stage of the intervention, the Y-BOCS scores were 27.33 and 24.07 in the control and treatment groups, respectively, indicating the significantly lower mean score of the treatment group (P=0.044). Besides, the normality of data distribution was investigated based on skewness and kurtosis measures. All values were in the range of +2 to -2, which confirmed the normal data distribution.

In Table 4, the results of repeated measures ANOVA are presented. The assumption of homogeneity of covariance was evaluated using Mauchly's test of sphericity, where a P-value under 0.05 approves the hypothesis. In this study, Mauchly's test of sphericity was performed to investigate the homogeneity of covariance, which was equal to 0.960 with a corresponding significance level of 0.178, approving the assumption.

Table 4. The results of repeated measures ANOVA investigating the time and time×group interaction effects on obsessive-compulsive disorder (OCD) and the results of covariance analysis for the group effects on OCD

Source	Sum of Squares	df	Mean sum of squares	F	P-value	η^2	Observed power
Time	54.61	1	54.61	46.81	<0.001	0.626	1
Time×group	81.12	1	81.12	69.53	<0.001	0.713	1
Group	85.69	1	85.69	53.69	<0.001	0.665	1

The results of repeated measures ANOVA showed the significant effect of time (P<0.05). In other words, there was a significant difference regarding the Y-BOCS score between the five stages of intervention (a significant difference between at least two stages). The effect size was measured to be 0.626. The results indicated the significant interaction effect of time and group on OCD (P<0.05); in other words, there was a significant difference between the two groups depending on the time of assessment.

Moreover, the group effect was investigated using the analysis of covariance. The pretest Y-BOCS score was considered as the control variable or covariate, and the posttest Y-BOCS score was considered as the dependent variable. According to the results, the group effect was significant (P<0.05). In other words, the effect of adjuvant treatment with rTMS (according to the abovementioned protocol) on OCD was significant, and there was a significant

reduction in the mean Y-BOCS score after the intervention. The effect size was measured to be 0.665. In the intervention group, the mean score of Y-BOCS increased from 27.53 before the intervention to 24.07 after the intervention (a reduction of 3.46 points). However, in the control group, the mean score of Y-BOCS decreased insignificantly from 27.40 at baseline to 27.33 after the intervention. The results of paired sample *t*-test for comparison of Y-BOCS scores between different stages in the two groups are presented in Table 5.

Table 5. The results of paired sample *t*-test for comparison of the mean Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) scores between different stages of treatment in each group (df=14)

Groups	Intervals for comparisons	Mean difference	SD	Standard error of difference	t	P-value
Control	Pretest–during treatment 1	0.20	1.70	0.439	0.46	0.655
	Pretest–during treatment 2	0.47	1.30	0.336	1.39	0.187
	Pretest–posttest	0.07	1.58	0.408	0.16	0.872
	Pretest–follow-up	-0.40	1.06	0.273	-1.47	0.164
	During treatment 1–during treatment 2	0.27	1.91	0.492	0.54	0.597
	During treatment 1–posttest	-0.13	2.07	0.533	-0.25	0.806
	During treatment 1–follow-up	-0.60	1.84	0.476	-1.26	0.228
	During treatment 2–posttest	-0.40	1.92	0.496	-0.81	0.433
	During treatment 2–follow-up	-0.87	1.51	0.389	-2.23	0.043
	Posttest–follow-up	-0.47	1.36	0.350	-1.33	0.204
Treatment	Pretest–during treatment 1	0.67	1.18	0.303	2.20	0.045

	Pretest–during treatment 2	2.13	1.25	0.322	6.63	<0.001
	Pretest–posttest	3.47	1.25	0.322	10.87	<0.001
	Pretest–follow-up	3.3	1.50	0.386	8.63	<0.001
	During treatment 1–during treatment 2	1.47	1.36	0.350	4.19	0.001
	During treatment 1–posttest	2.80	1.66	0.428	6.55	<0.001
	During treatment 1–follow-up	2.67	1.95	0.504	5.29	<0.001
	During treatment 2–posttest	1.33	1.11	0.287	4.64	<0.001
	During treatment 2–follow-up	1.20	1.70	0.439	2.74	0.016
	Posttest–follow-up	-0.13	1.92	0.496	-0.27	0.792

According to the findings, in the control group, there was no significant difference regarding the mean score of Y-BOCS before and after the intervention and in the three or six-month follow-up. Except for the difference observed between the stage after treatment 2 and follow-up, other comparisons revealed no significant differences ($P>0.05$).

In the intervention group, the mean baseline score was significantly higher than the scores of other stages ($P<0.05$). In other words, in the treatment group, the mean score of Y-BOCS significantly reduced during treatment, after the treatment, and in the three or six-month follow-up ($P<0.05$). The results also showed that the mean score of Y-BOCS significantly reduced after the intervention and in the follow-up. In the intervention group, the mean score of Y-BOCS in the follow-up was almost similar to the end of the treatment, and there was no significant difference, indicating the stability of the intervention effects over time ($P=0.792$). Overall, in the intervention group, the mean scores of Y-BOCS were significantly lower at

the end of the intervention and in the follow-up compared to the scores measured at baseline and during treatments.

In Table 6, the mean score of Y-BOCS is compared between the baseline and the end of the study in the intervention group. Besides, the effects of demographic variables, such as sex, consumption of antipsychotic drugs as adjuvants, and disease duration (≤10 years or >10 years), on the Y-BOCS score are shown in this table.

Table 6. The results of covariance analysis regarding the effects of underlying variables on obsessive-compulsive disorder (OCD)

Variables	**Categories**	**n**	**Pretest**		**Posttest**		**F**	**P-value**	**η^2**
			Mean	SD	Mean	SD			
Sex	Male	6	25.67	3.83	22.50	4.14	0.119	0.736	0.010
	Female	9	28.78	4.87	25.11	4.40			
Consumption of antipsychotic drugs	Yes	7	27.29	5.71	23.00	5.29	11.29	0.006	0.485
	No	8	27.75	3.81	25.00	3.42			
Duration of disease	≤10 years	7	27.14	4.63	24.14	4.06	1.75	0.210	0.128
	>10 years	8	27.88	4.88	24.00	4.87			

The results indicated the effect of antipsychotic drug consumption as adjuvants on the reduction of Y-BOCS scores at the end of the study ($P<0.05$). In patients consuming antipsychotic drugs, the mean score of Y-BOCS reduced from 27.29 to 23 (a reduction of 4.29 points), while it reduced by 2.75 points in other participants; the observed decline was significant in those consuming antipsychotic drugs. Figure 1 presents a linear diagram of the mean Y-BOCS scores of the intervention and control groups over the five period of time.

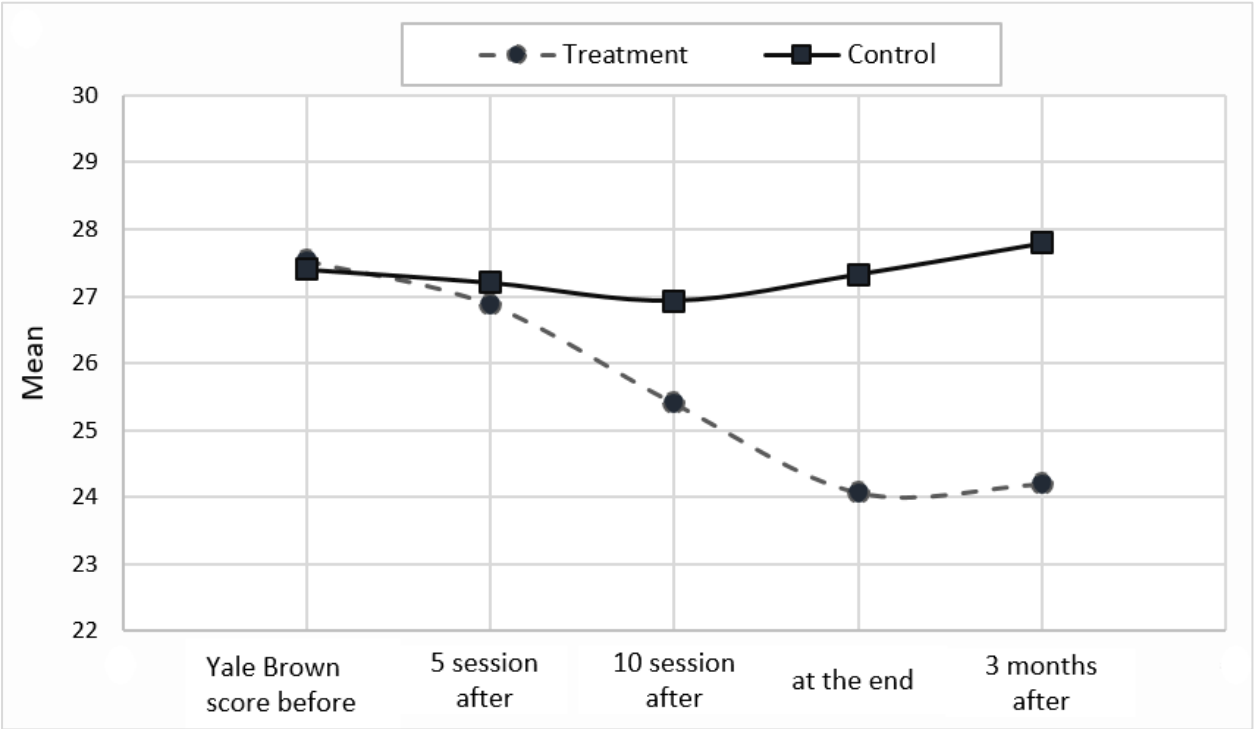

Figure 1. The graph of Yale-Brown Obsessive-Compulsive Scale (Y-BCOS) scores in each study group

No major side effects, such as seizures, were observed during the study, and only four patients in the treatment group and two patients in the control group reported mild headaches for several hours after the treatment sessions.

Discussion

The current study aimed to evaluate the effectiveness of rTMS applied at a frequency of 1 Hz in combination with drug therapy over the left DLPFC area in patients with drug-resistant OCD. The present findings indicated a reduction in the Y-BOCS scores of almost all patients in both groups after the intervention, although the difference was only significant in the treatment group.

Several studies have investigated the effect of rTMS on the treatment of OCD and have reported inconsistent results. The observed discrepancy between the results of these studies can be explained by differences in the brain area where rTMS was applied, the brain side (left, right, or bilateral), stimulation frequency, number of pulses received per session, number of treatment sessions, and intervals between the treatment sessions. Some studies have reported the significant effect of rTMS on the treatment of drug-resistant OCD (12, 18, 27, 33). In this regard, Rostami et al. performed a bilateral stimulation of DLPFC (1 Hz for the right side and 10 Hz for the left side) (27). Haghighi et al. also applied a bilateral approach at a frequency of 10 Hz and reported positive outcomes (23). Moreover, Seo et al. performed unilateral stimulation of the right side of the brain at a frequency of 1 Hz.

The frequent use of the DLPFC area can be attributed to the physiological cause of OCD, which is hyperactivity at the orbitofrontal-subcortical circuit. Besides, the ease of access to DLPFC for rTMS should be considered, as it is a higher-order area implicated in executive processes and cognitive control, including the ability to focus and shift flexibly; also, DLPFC can be an important gateway for indirect effects on subcortical structures (10, 17, 18). Meanwhile, neuroimaging findings have not been consistent regarding the hemisphere-dependent functional differences of DLPFC (18).

Some previous studies investigated the bilateral stimulation of DLPFC at high frequencies and reported supporting results, as bilateral stimulation of this area can inhibit striatal structures, thereby producing a treatment response (23). However, some studies suggested hemispheric asymmetries and argued that predominantly right-sided changes in the cerebral function affect the treatment response. Moreover, in a study by Seo et al.," application of rTMS over the DLPFC suggested a relatively strong lateralization effect. It seems that low-frequency rTMS over the right DLPFC affects the same parts of the cortico-subcortical

circuits as does high-frequency rTMS of the left DLPFC; Accordingly, they performed unilateral stimulation of the DLPF, which yielded positive outcomes (18).

So far, only few studies have performed unilateral stimulation over the left DLPFC to treat OCD, and almost none of them have reported greater effects than the placebo. Nevertheless, it should be noted that there are significant methodological differences between these studies and the present study. In a study by Prasco et al., patients with OCD received 10 treatment sessions over the left DLPFC daily at a frequency of 1 Hz (13), while in the present study, patients received three sessions of therapy per week (14.47 sessions on average). Figure 1, which compares the Y-BCOS scores of each study group, indicates a significant difference after the 10^{th} session between the groups. As shown in Table 5, the difference in the Y-BCOS score was only statistically significant after the intervention (15^{th} session) and in the three- and six-month follow-ups in the treatment group.

According to the literature, the duration and number of treatment sessions can affect the patient's response to treatment (21, 27). In a study by Sakhdev et al., not only few cases were recruited in each group (8 and 10 cases in the control and intervention groups, respectively), which probably affected their findings, but also patients received a daily high-frequency (10 Hz) treatment using rTMS (14). As mentioned earlier, the frequency of rTMS can cause either stimulatory or inhibitory effects, which can explain the inconsistent results of previous studies. In line with previous research on the left DLPFC, at the beginning of the present study, we did not expect better outcomes than the placebo effect. While most patients reported relative improvements in their symptoms during treatment, the statistical analysis showed that only the treatment group experienced significantly improved symptoms after the treatment and during the follow-up; this finding indicates the greater effects of the intervention compared to the placebo.

In the current study, not only the treatment and control groups were compared, but also the final outcomes of each group were compared with the baseline. The participants in the treatment group also described relative improvements in their symptoms during the treatment. However, the interactive effect of time and group was not significant in reducing the mean score of Y-BCOS during treatments in the intervention group. Overall, in the treatment group, the score of Y-BCOS reduced by 3.46 points after the intervention. While the difference was significantly higher than the control group, the improvement of symptoms was not phenomenal according to the Y-BCOS scoring.

Considering the significant difference observed between the groups considering the score of Y-BCOS, a comparison was made between the groups in terms of sex, consumption of antipsychotic medications, and disease duration, to identify predictive factors or factors that can enhance the effect of rTMS after the intervention and during follow-up. The findings indicated that consumption of antipsychotic drugs significantly improved the effect of rTMS based on our protocol. In contrast, sex and disease duration had no significant effects.

To evaluate the durability of response to rTMS, all participants were evaluated using Y-BCOS at three or six months after the intervention. In both groups, the Y-BCOS score increased after the intervention; however, it was not significant in the treatment group, which suggests that the positive therapeutic outcomes persist 3 to 6 months after the intervention.

Conclusion

In this double-blind study, all patients received 15 sessions of unilateral rTMS over the left DLPDC at a frequency of 1 Hz in combination with drug therapy. The findings indicated the significant improvement of clinical symptoms in patients with drug-resistant OCD; the observed improvement persisted for at least 3-6 months. The present findings also showed that consumption of antipsychotics, as a predictive factor, was associated with better

responses to treatment. However, currently, we cannot precisely interpret the present findings. Considering the inconsistent results of neuroimaging and fMRI studies, it is obvious that we have not fully understood the physiopathology of OCD yet, which might explain the high rate of patients who do not respond well to medication or CBT therapy (or even new treatments). Besides, considering the inconsistent results of previous studies on DLPFC and the present results, further research is needed using stimulatory and inhibitory frequencies delivered to this area, either unilaterally (right or left) or bilaterally.

Limitations and suggestions:

This study was a primary investigation with several limitations, the most important of which was the small sample size (n=15 per group), which could be attributed to the low number of patients with drug-resistant OCD and no psychiatric comorbidities. Besides, some participants did not continue the study due to transportation problems caused by the COVID-19 pandemic (e.g., active hours of the clinic or general restrictions). Also, the low number of participants did not allow us to investigate the effects of each type or category (i.e., primary or new generation) of antipsychotics. Another significant limitation of this study was the impossibility of performing Y-BCOS exactly three months after the end of the study for each patient, primarily due to restrictions imposed by the COVID-19 pandemic. Other limitations include limited financial resources and limited time to conduct the study. Also, the 5-cm rule was used to find the location of the DLPFC, on which the shape or size of the skull was not considered.

Despite the mentioned limitations, the two groups examined in this study were homogeneous in terms of the underlying characteristics, such as age, duration of disease, and number of treatment sessions. Besides, there was no significant difference between the groups

concerning the scores of Y-BCOS and BDI. Meanwhile, all participants were screened for psychological comorbidities, and the examiners were the same for the two groups. Also, both patients and examiners were blinded to the intervention until the end of the follow-up phase. Overall, the findings of the present study are acceptable and realistic. However, future studies are recommended to examine a larger sample size in each group to evaluate the effect of each medication. Also, according to the results of some studies, it is recommended to increase the number of treatment sessions to improve therapeutic responses (27). Also, sham coils can be used under sham conditions in future studies.

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Figures

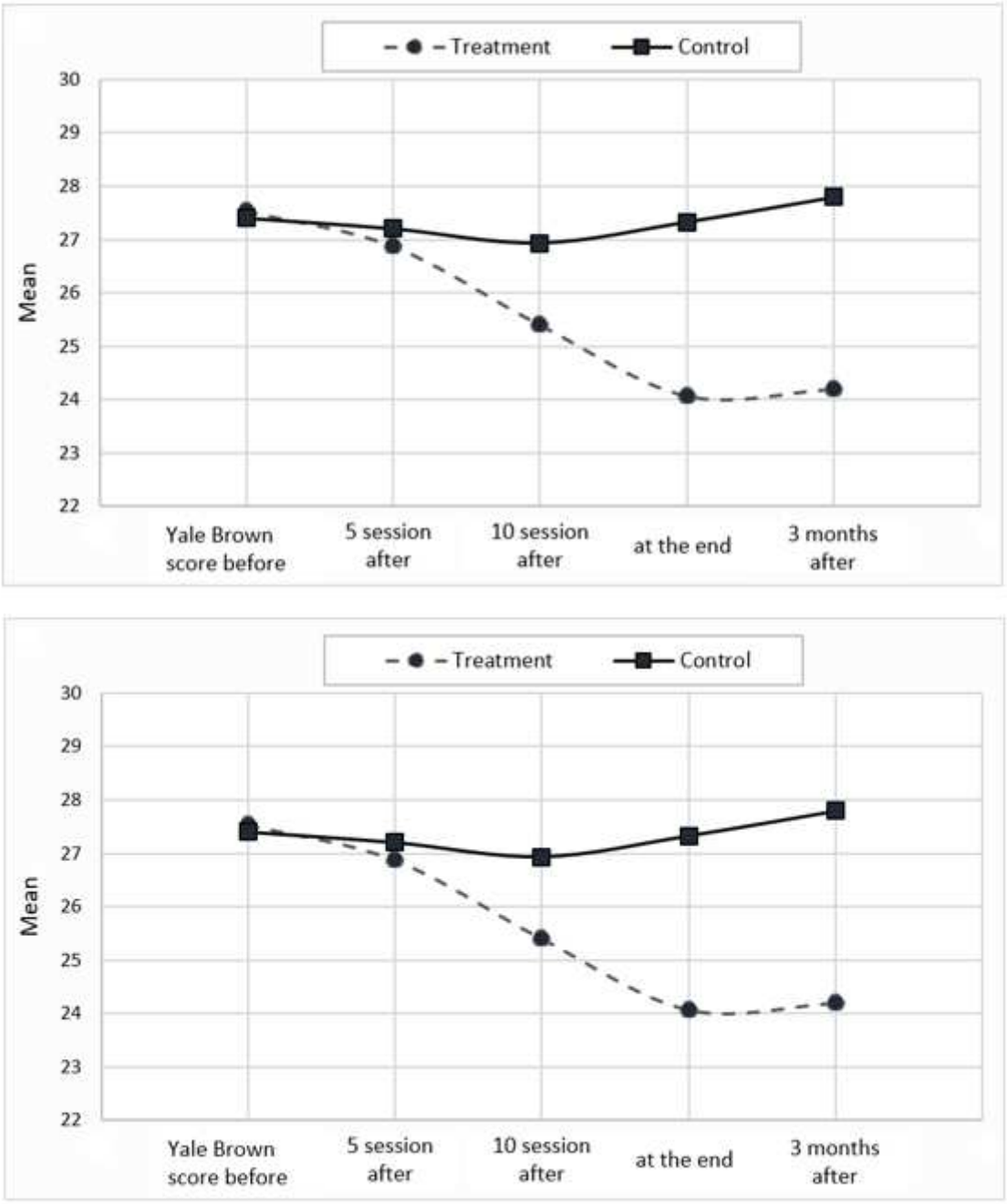

Figure 1

The graph of Yale-Brown Obsessive-Compulsive Scale (Y-BCOS) scores in each study group