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ORIGINAL ARTICLE

Repetitive Transcranial Magnetic Stimulation in a Group of Treament-Resistant Obsessive-Compulsive Disorder Patients: A Descriptive Study

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ABSTRACT

Objective: This study aims to investigate the effects of repetitive transcranial magnetic stimulation (rTMS) treatment in a group of treatment-resistant obsessive-compulsive disorder (OCD) patients and to examine the relationship between various sociodemographic and clinical variables and treatment response.

Materials and Methods: Data including The Yale–Brown Obsessive Compulsive Scale (Y-BOCS) scores and various clinical and sociodemographic characteristics of 27 treatment-resistant OCD patients who received 30 sessions of low-frequency rTMS (LF-rTMS) treatment on the left dorsolateral prefrontal cortex (DLPFC) were analyzed.

Results: Mean Y-BOCS scores decreased significantly across week 0 and the 3rd week ($t(26)=10.59$, $p<.001$) and continued to decrease significantly across weeks 3 and 6 ($t(26)=11.47$, $p<.001$). 21(78%) patients were responders with at least a %25 decrease in the mean Y-BOCS scores, and 10(47.6%) of these 21 patients also met the complete response criteria with a 35% or more reduction in Y-BOCS. No significant difference was observed between responders and non-responders regarding various clinical and sociodemographic variables. The only reported side effects were headaches and local scalp tenderness, which improved in a short time.

Conclusion: This descriptive study has demonstrated the efficacy of a long-duration LF-rTMS application on the DLPFC in a group of drug-resistant OCD patients. This finding might contribute to the available literature, especially in drawing out a standardized treatment protocol in these cases.

Keywords: Neuromodulator, Obsessive-Compulsive Disorder, Transcranial Magnetic Stimulation, Treatment

INTRODUCTION

Obsessive-Compulsive Disorder (OCD) is a psychiatric disorder with a recurrent course in general, in which obsessions and/or compulsions are observed, leading to significant impairment in the functionality and quality of life of the individual [1]. The estimated lifetime prevalence of OCD in the general population is 2-3% [2]. The treatment guidelines published worldwide indicate the efficacy of both pharmacological and non-pharmacological treatments in OCD [3,4]. Medications such as selective serotonin reuptake inhibitors (SSRIs) or clomipramine and cognitive behavioral therapy (CBT) that include exposure and response prevention strategies are recommended as the first-line therapies in the treatment of OCD [5]. Treatment response in OCD is defined as a 35% or more decrease in the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score compared to the baseline score [6, 7]. Criteria to assess treatment response in OCD include the use of at least 2 anti-obsessive drug treatments at the maximum recommended doses for at least 12 weeks and at least 20 hours of CBT [8, 9]. Partial response is defined as a reduction between 25% and 35% on the Y-BOCS; treatment resistance is defined as failure to respond to the above adequate treatment trial and less than 25% reduction on the Y-BOCS [6, 10, 11]. Literature shows that 20-30% of the patients do not respond clinically to the first-line treatments [10, 12]. In search of more treatment options, repetitive transcranial magnetic stimulation (rTMS) has been used in the treatment of OCD.

OCD has been associated with dysfunctions in the Cortico-Striato-Thalamo-Cortical (CSTC) circuits, including the Dorsolateral Prefrontal Cortex (DLPFC), Anterior Cingulate Gyrus, Supplementary Motor Area (SMA), Orbitofrontal Cortex (OFC), Medial Prefrontal Cortex (MPFC), and basal ganglia [13]. Neurophysiological studies have revealed that DLPFC, SMA, and OFC are hyperactive in patients with OCD. This hyperactivity is associated with motor planning and response control deficiencies and plays a role in the generation of ritualized behavioral responses and the regulation of negative emotional states such as fear and anxiety [14]. Hence, alternative treatment options are under investigation, especially those which directly affect OCD neurocircuits.

rTMS is a safe and non-invasive neuromodulatory method that uses repetitive magnetic waves to induce a depolarizing current in a localized region of the cerebral cortex. Magnetic pulses in rTMS can be delivered either at high (10-20 Hz) or low (<1 Hz) frequency. Low-frequency stimulation causes a decrease in neuronal activity, whereas high-frequency stimulation increases neuronal activity [15]. That is, TMS could be effective for OCD treatment by modulating cortical excitability and normalizing hyperactivity of the corticostriatal network. However, because TMS only temporarily alters cortical excitability, repetitive TMS is required when used for treating OCD. Indeed the evidence shows that rTMS is a safe and effective treatment strategy for drug-resistant OCD [16]. Successful treatment of OCD symptoms has been associated with a decrease in CSCT circuit hyperactivity produced by applying low-frequency rTMS (LF-rTMS) on the related cortical areas [17]. Despite all this evidence, the optimum TMS treatment protocol for OCD has not been established yet. Individual variations in response to TMS may perhaps influence this. There is also a lack of information about different demographic and clinical variables that may predict the response to rTMS in OCD patients [18]. Therefore, more research is needed to establish the optimal TMS treatment protocol (such as cortical target and stimulation frequency) for OCD [19].

The DLPFC, which is connected to the striatum, the anterior cingulate cortex, and the thalamus, is one of the most common targets for rTMS [20], and stimulation of this region can also affect connected areas, some of which are associated with OCD symptoms. While initial studies in the literature using rTMS on the DLPFC did not report superiority over placebo [6, 21], subsequent studies showed improvements in OCD symptoms between the active and sham groups [22, 23]. Due to conflicting results in the limited literature on the use of rTMS in the treatment of OCD and the heterogeneity in protocols, it is difficult to conclude whether rTMS is effective or not [16, 24]. Therefore, this study aims to expand the existing literature by evaluating the effects of left DLPFC targeted rTMS on various patients in the treatment of OCD. This study also retrospectively investigates the efficacy of rTMS in drug-resistant OCD patients treated with

rTMS and analyzes the relationship between the sociodemographic and clinical variables and the rTMS response.

MATERIALS AND METHODS

Study Design and Participants

Medical records of 36 patients treated with rTMS with a diagnosis of OCD at Akdeniz University Medical Faculty Department of Psychiatry between May 2019 and May 2020 were retrospectively analyzed. Four of the patients who underwent rTMS were excluded the study due to treatment discontinuation. In addition, 2 patients who previously received electroconvulsive therapy (ECT), 1 patient who was pregnant, and 2 patients with a history of neurological disorders were also excluded from the study. Except for the patients who were excluded from the study, 27 treatment-resistant OCD patients were found to be suitable for the study criteria and included in the study. Patients over the age of 18 with an OCD diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) diagnostic criteria were included in the study. The patients also scored moderate to severe (scores of 16 and above) in Y-BOCS and did not respond to at least two anti-obsessive drug treatments of adequate dose and duration and thus were defined as treatment-resistant. The patients continued to take their medications during the four weeks before starting treatment and during the treatment. All patients were informed in detail about the treatment procedure and gave their written consents before rTMS. This study was conducted by the latest version of the Declaration of Helsinki and approved by the Akdeniz University Medical Faculty Clinical Research Ethics Committee (KAEK-865 / 11.11.2020).

Repetitive Transcranial Magnetic Stimulation (rTMS) Protocol

In the study, rTMS was applied using the Neuro-MS / D stimulator with eight shaped coils (Neurosoft, Ivanovo, Russia) by the updated safety guidelines [25]. The patients were comfortably seated on an adjustable chair in a semi-reclining position, with their heads placed on a head restraint and their arms on bilateral armrest. The patients' resting motor threshold was defined as the minimum stimulus intensity that produces a motor response during active contraction of the right abductor pollicis brevis muscle (APB) [26] and was determined using visual inspection of the relevant finger movement. After determining the resting motor threshold of the patients, the position of the coil was positioned on the anterior 5 cm along a parasagittal line from the optimum APB stimulation area to localize the DLPFC, which is the stimulation zone used for treatment [27]. After the coil is positioned and fixed on the stimulation area, the rTMS protocol was determined as 1200 pulses per session using a 1 Hz stimulation frequency, stimulation intensity at 100% of RMT. A total of 30 sessions of LF-rTMS was applied to each patient over the left DLPFC for six weeks, five days a week, excluding weekends.

Measurement and Assessment Tools

Patients included in the study were followed by clinical rating scales at regular time points, every three weeks from the first session to the end of the treatment. The Y-BOCS scale was applied to all patients on the day before the first rTMS session (0th week), on the 3rd week of rTMS treatment, and after 30 sessions of rTMS treatment (6th week) and clinical evaluation was performed. The Y-BOCS is the most widely used scale to assess the severity of OCD symptoms, equally weighing obsessions and compulsions, consisting of 10 items, each item graded between 0 and 4 points, and evaluated by the clinician [28]. The patients included in the study were evaluated according to the changes in Y-BOCS scores over 6 weeks. 35% or more reduction in Y-BOCS score from baseline was regarded as a complete response; A decrease of 25% or more in Y-BOCS score from baseline was classified as a partial response [10].

Statistical Analysis

Descriptive statistics were reported as percentage rates with frequency for categorical variables and mean (± standard deviation) or median for continuous variables. To compare independent groups, independent samples t-test was used in the case of normally distributed variables and the Mann-Whitney-U test for non-normally distributed variables. The Chi-Square test of independence was used to assess the relationships between categorical variables. Moreover, the repeated measures ANOVA test was used to evaluate the patients' mean YBOCS scores across three-time points (paired sample comparisons). Significance

was evaluated at $p \leq 0.05$ in the statistical analyses which were performed using the SPSS version 23.0.

RESULTS

Sociodemographic and Clinical Characteristics

Twenty-seven patients were included in this study, 59.26% (n=16) of whom were female. The mean age of the patients was 34.70 (SD=14.05, range= 19-66). The rate of the high school graduates (51.85%, n=14) was the highest in the study sample. Six patients (22.22%) were employed at the time of the study, and 16 (59.26%) were single. Twelve (44%) patients had a comorbid psychiatric illness, which was depression (30%, n=8), bipolar disorder (7.40%, n=2), and psychotic disorder (7.40%, n=2), respectively according to their frequency. The mean duration of illness in OCD patients 12.81 years (SD=10.41, range=2-38 years). Eighteen patients (66.67%) had comorbid nicotine addiction, whereas two patients (7.40%) met the alcohol use disorder criteria. The sociodemographic and clinical characteristics of the study group are summarized in Table 1.

Clinical Follow-up with the Yale-Brown Obsessive Compulsive Scale (Y-BOCS)

A repeated-measures ANOVA determined that mean YBOCS scores differed significantly between the three time points of assessment ($F(2, 52) = 206.82$, $p < .001$). Post hoc tests with the Bonferroni correction showed that the mean Y-BOCS scores decreased significantly across week 0 and the 3rd week ($t(26) = 10.59$, $p < .001$) and continued to decrease significantly across weeks 3 and 6 ($t(26) = 11.47$, $p < .001$). (Table 2 and Figure 1).

To figure out response rates, improvement in YBOCS scores were calculated as a percentage for every patient. Accordingly, 21 (78%) patients out of the 27 patients who showed at least a %25 decrease in the mean Y-BOCS scores compared to the baseline score (thus who also met the partial response criteria) were regarded as responders to rTMS treatment, whereas 10 (47.6%) patients in among these responders (N=21) also met the complete response criteria with at least %35 decrease in the mean YBOCS scores. The remaining 6 (N=27, % 22) patients in the study group were defined as non-responders.

No significant difference was found between the responders and non-responders compared to each other regarding various sociodemographics (gender, age) and clinical variables (illness duration, psychiatric comorbidity, suicide history) to evaluate the relationship between clinical response and these variables. (Table 3).

Side-effects of the rTMS Treatment

Five patients (18.52%) reported side effects after the rTMS treatment. Thus, three patients complained of headache and the other two patients complained of localized scalp tenderness. No significant difference was found between responders and non-responders in terms of the incidence of side effects (headache: $\chi2\ (1)=0.428$, $p=0.51$; localized scalp tenderness: $\chi2\ (1)=0.206$, $p=0.76$).

Table 1. Demographic and clinical characteristics of the patients.

Demographic and clinical characteristics	n	%
Gender		
Female	16	59.26
Male	11	40.74
Marital Status		
Single	16	59.26
Married	9	33.33
Divorced	2	7.41
Educational Status		
Primary education	6	22.22
Secondary education	14	51.85
Undergraduate education	7	25.93
Employment Status		
Employed	6	22.22
Unemployed	14	51.85
Student	4	14.81
Retired	3	11.11
Comorbidity/Comorbidities		
Yes	12	44.44
Depressive disorder	8	22
Bipolar disorder	2	7
Psychotic disorders	2	7
No	15	55.56
Smoking		
Yes	18	66.67
No	9	33.33
Alcohol Use Disorder		
Yes	2	7.41
No	25	92.59

*Descriptive statistics were reported as percentage rates with frequency for categorical variables. n: sample size.

Table 2. Comparison of mean Y-BOCS scores.

	Difference	*SE*	*df*	*t*	*p*
0th week Y-BOCS score - 3rd week Y-BOCS score	3.22	0.40	26	7.97	**< .001**
0th week Y-BOCS score - 6th week Y-BOCS score	6.52	0.62	26	10.46	**< .001**
3rd week Y-BOCS score - 6th week Y-BOCS score	3.30	0.44	26	7.44	**< .001**

*The repeated measures ANOVA test was used to evaluate the patients' mean YBOCS scores across three-time points (paired sample comparisons). To compare independent groups, independent samples t-test was used in the case of normally distributed variables. Significance was evaluated at p ≤ 0.05 in the statistical analyses. Y-BOCS: Yale-Brown Obsessive-Compulsive Scale, SE: Standard Error, df: Degrees of Freedom.

Table 3. Comparison of responders and non-responders.

	Response			*U*	*z*	*p*
	responders	non-responders	OR			
Female	11[12.44]	5[3.56]	0.23			.350
Male	10[8.56]	1[2.44]				
Smoking (+)	12[14.00]	6[4.00]	0.00			.071
Smoking (-)	9[7.00]	0[2.00]				
	Mean Rank					
Age	13.71	15.00		57.00	-0,35	.726
rTMS - power	13.57	15.50		54.00	-0.53	.598
rTMS – motor Treshold	13.55	15.58		53.50	-0.56	.578

Values are presented as numbers of patients (percentages of the sample).
*The Chi-Square test of independence was used to assess the relationships between categorical variables. Significance was evaluated at p ≤ 0.05 in the statistical analyses. rTMS: repetetive Transkranial Magnetic Stimulation, OR: Odds Ratio.

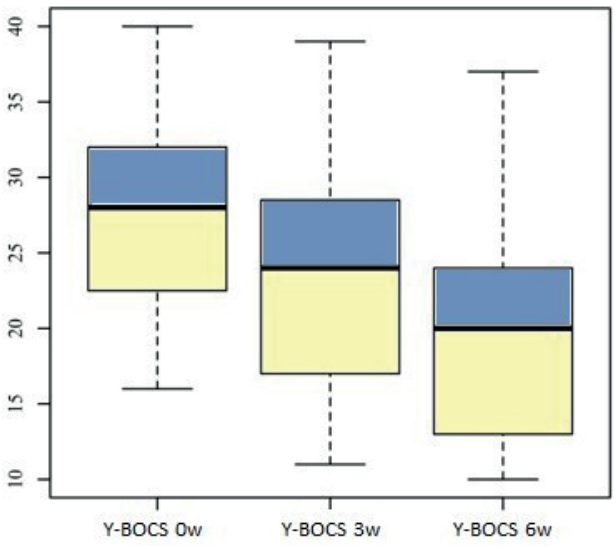

Figure 1. The changes of mean scores on Y-BOCS from the baseline to the third and sixth week of the rTMS treatment. Y-BOCS: Yale-Brown Obsessive Compulsive Scale; rTMS: repetitive transcranial magnetic stimulation. *p < 0.05 (Significance was evaluated at p ≤ 0.05 in the statistical analyses).

DISCUSSION

Data from studies on the role of rTMS in the treatment of OCD symptoms so far are limited. Moreover, most of the existing studies include small sample groups and target different cortical regions using different stimulation parameters [29, 30]. Therefore, the application of rTMS cannot be standardized and there is an increasing need for new studies addressing the possible use of rTMS as an efficacious therapeutic intervention for OCD.

To the best of our knowledge, this study is the first study conducted in Turkey on treatment-resistant OCD patients who underwent rTMS treatment. Our study showed the efficacy and safety of rTMS treatment in a group of treatment-resistant OCD patients. Treatment efficacy in this study was observed as a gradual decrease in YBOCS scores over time from the start to the completion of 30 sessions of rTMS treatment. 78% of the patients who received rTMS treatment responded to the rTMS treatment in general, whereas 37.03% met the "complete response" criteria. This finding is comparable to the findings reported in most previous studies with OCD patients in which the target application site was the DLPFC [31, 23]. For example, in a study by Sachdev et al., rTMS targeting the DLPFC was found to be effective in treatment-resistant OCD patients [23]. In addition, the recent evidence-based guidelines for the therapeutic use of rTMS in OCD patients indicate that LF-rTMS administered over the DLPFC may be efficacious [31]. And this supports our findings that LF-rTMS applied on DLPFC may be effective. Nevertheless, some studies report lower response rates to rTMS

treatment in OCD patients [32-34]. Different stimulation protocols or variations in the clinical characteristics of the patients might account for these inconsistent findings. For example, Prasko et al. [35] applied low frequency rTMS to the left DLPFC in their study, and no statistically significant difference was found between active and sham treatments. However, this may be attributed to the short-term (2 weeks) application of rTMS and the significant difference between the active and sham groups (the active group had higher initial YBOCS scores) in the initial YBOCS scores of the OCD patients included in their study. On the other hand, a recent network meta-analysis by Liang et al. showed that LF-rTMS applied to the DLPFC is more effective than sham rTMS. Moreover, in the same study, all rTMS treatment strategies were found to be similar to sham rTMS regarding tolerability [36].

The rTMS protocol used in a study might also be an important factor in treatment response to rTMS, and thus should be taken into consideration as well. Indeed, studies show that a short-duration protocol (1-2 weeks / 5-10 sessions) and a low stimulation intensity (80%) targeting DLPFC [32] are associated with poor response to rTMS. Conversely, rTMS was found to be effective when applied for longer durations (4-6 weeks / 20-30 rTMS sessions) and with a high stimulation intensity (100-120%) [1, 37]. The clinical heterogeneity and the variations between rTMS protocols make it difficult to draw a conclusion acceptable to everyone [24]. Therefore, it might help develop a standardized stimulation protocol to reduce the heterogeneity between studies that investigate rTMS effects in OCD. The high response rates observed in this study suggest that the stimulation protocol implemented here (LF-rTMS) is effective in treatment-resistant OCD patients. Although it might be unnecessarily long for research purposes, this protocol seems feasible for treatment success.

Comorbidity is common in patients with OCD [38]. Similar to the literature, a significant portion of the OCD patients included in this study had comorbidities (most commonly major depression). In some studies, it has been suggested that rTMS applied to the DLPFC causes improvements in comorbid anxiety and depression rather than specific OCD symptoms [6, 32, 39]. Therefore, rTMS applied to the DLPFC in our study may have produced improvements in OCD symptoms that were secondary to improvements in depression and anxiety. In addition, since the pharmacological treatments of the patients were continued during rTMS in this study, there may be a synergistic effect between rTMS and these drugs, which may affect recovery.

In the study group, no significant difference was found between responders and non-responders to rTMS treatment in terms of sociodemographic and clinical characteristics, similar to the previous findings reported in the literature [40, 41, 42]. In the study, headaches and localized scalp tenderness were the only complaints reported by three and two patients, respectively. Nevertheless, both of these complaints disappeared spontaneously within 3-4 days. No serious side effects such as seizures, acute psychiatric symptoms, or changes in cognitive functions were observed in patients. These results are consistent with most of the previous findings reported in rTMS studies [22, 43] and support the application of rTMS targeting the DLPFC as a safe and well-tolerated treatment modality in OCD patients.

However, this study has some limitations. First, the study is a retrospective study with a relatively small sample size and no control group. Hence, it is difficult to exclude the placebo effect and generalize the results of the study. Although no change was made in medication type or dosing, we should bear in mind that patients continued their medications which might also have an effect on the treatment response. Thus, further studies which keep out medication effects are needed to clarify this problem.

CONCLUSION

In conclusion, this study provides evidence that rTMS targeting DLPFC is an effective method in the treatment of drug-resistant OCD patients. Besides, it has been demonstrated that rTMS has a low side-effect profile. Large-scale RCTs will provide a better understanding of this method with regard to establishing a standardized rTMS protocol for OCD treatment in clinical practice.

Author contribution

Study conception and design: AE, BC, MT, NN; data collection: MT, NN; analysis and interpretation of results: BC, AE; draft manuscript preparation: AE, BC, MT, NN. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Akdeniz University Medical Faculty Clinical Research Ethics Committee (Protocol no. KAEK-865 / 11.11.2020).

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Conflict of interest

The authors declare that there is no conflict of interest.

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