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THE EFFICACY AND SAFETY OF TRANSCRANIAL MAGNETIC STIMULATION IN TREATMENT-RESISTANT BIPOLAR DEPRESSION

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SUMMARY

Background: *The aim of the current study is to investigate the efficacy and safety of Transcranial magnetic stimulation (TMS) treatment, a non-invasive brain stimulation technique, on depressive symptoms in treatment-resistant bipolar depression (TRBD).*

Subjects and methods: *The study included 29 patients between the ages of 18-65, with bipolar disorder depressive episode according to DSM-5 and with the decision of non-response to treatment according to the Canadian Mood and Anxiety Treatment Network (CANMAT). Patients were divided into two groups double-blind-randomly, 20 sessions of TMS and 20 sessions of sham TMS were applied crossover. Hamilton Depression Rating Scale (HAM-D), Beck Depression Inventory (BDI), Young Mania Rating Scale (YMRS) and TMS Side Effect Questionnaire were applied to the patients before the treatment, at the 2nd week which is the crossover phase, and at the end of the treatment at 4th week.*

Results: *In both groups, the severity of depression was decreased significantly according to HAM-D and BDI scores after the procedure. As well as active stimulation, some positive placebo effects were observed with sham stimulation. But the decreases seen in HAM-D and BDI scores and response to the treatment were higher during the weeks when the groups received active stimulation (respectively p=0.000, p=0.001, p=0.005). At the end of the study, according to HAM-D, 55.7% of the patients showed response to the treatment, 24.13% partial response. According to BDI, 41.37% of the patients showed response to the treatment, and 31.03% partial response. No associations were found between TMS response and sociodemographic - clinical features, or type of the disease (p>0.05). During the study, no serious adverse effects such as seizures or manic / hypomanic switches were observed.*

Conclusions: *The results of our study showed that TMS treatment is an effective and safe treatment for patients with treatment-resistant bipolar depression.*

Key words: *bipolar depression - treatment resistant - Transcranial magnetic stimulation*

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INTRODUCTION

Despite advances in the treatment of bipolar disorder (BD), it may remain insufficient in the basic treatment aims of recovery from an acute episode, preventing recurrence, restoring functionality and ensuring minimum cognitive loss (Poon et al. 2012). The depressive periods in BD last longer than the manic periods, and have a greater effect on the functionality and quality of life of the patient (Judd et al. 2005, Sienaert et al. 2013).

Treatment resistance in BD is accepted as the inability for sufficient clinical recovery in a specific phase of the disease despite the application of a certain number of treatments and strategies (Poon et al. 2012). According to the Canada Mood and Anxiety Treatment Network (CANMAT) guideline, not reaching remission after 2 or more first stage, second stage, or third stage treatments is defined as treatment-resistant bipolar disorder (TRBD) (Yatham et al. 2013, Myczkowski et al. 2018). Combination treatment with more recommended additions is applied to these types of cases (Bowden 2004, Özalp & Karslioglu 2015).

Due to side-effects such as a shift to manic hypomania in addition to the partial efficacy of pharmacological options, somatic treatments such as electroconvulsive therapy (ECT), deep brain stimulation, and transcranial magnetic stimulation (TMS) may sometimes be required in the combination. TMS, which is a non-invasive brain stimulation approach, has become a focus of interest in recent years (Sampaio-Junior B et al. 2017). In TMS, electrical stimulation occurs in the cerebral cortex from the magnetic field created with the placement of a coil on the scalp, thereby creating neurophysiological corrections in different regions of the brain (Cocchi & Zalesky 2018, Sadock 2016). It is thought that dentrites, presynaptic terminals, cell bodies, and efferent axons can be stimulated by the magnetic field that is created (Younf & Cracco 1985). With TMS treatment in psychiatric diseases, it is attempted to normalise the ability for pathological stimulation of the cortical focus thought to be linked to a specific disease. Clinical studies have suggested that TMS is beneficial in BD by stimulating the left prefrontal cortex or by inhibiting the right prefronatal cortex (Tan & Sayar 2017). The application of TMS in treatment-resistant depression was approved by the Food and Drug Administration (FDA) in 2008.

There are randomised, controlled studies in literature that have investigated the efficacy of TMS treatment in bipolar depression. In a double-blind, randomised,

controlled study by Tavares et al. (2017), it was shown that TMS was potentially effective and was a well-tolerated additional treatment in resistant bipolar depressive patients. Dolberg et al. (2002) also conducted a double-blind, controlled study, in which 20 sessions of active TMS were applied to 10 patients with bipolar depression, and to 10 patients, first 10 sessions of sham-TMS treatment followed by 20 sessions of active TMS. At the end of 10 sessions, the patients who received active TMS showed a significant improvement compared to those who received the sham-TMS. Following the application of 20 sessions of active TMS to those who had received the sham treatment, the difference between the groups was eliminated, and the sham group patients were determined to have responded well to the active TMS treatment. However, there are also negative results in literature. In parallel, double-blind, randomised, controlled studies, Fitzgerald et al. (2016) determined no difference between active and sham stimulations in treatment-resistant bipolar depression. Nahas et al. (2003) reported similar negative results. Positive results of the use of TMS in bipolar depression as much as in major depression are increasing (Tan & Sayar 2017). In a meta-analysis by McGirr et al. (2017), 19 randomised, controlled studies were reviewed and it was reported that TMS could be an effective and safe treatment option in bipolar depression, treatment-related mood shifts were determined at extremely low rates, and there was observed to be no increased risk related to active TMS.

The aim of this double-blind, randomised, crossover study was to investigate the efficacy and reliability of high-frequency TMS applied to the left dorsolateral prefrontal cortex (DLPFC) in TRBD.

SUBJECTS AND METHODS

Subjects

The study sample comprised 29 patients treated as inpatients or outpatients in the Psychiatry Department of Pamukkale University Medical Faculty, who had been diagnosed with bipolar disorder depressive episode according to the DSM-5 diagnostic criteria, and had at least moderate severity depression corresponding to HAMD score >17, and had not responded to ≥2 interventions approved as first, second or third stage treatments according to CANMAT. Participants were at stage of 3 or 4 of treatment resistance.

All the patients were in the 18-65 years age range, were literate, and provided written informed consent for participation in the study. The other study inclusion criteria were defined as the use of mood-regulating drugs serum levels in the treatment range, and that no change The study exclusion criteria were defined as the presence of any accompanying neurological disease, had been made for at least 4 weeks in the treatment regimen dose or the agent used. mental retardation, any additional psychiatric disease, thoughts of suicide on first evaluation, pregnancy, psychotic findings and (hypo)manic symptoms corresponding to YMDS score of >12, or the presence of any object which could interact with metal or magnetism such as cardiac pacemaker, intracranial implant, or foreign body.

Approval for the study was granted by the Ethics Committee of the University (decision no: 60116787-020/28845, dated: 24.04.2019).

Stages of the Study

A total of 34 patients were initially enrolled in the study, and 5 were excluded; 1 patient who decided to stop treatment with the thought that he did not benefit from the treatment in the first week, and 4 patients who did not want to come to the hospital and decided to stop treatment because of the COVID-19 pandemic. Thus the study was completed with 29 patients (Figure 1).

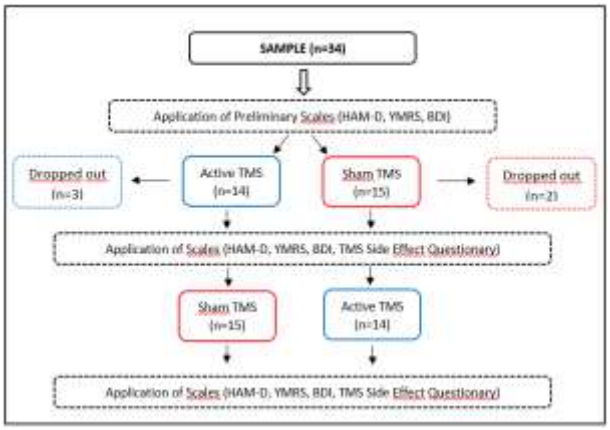

Figure 1. Flowchart of the study

Throughout the period of the study, no intervention was made to the psychiatric pharmacotherapies of the patients and the treatments being used were continued at the same dose. The patients were randomly separated into two groups, and in a double-blind, crossover manner, 20 sessions of high-frequency (10 Hz)TMS and 20 sessions of sham-TMS were applied to the left DLPFC.

In addition to completion of the sociodemographic form for all patients, depression severity was measured 3 times, at week 0 before treatment, at week 2 at the crossover stage, and at week 4 at the end of treatment. To determine the severity of depression, the Hamilton Depression Scale (HAM-D) was completed by the clinician, and the self-report scale of the Beck Depression Inventory (BDI) was completed by the patient. To determine findings of mania or hypomania, the Young Mania Rating Scale (YMRS) was used, and to evaluate side-effects of TMS, the TMS Side-Effects Questionnaire.

The TMS Side-Effects Questionnaire, which was developed by Bersani et al. (2013), questions headache, neck pain, pain in the scalp, pins and needles, itching, a feeling of burning, redness in the skin, sleepiness, difficulty in concentration, mood changes, and other symptoms.

All the scales used in the study were applied by a researcher blinded to the treatment groups.

TMS and Sham-TMS Protocol

The TMS treatment protocol was applied using a Neuro MS/D device (Neurosoft Ltd, Russia) with a figure-of-8 shaped coil according to manufacturer protocols. First, the resting motor threshold was determined by gradually increasing stimulation to 5cm lateral of the vertex of the mid interauricular line and observing the muscle activity of the abductor pollicis brevis muscle in the contralateral left thumb. The level of application was defined as 110% of the motor threshold determined. The site of application was accepted as 5 cm anterior over the parasagittal plane from the motor cortex point where the motor threshold was determined. This area corresponds to the left DLFPC (Herwig et al. 2001). The coil was then placed on the scalp at an angle of 45° in the sagittal line. Each TMS session was applied as 25 consecutive trains, at 10 Hz frequency, at 40 pulses in each trains, and intertrain interval was 20 sec. The total of 20 sessions (20000 pulses) were applied as 2 per day for 2 weeks. The sham-TMS application was performed using the same coil as in the active application but placed at a distance from the scalp at a 45° angle (90° in the sagittal line). The sham group patients were given sound and sensory effects similar to those of the active application, but no stimulus was given to the cortical structures below the placement area of the coil (Rossi et al. 2007).

The patients were separated into two groups. Patients in Group A were first administered 20 sessions of active TMS (Total of 20,000 pulses) followed by 20 sessions of sham stimulation. Patients in Group B were administered the reverse, first 20 sessions of sham stimulation followed by 20 sessions of active TMS (Total of 20,000 pulses). The treatments for both groups lasted a total of 4 weeks.

Statistical Analysis

Data obtained in the study were analyzed statistically using SPSS vn. 22.0 software (Statistical Package for the Social Sciences version 22, Chicago, IL, USA). Continuous variables were stated as mean ± standard deviation (SD) values and categorical variables as number (n) and percentage (%). Independent groups that met parametric assumptions were compared using the Significance of the Difference between Two Means test, and for groups that were not parametric, the Mann Whitney U-test was applied. In comparisons of dependent groups, when the parametric test assumptions were met, the Significance of the Difference Between Two-Matches test was used, and when the parametric test assumptions were not met, the Wilcoxon Paired-Sample test. Chi-square analysis was applied to examine the differences between categorical variables. In all the analyses, a value of $p<0.05$ was accepted as statistically significant.

RESULTS

Evaluation was made of a total of 29 patients, comprising 15 (51.7%) females and 14 (48.3%) males with a mean age of 40.59±9.95 years. The diagnosis of bipolar disorder was BD type I in 23 (79.3%) cases and BD type II in 8 (20.7%) cases.

In the examination of the sociodemographic data and clinical characteristics of all the patients, no statistically significant difference was determined between Group A and Group B in respect of age, gender, marital status, education level, employment status, place of residence, number of depressive episodes, number of hospital admissions, history of ECT, suicide attempts, family history of BD, and the presence of physical disease (Table 1). The characteristics of the pharmacological treatments taken by the patients are shown in Table 2. The number of patients taking lithium was determined to be statistically significantly higher in Group A than in Group B ($p=0.021$). Other than for lithium, no statistically significant difference was determined between the groups in respect of pharmacological treatments.

The scale points of the groups are summarised in Table 3. Changes in the scale points were examined within and between the groups from week 0 to the crossover stage at week 2 and the end of treatment at week 4. No significant difference was determined between the groups in respect of the HAM-D and BDI points at the begining of the study (severity of the diseases are similar in each group). In Group A, a significant decrease was determined in the scale points after the active TMS (0-2 weeks) and after the sham TMS (2-4 weeks). In Group B, a significant decrease was determined in the scale points after the sham TMS (0-2 weeks) and after the active TMS (2-4 weeks). These decreases in the HAM-D and BDI points of the groups were greater in the weeks after receiving active TMS, and at the end of the study, there was seen to be a significant decrease in the severity of depression in both groups. The statistical differences between weeks 0-1, 2-4, and 0-4 to evaluate the treatment periods in both groups were stated as p1, p2, and p3, respectively (Table 3) (Figure 2). In Group A, the HAM-D points fell by 6.1±4.6 points after active TMS and by 3.7±2.2 after sham-TMS. In Group B, the HAM-D points fell by 3.2±4.1 points after sham-TMS and by 6.5±4.0 after active TMS. In Group A, the BDI points fell by 9.7±12.8 points after active TMS and by 6.3±5.8 after sham-TMS. In Group B, the BDI points fell by 3.2±4.8 points after sham-TMS and by 9.5±8.2 after active TMS. The difference in the change in HAM-D and BDI points was seen to be greater in both groups after active TMS than after sham-TMS. The effect size (Cohen's d) (Cohen 1988) according to the difference in the change of the HAM-D points of the groups in the periods when they received TMS treatment were determined to be 0.67 in Group A, and -0.85 in Group B. For the BDI points, these values were 0.68 for Group A, and -0.45 for Group B.

The changes in response to treatment of the groups are shown in Table 4. According to the HAM-D and BDI, the response to treatment was determined to be greater in the weeks when they received active TMS treatment.

Table 1. Sociodemographic and Clinical Characteristics of the Groups

Demographic Features		Group A who received TMS first	Group A who received Sham first	P
Age(Mean±SD)		42.36 ±9.5	38.93±10.3	0.364
Gender(n,%)	Female	8 (57.1)	7 (46.7)	0.573
	Male	6 (42.9)	8 (53.3)	
Marital status (n,%)	Single	2 (14.3)	5 (33.3)	0.462
	Married	9 (64.3)	7 (46.7)	
	Divorced	3 (21.4)	3 (20.0)	
Education (n,%)	Primary school	4 (28.6)	7 (46.6)	0.328
	High school	3 (21.4)	5 (33.3)	
	University	7 (50.0)	3 (20.0)	
Working Status (n,%)	Employed	7 (50.0)	5 (33.3)	0.216
	Unemployed	7 (50.0)	10 (66.7)	
Living (n,%)	Rural	0 (0.0)	1 (6.7)	0.331
	Urban	14 (100)	14 (93.3)	
Smoking status (n, %)	Yes	9 (64.3)	11 (73.3)	0.700
	No	5 (35.7)	4 (26.7)	
Alcohol drinking (n, %)	No	8 (57.1)	10 (66.7)	0.861
	Rarely	5 (35.7)	4 (26.7)	
	2-3 times a week	1 (7.1)	1 (6.7)	
Disease onset age (Mean±SD)		25 ±6.8	25.4±8.4	1.000
Type of Disease (n,%)	Bipolar Type I	12 (85.7)	11 (73.3)	0.651
	Bipolar Type II	2 (14.3)	4 (26.7)	
Depressive Episode (n,%)	1-5 Episode	2 (14.3)	5 (33.3)	0.254
	6-10 Episode	8 (57.1)	8 (53.3)	
	11-15 Episode	2 (14.3)	2 (13.3)	
	>15 Episode	2 (14.3)	0 (0.0)	
Hospitalizations (n, %)	1-5 Times	12 (85.7)	10 (66.7)	0.627
	6-10Times	1 (7.1)	2 (13.3)	
	None	1 (7.1)	3 (20.0)	
Electroconvulsiveterapy (n, %)	Yes	5 (35.7)	4 (26.7)	0.700
	No	9 (64.3)	11 (73.3)	
Suicide attempt (n, %)	Yes	7 (50.0)	9 (60.0)	0.588
	No	7 (50.0)	6 (40.0)	
Family History (n,%)	Yes	7 (50.0)	7 (46.7)	0.858
	No	7 (50.0)	8 (53.3)	

Table 2. Pharmacological Treatment Characteristics of the Groups

Pharmacological Treatment	Group A (n=14) - n (%)	Group B (n=15) - n (%)	P
Lithium	8 (57.1)	2 (13.3)	0.021*
Valproate	6 (42.9)	11 (73.3)	0.096
Carbamazepine	1 (7.1)	1 (6.7)	1.000
Lamotrigine	10 (71.4)	7 (46.7)	0.176
Quetiapine	7 (50.0)	12 (80.0)	0.128
Olanzapine	5 (35.7)	3 (20.0)	0.427
Risperidone	4 (28.6)	2 (13.3)	0.390
Aripiprazole	6 (42.9)	9 (60.0)	0.356
Risperidone depot	1 (7.1)	0 (0.0)	0.483
Aripiprazole depot	1 (7.1)	0 (0.0)	0.483
Paliperidone depot	2 (14.3)	1 (6.7)	0.598
Flupenthixol depot	1 (7.1)	0 (0.0)	0.483
Zuclopenthixol depot	2 (14.3)	0 (0.0)	0.224
Venlafaxine	1 (7.1)	2 (13.3)	1.000
SSRI*	3 (21.4)	4 (26.7)	1.000
Bupropion	5 (35.7)	5 (33.3)	1.000
Modafinil	1 (7.1)	1 (6.7)	1.000

*SSRI: Selective Serotonin Reuptake Inhibitors

Table 3. HAM-D and BDI Scores of the Groups

Scale Type	Process	Group A (Mean±SD)	Group B (Mean±SD)	P
HAM-D	0. week	20.4±2.8	20.1±2.6	0.774
	2. week	14.2±5.7	16.8±2.8	0.158
	4. week	10.5±5.4	10.3±4.6	0.900
BDI	0. week	34±12.2	29.5±7.2	0.210
	2. week	24.6±16.8	26.2±7.6	0.745
	4. week	18.2±15.4	16.7±7.6	0.731
p1		0.000	0.014	
p2		0.000	0.001	
p3		0.000	0.000	

HAM-D: Hamilton Depression Scale; BDI: Beck Depression Inventory;
(p1: Between 0. week - 2. week; p2: Between 2. week - 4. week; p3: Between 0. week - 4. week)

Table 4. Treatment Responses of the Groups

		HAM-D			BDI		
	Response*	Group A - n (%)	Group B - n (%)	P	Group A - n (%)	Group B - n (%)	P
2. week	No	6 (42.9)	14 (93.7)	0.005	7 (50.0)	14 (93.3)	0.015
	Partial	4 (28.6)	0 (0.0)		3 (21.4)	0 (0.0)	
	Yes	4 (28.6)	1 (6.7)		4 (28.6)	1 (6.7)	
4. week	No	3 (21.4)	3 (20.0)	0.947	4 (28.6)	4 (26.7)	0.962
	Partial	3 (21.4)	4 (26.7)		4 (28.6)	5 (33.3)	
	Yes	8 (57.1)	8 (53.3)		6 (42.9)	6 (40.0)	

HAM-D: Hamilton Depression Scale; BDI: Beck Depression Inventory; *No response: Decrease in scale scores <25 %; Partial response: Decrease in scale scores 25-50%; Response: Decrease in scale scores ≥ 50%;

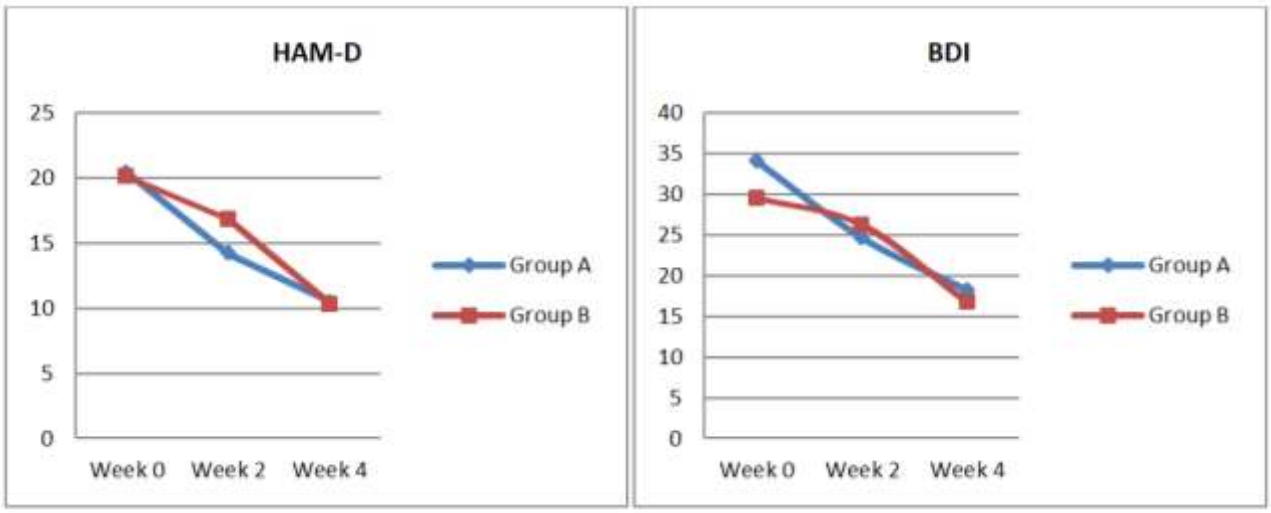

Figure 2. HAM-D and BDI score changes of the groups

At the end of the study, 55.17% (n:16) of the cases showed a response to treatment and 24.13% (n:7) a partial response according to the HAM-D points, and 41.37% (n.12) showed a response to treatment and 31.03% (n:9) a partial response according to the BDI points. When the treatment response rates of the groups were examined there was seen to be a greater number of patients responding to treatment in the periods when they received active TMS according to both HAM-D and BDI (Table 4). No significant differences were found in TMS response between patients with BD I or BD II (p>0.05). Similarly, no significant differences were found in TMS response according to sociodemographic features and clinical features (Marital status, education level, employment status, place of residence, number of depressive attacks, number of hospital admissions, history of ECT, suicide attempts, family history of BD or the presence of physical disease) (p>0.05).

To evaluate side-effects associated with the procedure, the TMS Side-Effects Questionnaire and the YMRS were applied to the patients in the 2nd week at the crossover stage and in the 4th week at the end of treatment. According to the YMRS points, there was no shift to hypomania/mania after TMS, and no serious side-effects were observed. Minor side-effects were reported in 9 cases; 6 (20.7%) patients with headache, 2

(6.9%) with sleepiness, and 1 (3.4%) with headache, neck pain, and sleepiness. There were no patients who could not complete the study because of side-effects, and all the complaints described were resolved without the need for medical intervention.

DISCUSSION

In this study which investigated the efficacy and reliability of the therapeutic application of high-frequency TMS to bipolar depression patients, the results demonstrated that TMS provided a significant improvement in treatment-resistant bipolar depression and was a well-tolerated safe method which obtained positive results.

In the current study, active TMS and sham-TMS were applied as 2 sessions a day for 4 weeks. There are studies in literature that have shown that the efficacy of treatment increased with a longer period of stimulation (O'Reardon et al. 2007, Cohen et al. 2010). It has also been reported that although efficacy can be increased when applied for a longer time (6-8 weeks), there can also be a higher rate of dropouts (Fitzgerald et al. 2006, Galletly et al. 2012). Therefore, for the applicability of TMS treatment, current treatment protocols are used for a shorter period (2-4 weeks), as in the current study (Tavares et al. 2017, Myczkowski et al. 2018, Gold et al. 2019). Furthermore, as there are studies in literature which have observed better response to treatment and remission rates in patients receiving 2 TMS sessions a day compared to those receiving 1 session a day (Theleritis et al. 2017), the current study was planned as the application of 2 sessions a day.

In studies in literature that have investigated the efficacy of TMS treatment in TRBD, the data are extremely heterogenous in respect of the region of TMS application, frequency, motor threshold, total number of stimulations, duration of application, coil type, and unilateral or bilateral application. Dell'Osso et al. (2009) applied 15 sessions of TMS over the right DLPFC with a figure-of-8 shaped coil, and reported that after the treatment, 6 of 11 patients responded to the treatment, 3 partially responded, and 4 patients achieved remission. Harel et al. (2011) applied 20 sessions of deep TMS with 1680 stimulations per day, with 120% motor threshold, at 20 Hz high frequency, over the left DLPFC using an H coil, and reported the response to treatment as 63.2% and a remission rate of 52.6%. Following 20 sessions of dTMS with with 1980 stimulations per day, with 120% motor threshold, at 18 Hz high frequency, over the left DLPFC using an H coil, Rapinesi et al. (2015) determined that the mean HAM-D score fell from 23.83±3.27 to 9.83±1.27. In another study by Wozniaki-Kwasniewska et al. (2015), a response to treatment was determined in 6 of 10 patients applied with 10 or 20 sessions of TMS with 2000 stimulations per day, with 120% motor threshold, at 10 Hz high frequency, over the left DLPFC using a figure-of-8 coil. Dell'Osso et al. (2015) compared 3 different stimulation methods: Group 1 was applied with 420 stimulations a day at 1 Hz, 110% motor threshold over the right DLPFC, Group 2 received 900 stimulations a day at 1 Hz, 110% motor threshold over the right DLPFC, and Group 3 received 7500 stimulations a day at 10 Hz, 80% motor threshold over the left DLPFC. After the treatment, there was seen to be a significant improvement in HAM-D and MADRS scores with no significant difference between the 3 groups. Differences between the TMS stimulation parameters lead to differences in the response rates of TMS efficacy. Cohen et al. (2010) examined this situation and found that remission rates were associated with the severity of depression, resistance to previous treatments, the number of previous depressive episodes, age, and more than 15 sessions. These data show that patients not responding to a certain TMS protocol could benefit from different protocols (place/frequency combination). There are studies which have determined no difference between unilateral or bilateral DLPFC application in bipolar depression, some which have reported a decrease in depressive symptoms in both forms, and others which have found a higher effect with bilateral application (Gold et al. 2019). As a combination of localisation/frequency for depression, the data in various studies supports the efficacy of high frequency stimulation applied to the left DLPFC (Tan & Sayar 2017, Gold et al. 2019). Consistent with the literature, the TMS treatment in the current study was applied over the left DLPFC at 10Hz (high) frequency, with 110% motor threshold, as a total of 20,000 pulses per day with a figure-of-8 coil.

Regarding the application location, the "5 cm technique" was used in our study. According to this rule, 5 cm anterior over the parasagittal plane from the motor cortex point where the motor threshold was determined was accepted as the application site. This area corresponds to the left DLPFC. Indeed, the "5 cm technique" is one of the most commonly used and most practical techniques to find the projection of the left DLPFC (Herwig et al. 2001) But there are criticisms and suggestions in the literature about the application described above. These are the neuroanatomical differences of the individual to be treated with TMS and the technical differences between practitioners. The distance difference between the head surface and the cortex surface and the determination of localization with this standard method is important in terms of neuroanatomical limitations, so the importance of the neuronavigation system is emphasized (Nauczyciel et al. 2011) There are also a neuronavigation methods using magnetic resonance imaging techniques to more clearly identify the left DLPFC location; however, it is less preferred due to its high cost (George et al. 2010, Johnson et al. 2013).

The current study included patients with at least a moderate level of depression, and ≥17 points on HAM-D. The relatively low average HAM-D scores of 20.27

and BDI of 31.59 in this study may have been caused by the exclusion of patients with psychotic symptoms and/or suicide risk as these could have created difficulties in outpatient follow-up or required urgent intervention. Moreover, the BDI and HAM-D scales do not include questions evaluating atypical depression symptoms such as hypersomnia and/or increased daytime naps and hyperphagia and/or weight gain, which are seen in the majority of bipolar depression patients. Therefore, the scale points do not reflect these symptoms in the patients.

In the current study, the effects of TMS on bipolar depression were evaluated with the HAM-D and BDI scales, and the data obtained showed that TMS is effective on depressive symptoms. Although significant reductions were determined in HAM-D and BDI points in both groups; when the effect size is taken into consideration, there was a greater numerical decrease in the HAM-D points and there were more patients significantly responding to the treatment in the weeks when active TMS was received. This showed that active TMS treatment was more effective than the application of sham-TMS in accordance with the literatüre (Tavares et al. 2017, Dolberg et al, 2002).

However, there are also studies in literature showing a mostly high rate of placebo responses in somatic treatments (Brunoni et al. 2009). In a previous study, it was reported that even after several unsuccessful pharmacological and psychotherapeutic interventions, the hopes and beliefs of patients in new treatments created strong placebo effects, and the opportunity of longer and more frequent interviews with the patients in the study may have resulted in a decrease in the complaints by having a positive effect on mood (Mommaerts et al. 2012). When the HAM-D and BDI points of the groups in the current study were evaluated within the groups according to the weeks, statistically significant decreases in the points were determined in both applications which could have been due to the placebo effect of the sham-TMS. Furthermore, the opportunity of longer and more frequent interviews with the patients in the study may have resulted in a decrease in the complaints by having a positive effect on mood with sham stimulation.

In the weeks in which both groups received sham-TMS, the difference in the change in scale points and the percentage of patients with a partial or full response to treatment were examined, and the numerical value were seen to be higher in Group A. This could have been due to a continuation of the effects of the TMS given to Group A in the first 2 weeks. This was seen to be consistent with the findings of a study by Theleritis et al. (2017) in which a decrease was seen in HAM-D points 2 weeks after the end of a 3-week treatment period of TMS applied to treatment-resistant depression patients.

In accordance with previous studies, the sham-TMS protocol used in the current study was applied at an angle of 45° to minimise the active stimulation effects (Nahas et al. 2003, Fitzgerald et al. 2016). However, this protocol created a degree of sensitivity in the scalp of most participants, and produced a limited degree of intracortical activity. There are studies suggesting that this limited degree of intracortical activity can create partially active stimulation, which could provide clinical improvement, thereby also indicating that the results are debatable (Lisanby et al. 2001, Fitzgerald et al. 2016). Although there are sham coils available to eliminate this effect, they are not in widespread use because of the high cost.

The data obtained in this study demonstrated that TMS treatment is well tolerated by patients. No side-effects such as epileptic seizure, vasovagal syncope, or the triggering of hypomania/mania were seen in any patient. Insignificant side-effects were reported in 9 patients, the most frequent of which was headache. The probable reason for the headaches was maintaining the same posture for 18-20 mins during each application, stimulation of the nerves within the magnetic field of the TMS, or the sound that accompanies the TMS application (Rossi et al. 2009). To be able to determine the TMS side-effect of hypomania/mania, the YMRS was applied. It was planned to evaluate the emergence of 2 or more manic symptoms (irritability, euphoria, grandiosity, decreased need for sleep) during the treatment period as treatment-related hypomania/mania (Tavares et al. 2017). No such side-effects were seen in any of the current study patients. The absence of serious side-effects facilitated participation and treatment compliance, suggesting that TMS treatment is a promising method.

There were some limitations to this study. With the onset of the COVID-19 pandemic, the data collection process was interrupted, some patients left the study, and as a result of the halting of outpatient TMS protocols, the number of study participants was relatively low. To minimise the potentially counfounding effects of the drugs on the results, although the patients included were those with fixed pharmacological treatment for approximately one month before the TMS treatment, as the patients continued the drugs, the effect of TMS alone could not be evaluated. Other limitations were that neuronavigation management was not used for localisation of the region where TMS was to be applied. Moreover, in future studies, the classification of patients according to symptom characteristics would be useful to be able to understand which disease symptoms respond better to TMS treatment.

CONCLUSION

In conclusion, the results of this double-blind, sham-controlled, crossover style study demonstrated that TMS is well tolerated and can provide clinical improvement in TRBD patients. This study can be considered to be of guidance for future studies with larger sample groups.

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Contribution of individual authors:

Gulizar Zengin conducted the literature review, conceptualized the study design, collected data, assisted with the analysis, wrote the first draft of the manuscript,

Osman Zulkif Topak conducted the literature review and handled subsequent drafts after receiving coauthors feedback and revised the manuscript.

Oyku Atesci conducted the literature review, translate the manuscript and assisted with the writing.

Figen Culha Atesci designed the study and leads the project, conducted the literature review, commented on drafts.

All authors read and approved the final version of manuscript.

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