ÖZGÜN ARAŞTIRMA ORIGINAL RESEARCH

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INVESTIGATION OF PREDICTIVE FACTORS FOR CLINICAL REMISSION IN RESPONSE TO REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (RTMS) TREATMENT IN DEPRESSIVE DISORDER

DEPRESİF BOZUKLUKTA TEKRARLAYAN TRANSKRANİYAL MANYETİK STİMÜLASYON (RTMS) TEDAVİSİNE YANIT OLARAK KLİNİK REMİSYON İÇİN PREDİKTİF FAKTÖRLERİN ARAŞTIRILMASI

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Öz

Amaç
Depresif bozukluk nedeniyle Tekrarlayan Transkraniyal Manyetik Stimülasyon (rTMS) tedavisi alan hastaların sosyo-demografik ve klinik verilerinin incelenmesi ve bu verilerin rTMS tedavisine verilen remisyon yanıtı ile ilişkisinin değerlendirilmesi amaçlandı.

Gereç ve Yöntem
120 hastanın tıbbi kayıtları retrospektif olarak değerlendirildi. Hamilton Depresyon Ölçeği (HAM-D), Beck Anksiyete Ölçeği (BAÖ), Richard-Campbell Uyku Ölçeği (RCUÖ) puanları analiz edildi.

Bulgular
Hastaların %60'ı (72/120) kadındı ve yaş ortalaması 42.80±12.80 idi. HAM-D skorlarına göre (7 ve altı) hastaların %41,4'ü (46/111) tedavi sonunda remisyondaydı. Ayrıca tedavi öncesi ve tedavi sonrası ölçek puanları değerlendirildiğinde, tedavi sonrası HAM-D puanları ve BAÖ puanları anlamlı olarak azalırken (sırasıyla; p<0.001, p<0.001), tedavi sonrası RCUÖ puanları anlamlı olarak arttı (p<0.001). rTMS tedavisi ile remisyon yanıtını yordayan faktörleri araştırmak üzere ikili regresyon analizi yapıldı. Tedavi başlangıcında HAM-D skorunun yüksek olması remisyon ile negatif prediktif ilişki gösterirken (p<0.001), tedavinin ikinci haftasında HAM-D skorlarında azalma remisyon ile pozitif prediktif ilişki gösterdi (p=0.009).

Sonuç
rTMS tedavisinin depresyon ve anksiyete belirtilerini azalttığını ve uyku kalitesini iyileştirdiğini söyleyebiliriz. Ayrıca rTMS tedavisi öncesi şiddetli depresyonun remisyona girme olasılığını azalttığı, tedavinin ikinci haftasında görülen depresyon şiddetindeki azalmanın ise bu olasılığı artırdığı söylenebilir.

Anahtar Kelimeler: Depresyon, Prediktif faktörler, Remisyon, Tekrarlayan transkraniyal manyetik stimülasyon, rTMS

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Abstract

Objective
It was aimed to examine the socio-demographic and clinical data of patients treated with Repetitive Transcranial Magnetic Stimulation (rTMS) for depressive disorder and to evaluate the relationship of these data with remission response to rTMS treatment.

Material and Method
The medical records of 120 patients were evaluated retrospectively. Hamilton Depression Scale (HAM-D), Beck Anxiety Scale (BAI), and Richard-Campbell Sleep Scale (RCSQ) scores were analyzed.

Results
60% (72/120) of the patients were women and the mean age was 42.80±12.80 years. According to the HAM-D scores (7 and below), 41.4% (46/111) of the patients were in remission at the end of the treatment. In addition, when the pre-treatment and post-treatment scale scores were evaluated, HAM-D scores and BAI scores decreased significantly after treatment (respectively; p<0.001, p<0.001), while RCSQ scores increased significantly after treatment (p<0.001). Binary regression analysis was performed to investigate the predictive factors for remission of depressive symptoms after rTMS treatment. A high HAM-D score at the beginning of the treatment showed a negative predictive relationship with remission (p<0.001), while a decrease in HAM-D scores at the second week of treatment showed a positive predictive relationship with remission (p=0.009).

Conclusion
We may suggest that rTMS treatment reduces depression and anxiety symptoms and improves sleep quality. In addition, it can be said that the severe depression before the rTMS treatment reduces the likelihood of going into remission, whereas the decrease in the severity of depression observed in the second week of the treatment increases this likelihood.

Keywords: Depression, Predictive factors, Remission, Repetitive transcranial magnetic stimulation, rTMS

Introduction

Depressive disorder (DD) is a widespread disease worldwide. Prevalence rates of depression are 5.0% and 5.7% among adults and those over 60 years of age, respectively. Affecting an estimated 3.8% of the total population (1), DD is one of the important causes of disability (2). Although there are several treatment options for DD, approximately 30% of people treated with first-line antidepressants do not achieve remission after two or more treatment trials and are considered treatment-resistant. There are various treatment options for treatment-resistant depression (3), one of which is Repetitive Transcranial Magnetic Stimulation (rTMS) therapy. TMS and rTMS are essentially similar methods. The most important difference between TMS and rTMS is repetition. In TMS, stimulation is applied only once. In rTMS, magnetic pulses are applied repeatedly at a certain time and frequency. Approved by the American Food and Drug Administration (FDA) in 2008 for this indication (4), rTMS has been increasingly used as a neuromodulatory treatment method in a variety of psychiatric diseases (5, 6)

Whereas rTMS has been shown to be effective in treatment-resistant DD patients (7, 8), the question of which patients will respond to the treatment is worthy of consideration. The predictive factors for treatment response to rTMS in depression can be classified as patient-related, disease-related, and TMS procedure-related factors (9). In a study with 388 depressive patients treated with rTMS, initial severe depressive and anxiety symptoms predicted a lower probability of remission, while having a job was a positive predictor of remission. Additionally, a higher number of treatment failures was associated with a lower probability of remission (10). In a meta-analysis, 16 double-blind randomized placebo-controlled studies using high-frequency rTMS on the left dorsolateral prefrontal cortex (DLPFC) were examined. It has been reported that the antidepressant effect of rTMS is better in patients with unipolar depression, less severe depressive episodes, treatment-resistant depression, non-psychotic depression, and those receiving concomitant antidepressant treatment (11). All these findings suggest that the response to rTMS can be predicted in DD. Understanding the predictors of response to rTMS treatment in DD will assist clinicians in selecting appropriate patients for rTMS treatment and possibly improving treatment outcomes.

This study aimed to examine the socio-demographic and clinical characteristics of patients who received rTMS treatment for DD and to evaluate their relationship with remission response to rTMS treatment.

Material and Method

Sample and Procedure
This study is a retrospective study conducted by scanning patients' medical records who applied to the

TMS unit of Akdeniz University, Faculty of Medicine, Department of Psychiatry, between February 1, 2019, and June 1, 2020. One hundred twenty outpatients diagnosed with depressive disorder according to DSM-5 diagnostic criteria were included in the study. In our TMS unit, patients are referred to rTMS with the treatment indication determined based on the evaluation of three clinicians. Thus, the study group included patients who did not respond to at least one antidepressant pharmacotherapy of sufficient duration and dose and thus were considered treatment resistant.

Following the evaluation process, all patients are required to sign a written informed consent form before treatment, and at the same time, detailed socio-demographic data of all patients are obtained. A variety of clinical rating scales is also regularly applied to all patients by psychiatrists during the whole treatment course.

Neurosoft brand Neuro-MS/D magnetic stimulator device is used for rTMS application. Computer software support is used to determine the application parameters, and the coil is manually manipulated. In the first session of the rTMS application, the region corresponding to the DLPFC in the patient's cranium is determined after the patient's motor threshold is determined with the "5 cm technique". Since this area will be used in later applications, it is marked on a white cap that the patient wears on his head. The area marked as DLPFC is checked with the EEG 10-20 system, and its accuracy is confirmed. After the coil is placed on the patient's head manually, the appropriate protocol for the patient's diagnosis is selected via computer software, and the treatment is started. The rTMS parameters applied in our clinic for depressive disorder are listed in Table 1.

The inclusion criteria for the study were as follows: Being over the age of 18, having a diagnosis of either bipolar or unipolar depression in accordance with the Diagnostic and Statistical Manual of Psychiatric Disorders (DSM-5) criteria, being literate and having a cognitive capacity to complete the rating scales. Patients with neurological disorders and metal implants in body parts close to the head and neck or pacemakers of any kind were not included.

Socio-demographic data and scores of Hamilton Depression Scale (HAM-D) (12), Beck Anxiety Scale (BAI) (13), and Richard-Campbell Sleep Scale (RCSQ) (14) were the data analyzed in the study.

The Clinical Research Ethics Committee of Akdeniz University, Faculty of Medicine, approved the study (KAEK-437, dated 24.06.2020), which was carried out following the rules of the Declaration of Helsinki.

Statistical Analysis

The data of the study were analyzed using the SPSS (Statistical Package for the Social Sciences version 22, Chicago, IL, USA) program. Continuous variables are represented as mean ± standard deviation and median, and categorical variables as numbers and percentages. After normality testing with the Shapiro-Wilk test, the independent t-test was used to compare the normally distributed continuous variables between groups, whereas the Mann-Whitney U test was used for the non-normally distributed variables. Categorical variables were compared with the Chi-square test or Fisher exact probability analysis. Wilcoxon test was used to evaluate two dependent samples. Binary logistic regression analysis was used to examine the cause and effect relationship between the binary dependent variable and the independent variables.

Table 1 rTMS* parameters in depression protocol

	Depression Protocol
Frequency	10
TMS* intensity (%RMT*)	120
Pulses per train	40
Inter-train intervals (seconds)	6
Pulses per session	3000
Total time per session	12 minutes 16 seconds

*RMT: Resting Motor Threshold; TMS: Transcranial Magnetic Stimulation; rTMS: Repetitive Transcranial Magnetic Stimulation

Table 2 Sociodemographic and clinical characteristics of the study group.

		n (120)	%
Gender	Female	72	60.0
	Male	48	40.0
Marital Status	Unmarried	43	35.8
	Married	65	54.1
	Divorced etc.	12	10.1
Education	Literate	3	2.5
	Primary	39	32.5
	Secondary	30	25.0
	University	48	40.0
Employment status	Employed	32	26.7
	Unemployed	56	46.7
	Student	15	12.5
	Retired	17	14.1
Diagnosis	Bipolar Depression	12	10.0
	Unipolar Depression	108	90.0
History of inpatient treatment	Yes	62	51.7
	No	58	48.3
History of suicide attempt	Yes	87	72.5
	No	33	27.5
History of self-mutilation (n=118)	Yes	18	15.2
	No	100	84.8
Post-partum onset of disease (n=72)	Yes	23	32.0
	No	49	68.0
Antidepressant use (n=110)	Selective serotonin reuptake inhibitor	41	37.3
	Selective serotonin-noradrenaline reuptake inhibitor	62	56.4
	Tricyclic	7	6.3
Physical illness	Yes	65	54.2
	No	55	45.8
Monthly income (Turkish Lira)	0-2500	31	25.8
	2501-5000	62	51.7
	5001-7500	17	14.2
	7501 and more	10	8.3
Stressful life event preceding the onset of illness	Yes	89	74.1
	No	31	25.9
Type of depression	Typical	73	60.8
	Catatonic	2	1.7
	Melancholic	25	20.8
	Atypical	12	10.0
	Psychotic	6	5.0
	Seasonal	2	1.7
Compliance with rTMS*	Completed	103	85.8
	Dropped out	14	11.7
	Maintenance	3	2.5
Age (years) (mean±SD) (min-max)		42.80±12.80 (18-73)	
Duration of index episode (months) (mean±SD) (min-max))		7.64±11.30 (1-84)	
Age at onset of first episode (years) (mean±SD) (min-max)		28.32±11.72 (13-60)	
Total illness duration (years) (mean±SD) (min-max)		11.53±9.11 (1-45)	
Total number of episodes(mean±SD) (min-max))		6.10±5.62 (1-25)	
Number of rTMS sessions (mean±SD) (min-max)		30.17±8.49 (7-51)	

*rTMS: Repetitive Transcranial Magnetic Stimulation

Statistical significance level was determined as p≤0.05 in the study.

Results

The mean age of the study group was 42.80±12.80 years, and 60% (n=72) were female. The number of patients with left-hand dominance was 5 (4.2%), and those with right-hand dominance were 115 (95.8%). 109 (90.8%) patients were treated with a 10-minute depression protocol, whereas the remaining 11 (9.2%) underwent a 20-minute session. The TMS application region was the left DLPFC in almost all patients (N=119) except for one patient who received magnetic stimulation on the left motor cortex (MC) area. The mean follow-up period after TMS treatment was 7.5 (min: 1, max: 12) months. 91.6% (n=110) of the patients used antidepressant medication. Also 55.8% (n=67) of the patients was on antipsychotics and 19.1% (n=23) on benzodiazepines. Nine (7.5%) patients had previously received electroconvulsive therapy (ECT). Other socio-demographic and clinical data of the patients are summarized in Table 2.

Table 3 Comparison of patients in remission and non-remission after treatment in terms of sociodemographic characteristics.

n		In remission (n=46)		Non-remission (n=65)		p
		n	%	n	%	
Gender	Female	27	58.6	41	63.1	0.641
	Male	19	41.4	24	36.9	
Education	Primary and lower	11	23.9	29	44.6	**0.025**
	Secondary and higher	35	76.1	36	55.4	
Diagnosis	Bipolar Depression	3	6.5	8	12.3	0.357
	Unipolar depression	43	93.5	57	87.7	
Type of depression	Typical	27	58.6	41	63.1	0.641
	Others	19	41.4	24	36.9	
History of inpatient treatment	Yes	19	41.3	31	47.7	0.505
	No	27	58.7	34	52.3	
Stressful life event preceding the onset of illness	Yes	28	60.8	52	80.0	**0.011**
	No	18	39.2	13	20.0	
History of suicide attempt	Yes	12	26.0	18	27.7	0.851
	No	34	74.0	47	82.3	
History of self-mutilation	Yes	9	19.5	7	10.7	0.161
	No	37	80.5	58	89.3	
Age (years) (Mean±SD)		41.57±12.97		44.57±12.71		0.227
HAM-D before treatment* (Mean±SD)		14.02±6.63		19.69±5.58		**<0.001**
BAI before treatment * (Mean±SD)		19.80±15.36		23.94±12.64		0.124
RCSQ before treatment * (Mean±SD)		78.71±13.13		69.35±17.88		**0.006**
Number of hospitalisations (Mean±SD)		0.80±1.29		1.08±1.87		0.401
Total number of episodes(Mean±SD)		5.46±6.15		6.46±5.22		0.098
Number sessions (Mean±SD)		31.78±6.96		31.26±7.61		0.804
Number of pulses (Mean±SD)		2797.83±586.70		2873.85±449.40		0.531

*HAM-D: Hamilton Depression Rating Scale, BAI: Beck Anxiety Inventory, RCSQ: Richard- Campbell Sleep Questionnaire

In our study, a HAM-D score of 7 and below indicated a clinical remission. To examine the factors associated with remission, data 111 patients who received at least 20 sessions of rTMS (optimal treatment dose) treatment was evaluated. Nine patients who did not complete the optimal treatment dose were not included in the evaluation. Among these, 46 (41.4%) patients met the criteria for remission. Patients in remission and non-remission were compared in terms of some characteristics (Table 3).

Binary regression analysis was performed to investigate the predictive factors for remission of depressive symptoms after rTMS treatment. In the regression model, remission status was taken as the binary dependent variable (i.e., remission vs. non-remission). The independent variables were the pre-treatment HAM-D mean score, the educational status of the patients, and the presence of a stressful life event, which indicated significant statistical differences between remitting and non-remitting patients. The difference between HAM-D scores measured pre-treatment and the second week of treatment was also included in the model as another independent variable. As a result; the regression model showed ($\chi2(4) = 35.53$, $p<0.001$) that higher HAM-D score at the beginning of treatment showed a negative predictive relationship with remission ($p<0.001$), while a decrease in HAM-D scores at the second week of treatment, that is, a decrease in the severity of depressive symptoms showed a positive predictive relationship with remission ($p=0.009$) (Table 4). A one-unit increase in HAM-D score before treatment increased the probability of non-remission by 20%, while a one-unit improvement in HAM-D score in the second week decreased the probability of remission by 13%.

Ratings of clinical scales pre-treatment and post-treatment were also evaluated. Accordingly, HAM-D scores decreased significantly after treatment (median=9) compared to before treatment (median=18) ($p<0.001$). BAI scores were significantly lower after treatment (median=13) than before treatment (median=22) ($p<0.001$). RCSQ scores increased significantly after treatment (median= 84.80) compared to pretreatment (median=79.20) ($p<0.001$).

Discussion

As a result of our study, 41.4% of DD patients who received optimal rTMS entered remission according to the HAM-D score. Additionally, in the whole study group, post-treatment HAM-D and BAI scores were significantly lower than before treatment, and post-treatment RCSQ scores increased significantly compared to pre-treatment. As for the factors associated with remission, this study showed that patients who did not go into remission after treatment had higher pre-treatment HAM-D scores, lower education levels, and more stressful life events at the onset of the first disease. A high HAM-D score at the beginning of treatment was also found to be a

Table 4 Binary logistic regression analysis, predictive factors for remission.

Değişken	Beta	SH	χ^2	p	OR	95% Confidence interval
Constatnt	2.33	0.85	7.59	0.006	-	-
HAM-D* difference in second week	0.12	0.05	6.88	**0.009**	1.13	[1.03, 1.24]
HAM-D* before treatment	-0.23	0.05	18.72	**<0.001**	0.80	[0.72, 0.88]
Stressful life event preceding the onset of illness (no)	0.54	0.52	1.06	0.304	1.71	[0.62, 4.74]
Education (high education level)	0.85	0.51	2.82	0.093	2.34	[0.87, 6.32]

OR=Odds Ratio, SH= Standart Hata, $\chi2(4) = 35.53$, $p<0.001$, McFadden R2 = 0.24.
*HAM-D: Hamilton Depression Rating Scale

negative predictor of remission, whereas a decrease in HAM-D scores in the second week of treatment was a positive predictor.

rTMS is an effective treatment in treatment-resistant DD (8). In a review of 18 studies including 1970 participants, Gaynes et al. reported that active TMS was more effective in reducing the severity of depressive symptoms than the sham procedure. Active TMS provided an average reduction of 4 or more points in HAM-D scores compared to the sham procedure (15). In another study with 33 patients, a significant decrease in HAM-D scores was reported with rTMS. In addition, no significant differences were found between unipolar and bipolar DD patients in terms of efficacy and tolerability (16). The findings of our study are compatible with the literature showing a significant decrease in HAM-D scores with rTMS.

A significant decrease was also found in BAI scores with rTMS in our study. Similar to our study, Trevizol et al. reported that when rTMS was used in the treatment of DD, there was also a significant decrease in anxiety symptoms (17). In another study, comorbid anxiety symptoms in DD and obsessive-compulsive disorder patients improved significantly with rTMS (5). Taken together, suggest that rTMS can also be an effective treatment option for anxiety disorders.

rTMS is a treatment that also affects sleep quality. Low-frequency rTMS, which stimulates the right DLPFC or posterior parietal cortex, has been found to be effective in reducing cortical hyperexcitability and improving sleep quality in patients with chronic primary insomnia (18). In another study, decreases in HAM-D, sleep-related components of HAM-D, and Athens Insomnia Scale scores were reported with rTMS (19). In our study, RCSQ scores increased significantly with rTMS, supporting the possibility that rTMS may also improve sleep quality, but it is not obvious whether this is due to the improvement of depression or not.

Although rTMS is an effective treatment for DD, some patients still do not go into remission. In a meta-analysis, remission rates for high-frequency and low-frequency rTMS were reported as 21.9% and 16.4%, respectively (20). In a randomized controlled study with 164 DD patients, the overall remission rate was reported as 39% (21). In our study, the remission rate among the patients was 41.4%, showing that rTMS does not provide remission in all patients with treatment-resistant DD. This raises the question of whether we can predict which patients will go into remission with rTMS. Studies suggest resting-state functional connections before treatment may be a biomarker of rTMS treatment response (22). It has also been reported that there may be patient-related predictive factors (9). In a study conducted with 102 treatment-resistant DD patients, rTMS was effective in treating resistant patients, but the effect decreased with increasing age, implying that age may be a predictor and that the protocol should be adjusted to age (23). A meta-analysis including 54 studies reported that studies with favorable response rates with rTMS treatment mainly consisted of female patients; and thus, gender could be a predictor of response (24). In another study which evaluated 19 patients with DD using the temperament and character inventory, higher persistence scores were found to be a significant predictor of response to rTMS (25). Rostami et al. studied 248 DD (102 unipolar, 146 bipolar) patients who received 20 sessions of DLPFC rTMS (High-frequency rTMS, low-frequency rTMS, bilateral rTMS) to investigate determinants of rTMS response. They reported that the type of depression (unipolar and bipolar) had no significant effect on the rTMS response, while age (young patients) was an important predictor of treatment response. In addition, when compared with somatic symptoms, cognitive, and affective symptoms were found to be an important predictors of treatment response to rTMS (26). Disease severity before treatment is also reported as a predictor. In a study evaluating 41 patients with a diagnosis of DD who received rTMS therapy, it has been reported that the remission rate is associated with the initial severity of depression, while the total number of rTMS sessions or the duration of treatment are not predictors of remission (27). A study analyzing the data from 11 studies, including 1132 participants, reported that lower depression severity before rTMS, shorter duration of the current episode, and recurrent depressive episodes increased the likelihood of treatment response (28). Similarly, in our study, low depression severity before treatment was associated with a favorable response to rTMS. Thus we can say that rTMS should be preferred in patients with less severe depression, and other treatment methods such as ECT should be considered primarily in patients with severe depression. In addition, the decrease in depression severity observed in the second week was another significant predictor of remission in our study. We think this finding is important because the earlier the change occurs, the earlier to decide about continuing the treatment. Prolonging the duration of untreated depression may lead to excessive loss in many areas related to the disease, especially in functionality. Thus, the lack of a sufficient improvement in depression in the second week will bring to mind the evaluation of other

treatment options for a particular patient and will save time in terms of effective treatment.

Having a relatively large sample and being one of the preliminary studies conducted regarding rTMS treatment in depression in our country are the important features of this study. Limitations, on the other hand, are the retrospective design, almost all the patients undergoing the same protocols and continuing to use pharmacotherapy, and the absence of a control group.

Conclusion

Findings of this study indicate that low depression severity before treatment and an improvement in depression symptoms in the second week of treatment is associated with a good response to rTMS treatment. These two predictive factors may be helpful in making a personalized treatment plan for the patient in clinical practice. That is to say; clinicians may predict which patient is likely to get remission with rTMS treatment and may start treatment accordingly. It may also help the clinician decide whether to continue the treatment by looking at the patient's clinical response in the early phase of the treatment. We suggest that studying predictive factors in different diseases with different protocols, using a prospective design, and having a control group might be of great use in future studies.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Ethical Approval
The Clinical Research Ethics Committee of Akdeniz University, Faculty of Medicine, approved the study (KAEK-437, dated 24.06.2020), which was carried out following the rules of the Declaration of Helsinki.

Consent to Participate and Publish
Written informed consent to participate and publish was obtained from all individual participants included in the study.

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Availability of Data and Materials
Data available on request from the authors.

Authors Contributions
ÖÖ: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Writing-original draft.

BC: Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing-review & editing.

AE: Investigation; Validation; Writing-original draft.

ÖM: Writing-original draft; Writing-review & editing.

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