Razavi Int J Med. 2024 May 12(2): e1285 doi: 10.30483/RIJM.2024.254470.1285

Published online 2024 May **Original Article**

Comparison of the Effectiveness of Repetitive Transcranial Magnetic Stimulation and Drug Therapy in the Treatment of Post-Traumatic Stress

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Received 2023 August **30; Accepted** 2023 October 18.

Abstract

Background: Repetitive transcranial magnetic stimulation (rTMS) to address Post-Traumatic Stress Disorder (PTSD) displays considerable potential and has received approval.

Objectives: The present study aimed to assess the relative efficacy of rTMS and pharmacological therapy in the treatment of PTSD.

Methods: The study was conducted based on a quasi-experimental control group pretest-posttest design. The statistical population consisted of all patients referred to specialized clinics in the 2nd, 3rd, and 7th districts of Tehran between July and September 2022. For the purposeful selection, 45 individuals with PTSD were recruited and assigned to two experimental groups (rTMS, drug therapy) and a control group (each group consisting of 15 participants). The rTMS treatment comprised three sessions per week over four weeks, employing the specified parameters outlined about the variables of the study. Specifically, PTSD was targeted using a frequency of 1 Hz for 20 min and 1200 pulses, with the stimulation centered around the F4 areas. Pre and post-interventions were measured using the Millon Clinical Multiaxial Inventory-III or Checklist-90-Revision. The data analysis was conducted in SPSS software (version 26) using g an analysis of the covariance test.

Results: As evidenced by the results, the reduction of PTSD symptoms achieved through rTMS surpasses that of drug therapy (P= 0.0001).

Conclusion: The obtained results indicated that rTMS interventions exhibited superior efficacy compared to others. In particular, protocols aimed at stimulating the right dorsolateral prefrontal cortex appear to outperform placebo interventions. Nonetheless, further knowledge is still needed regarding the optimal configurations for rTM treatment.

Keywords: Drug therapy, Post-traumatic stress disorder, Repetitive transcranial magnetic stimulation

1. Background

Post-traumatic stress disorder (PTSD) is an emotional condition that can make it difficult for individuals to function effectively in their daily lives (1). It is caused by experiencing traumatic events and can impact a person's ability to cope with stress and develop fears towards specific things (2). PTSD impacts three critical brain networks: the default mode, executive control, and salience. The executive control network is made up of the dorsolateral prefrontal cortex (DLPFC) and lateral posterior parietal cortex. The salience network consists of the anterior cingulate cortex, anterior insula, and amygdala. People with PTSD have been found to have increased activity in this network (3). According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, PTSD falls under the category of trauma-related disorders and stressors. Unlike anxiety disorders, it is associated with external events rather than mental illness (4). Research indicates that approximately 25% of individuals exposed to traumatic events may develop PTSD. Soldiers have an even higher risk, with the prevalence estimated at around 38% (5). The lifetime incidence of PTSD in high-risk groups, such as those who have experienced traumatic events, can range from 5%-75%. About 10%-12% of women and 5%-6% of men experience this condition at some point in their lives. Moreover, PTSD often coexists with other psychiatric disorders in more than 80% of cases. In addition, it can deteriorate an individual's occupational, social, and physical well-being (6).

While there are psychotherapy and pharmaceutical options based on evidence for the treatment of PTSD, the effectiveness of clinical outcomes can often be curtailed due to treatment resistance, adverse events, limited accessibility, and poor adherence. Consequently, it is imperative to develop new treatments (7) in addressing PTSD (8,9). Mixed modeling, time-group interaction, and an analysis of effect size were employed to observe the results. Accordingly, TMS at 5 Hz exhibited a remarkable enhancement in the treatment of PTSD (7). A study pointed to repetitive transcranial magnetic stimulation (rTMS), either alone or in conjunction with short-term stroke re-exposure, in addressing post-stroke PTSD. The findings indicated that rTMS effectively alleviates post-stroke PTSD, and the use of a brief exposure procedure can amplify its effects. In a systematic review conducted by Yan and Xie, it was demonstrated that low-frequency rTMS (LF) led to a significant reduction in the overall PTSD score. Consequently, high-frequency (HF) and LF

rTMS might serve as a means to alleviate the symptoms of PTSD. Although the available evidence is limited, LFrTMS shows promise in reducing the overall impact of PTSD. HF rTMS, on the other hand, may enhance both primary and associated symptoms of PTSD (1).

The authors conducted a thorough examination of randomized controlled trials to assess the effectiveness of rTMS in the treatment of PTSD. A total of 13 studies with 549 participants were included in this review. The goal of the study was to compare the outcomes of (1) rTMS versus placebo and (2) HF versus LF rTMS on PTSD scores post-treatment, as well as any adverse effects. In addition, the authors used the standardized mean difference to evaluate the effects of the intervention and considered the non-standardized mean difference to determine its efficacy. Following treatment, rTMS proved to be more effective than the placebo in reducing the symptoms of PTSD. While HF rTMS demonstrated somewhat better outcomes than LF rTMS, this difference was insignificant (10). Notably, unlike an electroconvulsive shock device that administers electric currents to the brain, a magnetic brain stimulator operates solely by stimulating nerve cells using a magnetic field and does not introduce any electrical current into the brain. Consequently, this approach does not entail any pain or associated side effects typically associated with electroshock devices. Furthermore, in many cases, the therapeutic benefits of magnetic brain stimulation surpassed those of the electric shock device (9-6).

Electromagnetic waves are employed to target specific regions of the brain during brain stimulation, leading to an increase in active cells and an enhancement in brain function. It offers patients the greatest therapeutic benefit when used alongside other forms of rehabilitation therapy and administered in the correct dosage and schedule within a treatment plan (5.6-8). The clinical manifestations of PTSD can vary, and symptoms often overlap with those of other mental disorders, such as depression, anxiety, and substance abuse. According to research, approximately 91% of individuals diagnosed with PTSD also meet the criteria for other mental health conditions (11). Common symptoms of PTSD include persistent emotional responses to fear and negative emotions, which have a profound impact not only on the lives of patients and their families but also on mental wellness. In addition, PTSD is linked to various diseases, such as chronic pain, metabolic cardiovascular disorders, and an increased susceptibility to dementia (12, 13).

This particular technique is observed as a non-intrusive manner of stimulating the brain, attracting significant interest due to its ability to avoid complex surgical procedures. Meanwhile, the patient remains conscious during the stimulation process and can observe the effects as they occur (6-4). To address PTSD, a combination of psychotherapy and medication is utilized, although its efficacy is restricted among patients with unbearable PTSD. Nonetheless, psychotherapies are often relied upon more heavily and produce longer-lasting therapeutic outcomes when compared to medication alone. Given its high rates of occurrence, heavy burden, and limited treatment alternatives, PTSD is a mental disorder in dire need of prompt attention.

2. Objectives

Different areas have investigated the effectiveness of rTMS; however, this particular study concentrated on comparing the effectiveness of this method with drug therapy in the treatment of PTSD. This research aimed to ascertain which is more efficient in relieving PTSD: rTMS or drug therapy. Ultimately, the goal is to suggest the most suitable approach for each disorder.

3. Methods

The present study was conducted based on a quasi-experimental control group pretest-posttest design. This research focused on all patients referred to specialized clinics in specific areas of Tehran from July to September 2022. A total of 45 individuals diagnosed with PTSD were selected via the purposive sampling method and assigned to two distinct groups: one group underwent a therapeutic approach known as rTMS (n=15), while the other group received drug treatment (n=15). An additional group of 15 individuals did not receive any form of treatment. To ensure fairness, the authors randomly assigned participants by employing a table of random numbers (Figure 1). A sample size of 42 was needed sufficiently, considering a mean effect size of 0.5, a significance level of 0.05, and a power level of 0.95. After accounting for potential dropouts, the final estimated sample size was 45.

Patients were considered eligible if they met the following criteria: (a) they were 18 years old or above, (b) they were diagnosed with PTSD of at least moderate severity according to the Millon Clinical Multiaxial Inventory-III (MCMI-III). On the other hand, patients were excluded if they: (a) had frequent absences from meetings, inability to fulfill responsibilities, or faced unexpected events, such as illness or the loss of a loved one affecting their work; (b) had a clinical history, actual psychosis, psychosurgery, borderline personality disorder, or dramatic personality type; and (c) had an alcohol or substance use disorder within the past year.

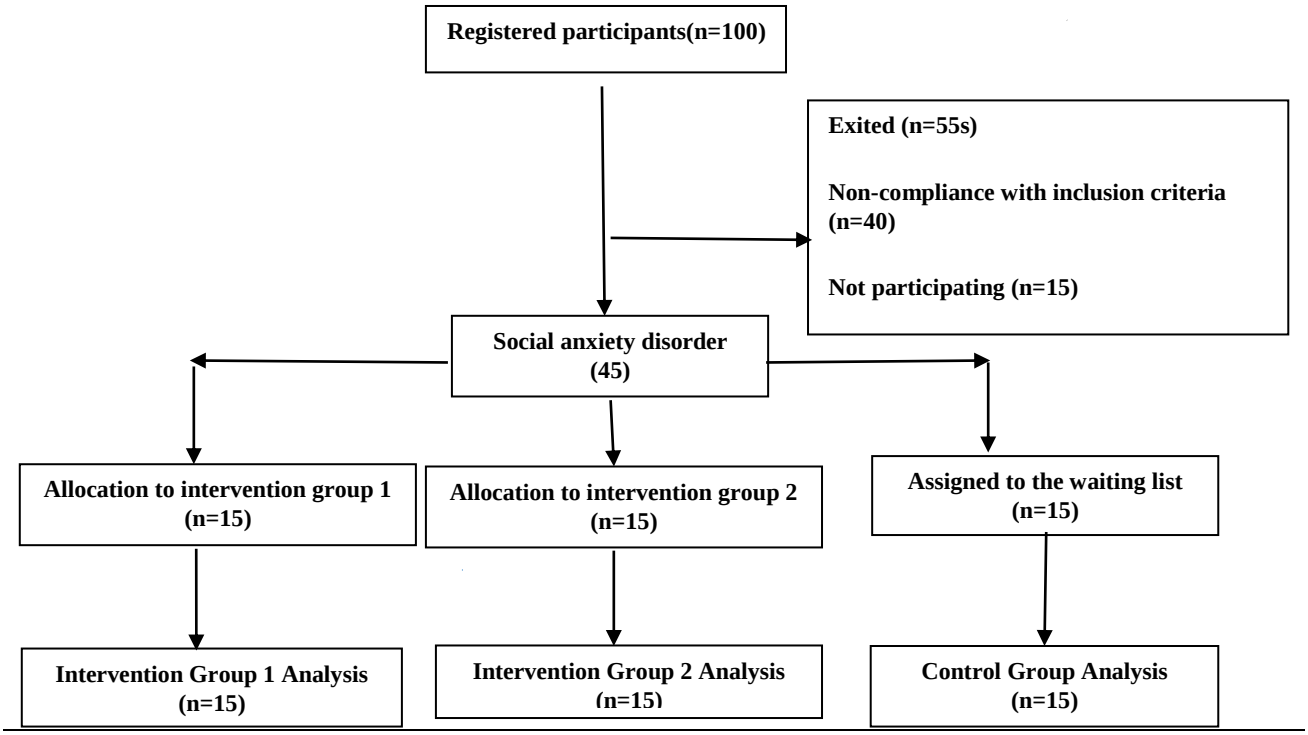

Figure 1. Flow diagram of the study

In the administrative phase of the research, it was necessary to collaborate with Sajad Hospital and counseling centers (Aram and Rayeheye Omid) located in District Three. The approach employed involved coordinating with the officials of these centers and providing them with information about the target sample. It is worth noting that once the sample was selected, the subjects were informed about the treatment courses and their objectives. They were also informed that participation in the treatment courses is voluntary and requires their consent, with no obligation to participate.

The duration of the sessions in a group where the brain is repeatedly stimulated with magnetic stimulation through the skull followed the specified parameters for three sessions a week over the course of four weeks. The coil was placed on the right side in DLPFC at point F4 and in the SMA region using the international 10-20 system of EEG electrode placement. The rTMS treatment was then applied based on the specific parameters set for this study. For the PTSD group, 1200 pulses were delivered to the F4 area in the DLPFC as part of the treatment, while the control group received treatment as usual. In the drug therapy group, the drug interventions were as follows:

After the intervention ended, a reassessment was conducted using the same tools as the initial evaluation. The drug treatments administered during the four weeks in the PTSD group were as follows: two tablets of sodium valproate 200mg. Initially, one tablet was given in the morning and one in the evening, and then the same dosage was distributed throughout the day. In addition, three tablets of Propranolol 40mg were prescribed, with half a tablet taken in the morning and half in the evening. The primary author of the article conducted all interventions. All participants involved in the study provided informed consent. The Kolmogorov-Smirnov test results demonstrated that PTSD data in both periods followed a normal distribution, with a significance level of 0.27. The Levine test, which assessed the equality of variances for PTSD, indicated homogeneity with a p-value of 0.091. Moreover, Box's M test supported the hypothesis about the equality of covariance matrices (Box's M=0.10; 6.70). Univariate and multivariate covariance analyses were conducted to detect differences in dependent variables between the two groups, based on the assumptions made. It should be noted that data analysis was carried out using SPSS software (version 26).

The tools used in this research are as follows:

Millon Clinical Multiaxial Inventory-III: The MCMI-III is a 175-item questionnaire that requires participants to answer with true or false responses. It is appropriate for individuals who are 18 years old and above, with a reading level equivalent to 8th grade. The questionnaire can be administered through paper-and-pencil, computer, or online methods, and it typically takes about 25-30 min to complete. Scoring options include web-based Qglobal™, Q local™ software, mail-in scoring, or manual scoring (14). Interpretive and profile reports are available as report options. The MCMI-III is widely acknowledged as a valuable tool for psychological assessment and has been translated into several languages. It has been used in various cross-cultural research, including studies

conducted in Iran (15). The selection of the MCMI-III was based on its reliability and validity in assessing personality disorders. As stated in the manual, a cutoff score of 85 or higher is recommended for diagnostic purposes. The Persian version of the MCMI-III exhibited good psychometric characteristics (15,16).

4. Results

The mean age scores of participants in the experimental and control group were determined to be 45.60±0.67 and 45.46±0.67 years, respectively. As presented in Table 1, both the magnetic stimulation and drug therapy groups experienced a decrease in mean scores from the pre-test to the post-test. The table data indicates that both rTMS and drug therapy were effective in reducing patients' PTSD scores.

The findings presented in Table 2 demonstrate that when the impact of the initial variable is eliminated and the F coefficient is taken into account, a significant disparity can be observed in the adjusted averages of PTSD scores among participants based on their membership in either the "experiment" or "control" group during the post-test phase (F=209.56; P=0.0001). Consequently, based on the outcomes provided in Table 2 and Figure 2, it can be deduced that there existed a distinction in the post-test scores of PTSD after accounting for the elimination of initial disparities (pre-test) across the three groups. Table 3 reveals that there is a significant distinction in the therapeutic approach between rTMS and drug therapy when it comes to PTSD (P=0.0001). The reduction of PTSD symptoms achieved through rTMS surpasses that of the drug therapy (P=0.0001).

Table 1. Descriptive indices (mean and standard deviation) of post-traumatic stress scores

Group	Pre-test	Post-test
	Mean ± SD	Mean ± SD
rTMS	80.23±4.20	47.40±5.48
Drug therapy	80.40±4.29	61.72±7.35
Control	80.40±4.59	72.83±4.91

Table 2. Analysis of covariance

Variables	SS	df	MS	F	sig	η^2
pre-test	1159.36	1.00	1159.36	50.40	0.0009	0.37
post-test (group)	9640.98	2.00	4820.49	209.56	0.0001	0.83
	1978.29	86.00	23			
error	12891.74	89.00				

Table 3. Bonferroni's post hoc test results for pair-wise comparison of mean scores in three groups

Variable	Comparison groups	The Mean difference	SD	P-value
Post-Traumatic Stress (PTSD)Post-test	Magnetic stimulation - Drug therapy	-14.18	1.24	0.0001
	Magnetic stimulation - control	-25.29	1.24	0.0001
	Drug therapy - control	-11.12	1.24	0.0001

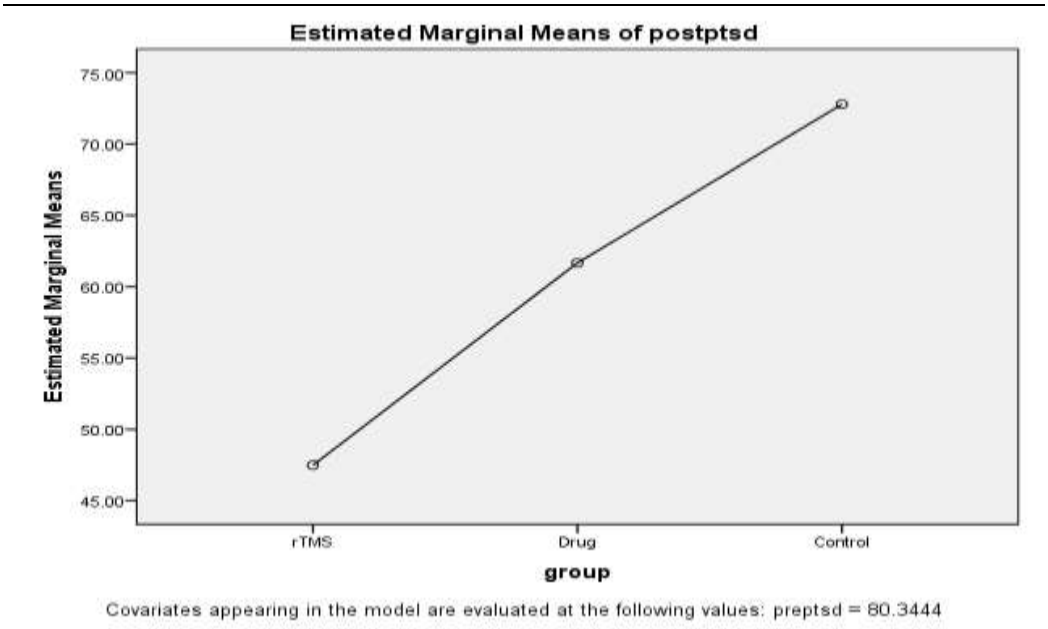

Figure 2. Modified mean of practical obsession in three groups

5. Discussion

As evidenced by the results of this study, both rTMS treatment and drug therapy, as compared to the control group, can significantly contribute to the reduction of PTSD symptoms. Alternatively phrased, the group subjected to rTMS treatment exhibited a more substantial alleviation of PTSD compared to the group undergoing drug therapy. It has been previously established through various research endeavors that the utilization of rTMS holds potential in the treatment of post-traumatic stress disorder PTSD. These prior studies amalgamated findings from diverse experiments, thereby demonstrating the efficacy of rTMS even when different regions of the brain are targeted or different forms of stimulation are employed (1,10).

In their study, Cheng et al. proposed that rTMS could be a promising and effective treatment for PTSD (17). Nonetheless, previous literature that was reviewed often illustrated significant variations in stimulus parameters, types of traumatic events, and characteristics of the sample. Concerning the domain of stimuli, most previous studies indicated the DLPFC as the preferred target for stimulation, although there were some discrepancies between frequencies or sides of stimuli. The notion of concentrating on the right DLPFC originates from earlier research suggesting that administering high-frequency rTMS could enhance brain activity and blood flow in the right hemisphere. Utilizing rTMS may be beneficial in alleviating PTSD symptoms, such as avoidance behaviors, hypervigilance, and intrusive thoughts (18).

Based on previous findings, 1 Hz rTMS yielded positive results for the treatment of PTSD. Research conducted by Kozel et al. involved 44 participants, 7 of whom were randomly assigned to receive 1 Hz rTMS, and 18 were allocated to 10 Hz rTMS. Both groups exhibited significant improvement in PTSD scores throughout the acute treatment period. However, only the 10 Hz group displayed a notable enhancement in functioning. Although both groups experienced considerable alleviation in PTSD symptoms, neither the 1 Hz nor the 10 Hz frequency group exhibited significant advantages in any of the demonstrated acquisition scales (19). In the same context, Yan et al. revealed that both high-frequency and low-frequency rTMS can contribute to relieving PTSD symptoms. High-frequency rTMS was able to alleviate the primary and associated symptoms of PTSD (1, 20).

It is worth mentioning that this study discovered that drug therapy was effective in the treatment of PTSD. Several other studies support these findings (1,11,19,20); nonetheless, no studies utilized the specific drug used in this research. Most studies take a different approach to managing drugs. For instance, in one study, the first-line drugs recommended were selective serotonin reuptake inhibitors serotonin and serotonin-norepinephrine reuptake inhibitors. In particular, a comprehensive analysis encompassing 37 randomized trials where a placebo was used disclosed that paroxetine, sertraline, and venlafaxine were more effective in diminishing the symptoms of PTSD compared to the placebo. Furthermore, an examination conducted later pointed out that venlafaxine proved to be beneficial for individuals of both genders who had undergone different traumatic experiences, whereas paroxetine or sertraline did not yield positive results for several specific groups. Another medication called buspirone, which impacts the serotonergic system, could also be employed in the treatment of PTSD (21). The findings regarding pharmacological enhancement in the studies that investigated different pharmacological agents have been inconclusive and diverse (22).

Psychiatrists are now using low-dose cortisone receptor antagonists or other glucocorticoids as possible treatments for patients with PTSD due to dysfunction in the hypothalamic-pituitary-adrenal axis. In addition, hydrocortisone, although not classified as an SSRI in this context, may have a preventative effect on PTSD (23). Recently, new drugs, such as ketamine and methylenedioxymethamphetamine, have been developed to assist individuals with PTSD and depression (24,25). The selection of the drug type in the study may not have been appropriate. It is important to note that benzodiazepines, commonly used to treat PTSD, can worsen avoidance and depressive symptoms due to their strong sedative, addictive, and dissociative properties (26). Currently, no single drug can effectively treat all PTSD symptoms. Combining psychotherapy with pharmacological therapy has displayed potential for improving PTSD treatment outcomes (11). Nevertheless, a study found that psychotherapy and drug therapy have a limited impact on patients with treatment-resistant PTSD, which is prevalent among veterans (27). These patients may benefit from neuromodulation techniques, as they are considered promising treatments.

Limitations

We need to take into account certain limitations of our study. One of these limitations is the absence of a follow-up test, which prevents the long-term evaluation of the treatments implemented for stress symptom relief. Moreover, another limitation is the absence of a comparison group that receives sham rTMS in this study.

6. Conclusion

This research has demonstrated that rTMS is a reliable method of neurostimulation therapy for

PTSD. Recent studies have pinpointed that specific interventions are more successful than others. Specifically, customized regimens that stimulate the DLPFC region of the brain appear to be more effective than sham treatments. In addition, there is still a need to understand the optimal parameters for rTMS therapy. Further studies with larger sample sizes are necessary to confirm whether low or high frequencies are more impactful or if individual differences play a role in determining the most effective frequencies. Moreover, additional research and replication studies are required to identify the specific pharmacological agents and their combinations that yield positive results in the treatment of PTSD and determine which patient groups benefit the most from such treatments.

Acknowledgments

All procedures performed in studies involving human participants were in adherence to the ethical standards of the institutional or national Research Committee (code: IR.IAU.SEMNAN.REC.1402.022).

Conflicts of interest

The authors declared no conflict of interest.

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