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Research Paper

Pattern of Compliance and Efficacy of Repetitive Transcranial Magnetic Stimulation Protocol for Treating Major Depressive Disorder Among Treatment Participants and Completers: A Report From Iran

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ABSTRACT

Introduction: Since the introduction of the Food and Drug Administration (FDA)-approved repetitive transcranial magnetic stimulation (rTMS) intervention in 2008, a breakthrough has been made in treating major depressive disorder (MDD). However, many sessions of treatment and its cost make it inconvenient for those who seek treatment, especially in large cities as well as in developing countries.

Methods: A total of 22 patients (out of initial 24 referrals) who met diagnostic and statistical manual of mental disorders, 4th edition (DSM IV) criteria for MDD were enrolled in the study. All subjects had to fail at least one prior treatment for depression. The patients received the FDA-approved protocol of high-frequency (10 Hz) rTMS over the left dorsolateral prefrontal cortex.

Results: Seventeen out of twenty-two cases showed significant improvements after two weeks of treatment. Only six patients continued their treatments for the next two to four weeks.

Conclusion: We have replicated other studies showing that the use of rTMS is effective for many patients with MDD without major side effects and their improvements are measurable mostly after two weeks. Our data highlight the importance of the application of more convenient protocols that require fewer sessions on fewer days to help with compliance and outcome, particularly in large populated cities and countries, such as Iran going through economic hardship.

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Highlights

- Repetitive transcranial magnetic stimulation (rTMS) is effective for treating major depresion.
- Improvemens are measurable after 2 weeks of treating with rTMS.
- Compliance is a major factorto for completing rTMS protocols.

Plain Language Summary

Major depression is one of the most common psychiatric disorders leading to debilitating course causing significant burden for the society. Many cases with major depression are resistent to treatment as they try multiple interventions with no success. This condition is also called refractory depression. rTMS is a novel intervention introduced first almost two decades ago to treat refractory depression among some other psychiatric disorders. In this intervention pulses generated by magnetic stimulation over the brain leads to improvement is depression. As this treatment is safe with no pain and discomfort there have been much interest in the field to use it more frequently. rTMS is usually done over 15-30 sessions with its maximum effects appearing within the first two weeks of treatment. The number of sessions is a potential factor contributing to poor compliance in some cases especially those living in large metropolitan areas. In this paper we explored compliance and effect of treatment within the first two weeks among a group of patients in a private outpatient clinic of a large metropolitan area.

1. Introduction

Major depressive disorder (MDD) is a recurrent disabling disorder that is the most prevalent psychiatric disorder (12.7%) according to the Iranian mental health survey in 2011 (Sharifi et al., 2015). Given the risk of functional impairment, relational problems, and increased suicide risk associated with MDD (Rush et al., 2006) along with its recurrence and chronicity, the disease imposes a great burden on society (Rush, 2007). Meanwhile, a significant proportion of patients with MDD fail to respond to psychotropic medications (Rush et al., 2006). Data on the prevalence of treatment-resistant depression is limited; however, it is estimated that approximately one-third of patients with depression do not respond to standard treatment (Rush, 2007), and about one-fifth of them become refractory to treatment (Little, 2009).

Although pharmacological therapies in MDD have been improved in recent years, the management of treatment-resistant depression (TRD) has remained a challenge, and brain stimulation methods have emerged as potential alternatives (Little, 2009; Daly et al., 2010). Transcranial magnetic stimulation (TMS) is a non-invasive method initially introduced in 1985 to study neural networks (Barker et al., 1985). Repetitive transcranial magnetic stimulation (rTMS) has been particularly effective for TRD in recent years (Janicak et al., 2002; Ren et al., 2014; Mutz et al., 2018; Sehatzadeh et al., 2019) and was approved by the US Food and Drug Administration (FDA) as a therapy for TRD in 2008.

TMS uses electromagnetic fields to induce electrical currents in special areas of the brain, leading to excitation or inhibition of neural activity. In rTMS, repeated trains of pulses are generated and applied to the brain, resulting in prolonged alteration of cortical excitability. Dysfunction in the dorsolateral prefrontal cortex (DLPFC) is well-established in MDD, and rTMS is believed to show antidepressant effects by targeting these regions (Cao et al., 2018; Du et al., 2018). Normalization of DLPFC function is reported in patients with MDD after rTMS treatment (Cao et al., 2018; Du et al., 2018).

The FDA protocol (2008) often takes 4 weeks to finish. TMS is an acceptable treatment for patients with MDD (McClintock et al., 2017; Horvath et al., 2010). However, given the cost and heavy traffic leading to major difficulties getting around in major metropolitan cities, it is anticipated that a proportion of cases will drop out prematurely. It is also thought that due to the cost and the number of sessions required for the treatment, dropouts may happen soon after improvement.

This study was conducted to evaluate the effect of left prefrontal rTMS on 22 patients with TRD using the FDA protocol (2008) (Horovath et al., 2008).

2. Materials and Methods

Subjects

As seen in Table 1 a total of 24 depressed adults (female: 15) were initially included in the study. All subjects were referred by psychiatrists (except for two cases which were referrals from neurologists). The diagnosis of MDD was reconfirmed by the structured diagnostic interview for DSM-IV (SCID) done by our team's psychiatrist, which resulted in the exclusion of 2 additional cases because they did not meet the required criteria for the trial. All participants, 18 years or older, had to have a history of at least one single failed treatment with an antidepressant. Clinical participants were excluded if they had a history of seizure or neurological disorders or taking medications known to lower seizure threshold (e.g. theophylline). Pregnancy and having ferromagnetic material in the body was also exclusionary.

Procedures

All the procedures were performed by a cognitive psychologist trained and certified to work with the TMS instruments. All sessions were closely supervised by the psychiatrist and the study of the principal investigator (PI) throughout the sessions. A prospective, duration-adaptive design was implemented with three weeks of daily weekday treatments (fixed-dose phase), followed by continued treatment for up to another six weeks if needed. rTMS pulses were delivered to the left prefrontal cortex at 120% motor threshold (10 Hz, 4-second train duration, and 26-second inter-train intervals) for 37.5 minutes (3000 pulses per session) using a figure-eight solid-core coil. The patients continued their medications while receiving their rTMS treatment.

Outcome measures

All subjects were assessed initially and at two-week intervals using a battery of tests used by the National Network of Depression Centers (NNDC), including quick inventory of depressive symptomatology (QIDS_SR16), a 16-item questionnaire validated by rush et al. for scaling symptom severity of depression (Rush et al., 2003); patient health questionnaire (PHQ-9) which scores all nine criteria of DSM-IV from 0 to 3 to scale the severity of depression and treatment response (Kroenke et al., 2001), generalized anxiety disorder scale (GAD_7) assessing the degree of anxiety in the previous two weeks by asking 7 questions and scoring the answers from zero to two (Spitzer et al., 2006), work and social adjustment scale (WSAS) as a validated 5-item questionnaire measuring the impairment of daily functions resulted from a disorder (Mundt et al., 2002), global assessment of functioning (GAF) scale (DSM-IVTR) which is a 10-section questionnaire scoring patients in the range 0 to 100 and afterward assessing their ability of daily functioning (Hall, 1995). PHQ-9 (Ardestani et al., 2019), QIDS_SR16 (Hedayati et al., 2009), and GAD_7 (Omani-Samani et al., 2018) have been reported to have good reliability and validity.

Statistical analysis

Statistical analyses were conducted using IBM SPSS software, version 22. The significance level was determined as $P<0.05$. Since the distribution of variables showed abnormality in the one-sample Kolmogorov-Smirnov test, the non-parametric Wilcoxon signed ranks test was performed to compare data before and after the intervention.

3. Results

Twenty-two patients were enrolled in the study; five patients dropped out before completing the first two weeks. Seventeen patients completed the two weeks and were assessed 2 weeks after a baseline of which only 6 patients completed the whole four weeks and the other 11 dropped out before the second assessment (Figure 1).

As seen in Table 2, the baseline scores for QIDS, PHQ, GAD, and work and social adjustment scale (WSAS) were lower and GAF was higher in patients who dropped

Table 1. Demographic charactristics of participants

Participants	Status of Participants Throught the Study			End of Study
	Dropped Out Before 2 Weeks (n=5)	2 Weeks Completers (n=11)	4 Weeks Completers (n=6)	
Gender (female/male)	3.2	4.7	3.3	0.690
Age (y)	40.25±15.96	30.90±12.48	36.66±9.54	0.396

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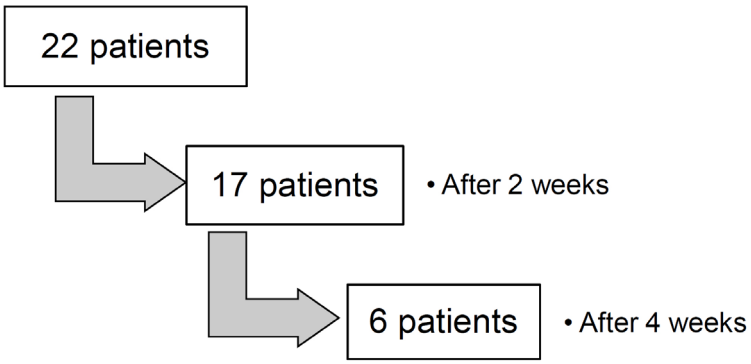

Figure 1. Patients flow in the study

Table 2. Difference in outcome measures in 4 weeks completers

	QISD1-QISD0	PHQ1-PHQ0	GAD1-GAD0	WSAS1-WSAS0
P	0.093	0.043	0.596	0.042

Abbreviations: QISD: Quick inventory of depressive symptomatology; PHQ: Patient health questionnaire; GAD: Generalized anxiety disorder; WSAS: Work and social adjustment scale.

out in the first 2 weeks compared to those who stayed on treatment. However, the difference was not significant statistically and thus not considered a true finding.

A significant improvement in all the measures was observed in patients after 2 weeks (Table 3).

For the next step, we separated the patients who dropped out after two weeks and patients who completed 4 weeks of treatment and repeated the analyses. Patients who dropped out after 2 weeks showed significant improvement in all measures (Table 4) while no such improvements were seen after the same 2 weeks in patients who continued treatment for 4 weeks.

4. Discussion

We found a significant improvement in depression symptoms after the rTMS course compared to the baseline. Similarly, anxiety symptoms were significantly decreased following the rTMS session. Also, we found improvement in functions as GAF and WSAS scores increased after two weeks. A high rate of comorbidity is observed between depression and anxiety disorders (Kessler et al., 2015). Unlike the well-established effect of the rTMS in depression, the data on the effects of the rTMS in anxiety disorders are not convincing. Most research on the efficacy of rTMS in the treatment of anxiety disorders is focused on post-traumatic stress disor-

Table 3. Outcome measures in patients at baseline and after two weeks

Measures	Scores		P
	Baseline	After 2 Weeks	
QISD	19.7619±7.31372	12.0000±6.66795	0.003
PHQ	17.4286±6.39978	7.9333±6.63827	0.001
GAD	11.8095±5.79326	6.0667±5.36479	0.003
WSAS	24.3500±10.82529	10.77342±10.77342	0.001
GAF	53.8889±9.27961	10.48809±10.48809	0.039

Abbreviations: QISD: Quick inventory of depressive symptomatology; PHQ: Patient health questionnaire; GAD: Generalized anxiety disorder; WSAS: Work and social adjustment scale; GAF: Global assessment of functioning.

Table 4. Difference in outcome measures in 2 weeks completers dropped out after 2 weeks

	Outcome Measures				
	QISD1-QISD0	PHQ1-PHQ0	GAD1-GAD0	WSAS1-WSAS0	GAF1-GAF0
P	0.017	0.008	0.008	0.012	0.039

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Abbreviations: QISD: Quick inventory of depressive symptomatology; PHQ: Patient health questionnaire; GAD: Generalized anxiety disorder; WSAS: Work and social adjustment scale; GAF: Global assessment of functioning.

der and obsessive-compulsive disorder, and the data on GAD are sparse (Bystritsky et al., 2008) . Dieffenbach et al reported an improvement in both anxiety and depressive symptoms in 32 patients with TRD after rTMS; anxiety symptoms had no attenuating effect on treatment response (Diefenbach et al., 2013). To evaluate the effect of rTMS on psychosocial outcomes, we utilized GAF and WSAS scales. Our findings reveal that rTMS has the potential to significantly improve psychosocial outcomes. A significant increase was observed in the GAF scale after rTMS sessions. Similarly, Anderson and colleagues reported an improvement in GAF scores in depressed patients after left DLPFC compared to a sham group (Anderson et al., 2007). The efficacy of rTMS in depression has been widely shown. According to a recent meta-analysis in 2018, rTMS on DLPFC results in a response rate of 3.75 times greater than sham (Mutz et al., 2018) . In 2013, a meta-analysis by Berlim et al reported rTMS to have clinically relevant antidepressant effects. It was also demonstrated that rTMS can be equally effective as both augmentation and monotherapy (Berlim et al., 2014). As seen in Figure 2, the patients who discontinued treatment after 2 weeks seemed to have significant improvement in their symptoms while patients who continued the sessions for at least 4 weeks did not have as much improvements in their anxiety and depressive symptoms. We speculate those who discontinued after two weeks simply felt that they need no further treatment sessions because they already felt better. This is perhaps understandable because some patients were from low-income households and had to spend 4 hours per day for travel back and forth for each treatment session. In our study, we cannot identify markers that predict who will continue treatment beyond two weeks.

The observation of improved symptoms in our sample by the end of week two is consistent with studies that increased inferior frontal lobe activity in depressed adults

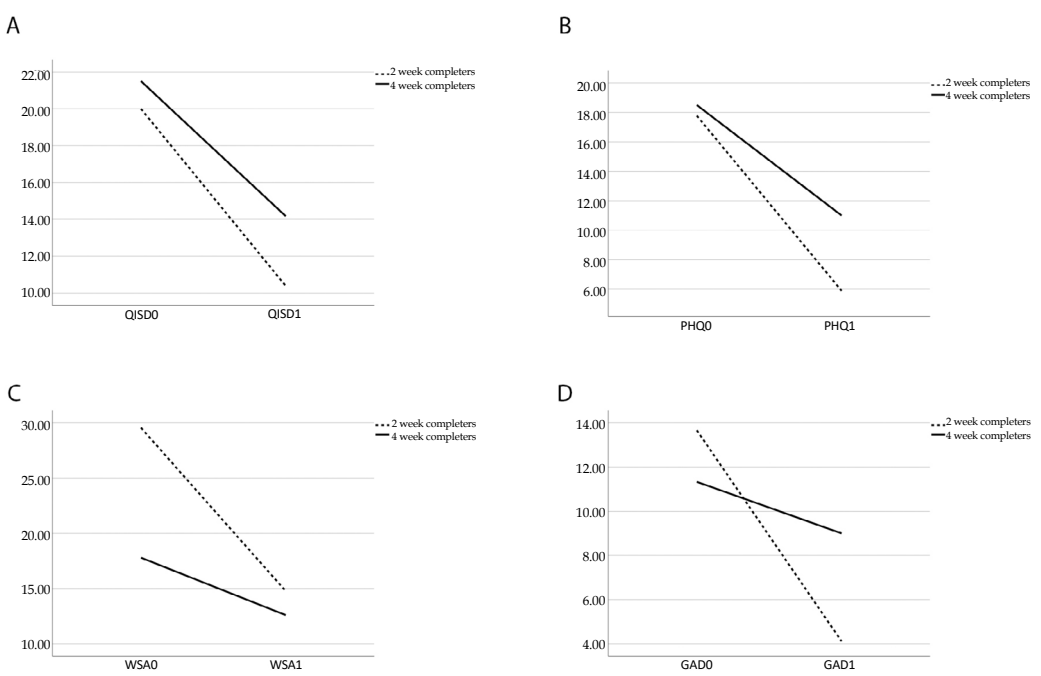

Figure 2. Scores for outcome measures in two week completers vs. four week completers

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who responded to TMS, compared to non-responders, is measurable after two weeks of treatment (Teneback et al., 1999). Recently, Fitzgerald B. et al published a new accelerated protocol performed in 6 days (three sessions per day) (Fitzgerald et al., 2018). This looks quite promising and will help better compliance in major metropolitan cities and especially in countries like Iran. Our results are consistent with the literature on compliance in clinical practice that emphasizes the importance of "hard" factors in considering compliance with particular clinical interventions (Jin et al., 2008). Of those factors, time commitment, therapy cost and income, and duration of the treatment period are critical. Other factors exist, such as patient's health literacy, healthcare system, and lack of social support whose impacts on non-compliance with our study intervention cannot be disputed. Our study highlights the practical implications of using rTMS in a society, such as Iran while its efficacy has been replicated in many studies; however, our study shows that compliance with its protocol is not similar across the globe and is considerably affected by factors, such as time commitment, costs and income. This further emphasizes our need for accelerated protocols to improve our patients' compliance.

5. Conclusion

We have replicated other studies showing that treatment of major depressive disorder using rTMS is very effective with no major side effects. However, our data highlight the importance of the application of more convenient protocols that require fewer sessions on fewer days to help with compliance and outcome particularly, in developing countries, such as Iran.

Limitations

Some limitations should be considered for our study. The major limitation of the study was the lack of a sham group which made us unable to control for placebo effects. Additionally, patients recruited in the study were taking different medications, which could potentially influence response patterns to rTMS. Finally, similar to many other studies, it was unable to conclude about the durability of improved symptoms over time. Further studies addressing these limitations may deepen our understanding of the rTMS efficacy in TRD.

Ethical Considerations

Compliance with ethical guidelines

This study complies with the principles of the declaration of Helsinki. The study protocol was approved by the local Ethics Committee of the Tehran University of Medical Sciences (Code: NCT01469325). Written informed consent was obtained from all patients.

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Authors' contributions

Conceptualization and supervision: Javad Alaghband rad; Investigation: All authors; Data collection: Parvaneh Farhadbeigi and Zahra Khazaei Pour; Data analysis: Mahtab Motamed, Parvaneh Farhad beigi and Zahra Khazaeipour; Writing the original manuscript: Mahtab Motamed and Zahra Khazaeipour; Methodology, Writing-review & editing: Javad Alaghband rad and Mahtab Motamed.

Conflict of interest

The authors declared no conflict of interest.

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