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Title: Pattern of Compliance and Efficacy of Rtms Protocol for Treating Major Depressive Disorder (MDD) Among Treatment Participants and Completers: A Report from Iran

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To appear in: *Basic and Clinical Neuroscience*

Received date: 2021/04/1

Revised date: 2021/06/7

Accepted date: 2021/07/10

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Please cite this article as:

Alaghband-rad, J., Motamed, M., Khazaeipour, Z., & Farhadbeigi, P. (In Press). Pattern of Compliance and Efficacy of Rtms Protocol for Treating Major Depressive Disorder (MDD) Among Treatment Participants and Completers: A Report from Iran. *Basic and Clinical Neuroscience*. Just Accepted publication Aug. 28, 2021. Doi: <http://dx.doi.org/10.32598/bcn.2021.3369.1>

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Abstract

Introduction: There has been a breakthrough in treating MDD since introduction of FDA approved repetitive transcranial magnetic stimulation (rTMS) intervention in 2008. However, the many sessions of treatment and its cost makes it inconvenient for those who seek treatment especially in large cities and also in developing countries.

Method: A total of 22 patients (out of initial 24 referrals) who met DSM IV criteria for MDD were enrolled into the study. The subjects all 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 cases 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.

Conclusions: We have replicated other studies showing that using rTMS is effective with no major side effects for many patients with MDD and their improvements are measurable mostly after two weeks. Our data highlights the importance of application of more convenient protocols which require fewer sessions on fewer days to help with compliance and outcome particularly in large populated cities and countries like Iran going through economic hardship.

Keywords: Depression, Rtms, Compliance, Outcome, Treatment

Introduction

Major depressive disorder (MDD) is a recurrent disabling disorder while being the most prevalent psychiatric disorder (12.7%) according to Iranian mental health survey, 2011 (Sharifi et al., 2015). Given the risk of functional impairment, relational problems, increased suicide risk associated with MDD (Rush et al., 2006) along with its recurrence and chronicity, the disease imposes a great burden to the society (Rush, 2007). Meanwhile, a significant proportion of patients with MDD fail to respond to psychotropic medications (Rush et al., 2006). Data on prevalence of treatment resistant depression is limited, however it is estimated that approximately one third of patients with depression does 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, management of Treatment Resistant Depression (TRD) has remained as a challenge and brain stimulation methods have been emerged as potential alternatives (Little, 2009)(Trivedi et al., 2010). Transcranial Magnetic Stimulation (TMS) is a non-invasive method initially introduced in 1985 for studying neural networks (Barker et al., 1985). Repetitive TMS (rTMS) has been particularly found effective for TRD in recent years (Janicak et al., 2002)(Ren et al., 2014)(Mutz et al., 2018)(Sehatzadeh et al., 2019) and in 2008 was approved by the US Food and Drug Administration (FDA) as a therapy for TRD.

TMS uses electromagnetic fields to induce electrical currents in special areas of the brain which leads to excitation or inhibition of neural activity. In rTMS repeated trains of pulses are generated and applied to the brain which results in prolonged alteration of cortical excitability. Dysfunction in dorsolateral prefrontal cortex (DLPFC) is well established in MDD and rTMS is believed to show antidepressant effects through 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. In general, TMS is an acceptable treatment for patients with Major Depressive Disorder (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 would drop out prematurely. It is

also thought dropouts may happen soon after improvement is achieved given the cost and the number of sessions required for the treatment.

In this study we aimed to evaluate the effect of left prefrontal rTMS on 22 patients with TRD using the FDA protocol (2008).

MATERIALS AND METHODS

Subjects

A total of 24 depressed adults (Female: 15) were initially included in the study. All subjects were referred from psychiatrists (except for two cases which were referrals from neurologists). The diagnosis of MDD was reconfirmed by structured diagnostic interview for DSM-IV (SCID) done by our team's psychiatrist which resulted in exclusion of 2 additional cases as 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 if they were taking medications known to lower seizure threshold (e.g., theophylline). Pregnancy and having ferromagnetic material in the body was also exclusionary. Written informed consents were obtained from all subjects prior to enrollment in the study. Study protocol was approved by local ethics review committee of Tehran University of Medical Sciences.

Procedures

All the procedures were performed by a cognitive psychologist trained and certified to work with the TMS instruments. All sessions were under the close supervision of the psychiatrist and the study 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 weeks intervals using a battery of tests belonged to used in 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 in order 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 question 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 afterwards assessing their ability of daily functioning (Hall, 1995). Patient Health Questionnaire (PHQ-9) (Ardestani et al., 2019) , Quick Inventory of Depressive Symptomatology (QIDS_SR16) (Hedayati et al., 2009) , Generalized Anxiety Disorder Scale (GAD_7) (Omani-Samani et al., 2018) have been reported to be of good reliability and validity.

Statistical analysis

Statistical analyses were conducted using IBM SPSS version 22. The significance level was determined as $P < 0.05$. As the distribution of variables showed abnormality in One-Sample Kolmogorov-Smirnov Test, the non-parametric Wilcoxon Signed Ranks Test was performed to compare data before and after intervention.

RESULTS

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

Table 1. Demographic characteristics of participants

	Dropped out before 2 weeks (N=5)	2 weeks completers (N=11)	4 weeks completers (N=6)	
Gender (F/M)	3/2	4/7	3/3	0.690
Age	40.25 ±15.96	30.90± 12.48	36.66± 9.54	0.396

The baseline scores for QISD, PHQ, GAD, and WSAS was lower and GAF was higher in patients who were dropped out at first 2 weeks in comparison 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 were seen in patients after 2 weeks. As seen in table 2.

Table 2. Outcome measures in patients at baseline and after two weeks.

	Baseline	After 2 weeks	P Value
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

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. A significant improvement was seen in all measures in patients who were dropped out after 2 weeks (Table 3) while in patients who continued treatment for 4 weeks such improvements were not seen after the same 2 weeks

Table 3. Difference in outcome measures in 2 weeks completers who were dropped out after 2 weeks

	QISD1 - QISD0	PHQ1 - PHQ0	GAD1 - GAD0	WSAS1 - WSAS0	GAF1 - GAF0
P value	.017	.008	.008	.012	.039

Table 4. Difference in outcome measures in 4 weeks completers

	QISD1 - QISD0	PHQ1 - PHQ0	GAD1 - GAD0	WSAS1 - WSAS0
P value	.093	.043	.596	.042

DISCUSSION

We found a significant improvement in depression symptoms after rTMS course compared to the baseline. Similarly, anxiety symptoms were significantly decreased following rTMS session. Also, we found improvement in functions as GAF and WSAS scores increased after two weeks. There is a high rate of comorbidity between depression and anxiety disorders (Kessler et al., 2015). Unlike the well-established effect of rTMS in depression, data on effects of rTMS in anxiety disorders is not convincing. Most of the researches on efficacy of rTMS in treatment of anxiety disorders are focused on PTSD and OCD, and data on GAD is 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 in treatment response (Dieffenbach et al., 2013). In order to evaluate the effect of rTMS on psychosocial outcome, we utilized GAF and WSAS scales. Our findings reveal that rTMS has the potential to significantly improve psychosocial outcome. There was a significant increase in GAF scale after rTMS sessions. Similarly, Anderson and colleagues reported an improvement in GAF scores in depressed patients after left DLPFC compared to sham group (Anderson et al., 2007). 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 patient 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 as they already felt better. This is perhaps understandable as some patients came 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 can not identify markers that predict who will continue treatment beyond two weeks.

Interestingly, our 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 who responded to TMS, compared with non responders, is measurable after two weeks of treatment

(Teneback et al., 1999). Recently, Fitzgerald B. et al published a new accelerated protocol which takes place on 6 days (three sessions per day) (Fitzgerald et al., 2018). This looks quite promising and as it helps with better compliance in major metropolitan cities and especially in countries like Iran. Our findings are in line with the literature on compliance in clinical practice that emphasizes the importance of “hard” factors in considering compliance with a particular clinical interventions (Jin et al., 2008). Of those factors, time commitment, therapy cost and income, duration of the treatment period are obviously critical. There are other factors such as patients’ health literacy, healthcare system and lack of social support that their impacts on non compliance with our study intervention can not be disputed as well. Our study highlights the practical implications of using rTMS in a society like 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 affected considerably by factors such as time commitment, costs and income. This would emphasize further our needs for accelerated protocols to improve our patients’ compliance.

Limitations

Some limitations should be considered for our study. The major limitation of the study was 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 potentially could influence response pattern to rTMS. Finally, similar to many other studies could not draw conclusions with regards to durability of improved symptoms over time. Further studies addressing these limitations may deepen our understanding of the rTMS efficacy in TRD.

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 highlights the importance of application of more convenient protocols which require fewer sessions on fewer days to help with compliance and outcome particularly in developing countries like Iran.

Ethics:

This study complies with the principles of the declaration of Helsinki. Study protocol was approved by local ethics review committee of Tehran University of Medical Sciences. Written informed consents were obtained from all patients. (NCT01469325)

Acknowledgment: The authors wish to thank those colleagues and staff at the department of psychiatry (Tehran University of Medical Sciences) and Rad Clinic who helped with referring patients and providing administrative support.

Author Contributions: Dr. Alaghband rad, as the principal investigator, has been involved with all steps of the work. All of the remaining authors have made substantial contributions (according to ICMJE Criteria for Authorship) to this work in the order their names are mentioned

Declaration of Interests: None

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Figure 1. Patients Flow in the Study

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

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