Acta Biomedica Scientia
e - ISSN - 2348 - 2168
Print ISSN - 2348 - 215X
Psychiatry
www.mcmed.us/journal/abs
Research Article

TREATMENT OF TREATMENT-RESISTANT OBSESSIVE-COMPULSIVE DISORDER WITH CONTINUOUS THETA-BURST STIMULATION OVER THE RIGHT ORBITOFRONTAL CORTEX: A RANDOMIZED CONTROLLED TRIAL

Sri Saipriya S*

Assistant Professor, Department of Psychiatry, Sri Venkateshwara Medical College Hospital & Research Centre, Ariyur, Puducherry – 605107, India.

ABSTRACT

Obsessive-compulsive disorder (OCD) is a highly prevalent psychiatric disorder. With a lifetime prevalence of 2.5 percent, it is characterized by pathological obsessions and compulsions. 1Meanwhile, OCD has a significant impact on the daily lives of patients and their families, resulting in a decrease in quality of life and frequently accompanied by anxiety and depression. While serotonin and cognitive-behavioral models can help with treatment, an etiology of OCD is still unknown. 3 Selective serotonin reuptake inhibitors (SSRIs) and cognitive behavior therapy are two evidence-based treatments for OCD (CBT). In the treatment of OCD, a combination of pharmacotherapy and CBT has been found to be more effective than single treatments. The treatment involved a total of 26 patients with OCD. They were randomly assigned to one of two groups: active treatment or sham treatment. Two patients dropped out in the active treatment group (one due to time constraints, the other due to COVID-19 prevention and control), while three patients in the sham group (2 due to time constraints, one due to personal reasons) withdrew during the treatment period. Finally, 26 patients were included in the study, with a 17.9% drop-out rate overall. The drop-out rate did not differ significantly between the two groups. The findings suggest that two weeks of cTBS may not be the best way to improve OCD symptoms in treatment-resistant OCD, but twice-daily cTBS for OCD patients is safe, well-tolerated, and has no apparent side effects. Future research should enlist a larger sample size and look into whether treatment duration should be lengthened to help maintain treatment gains.

Keywords :- OCD, Randomized Controlled Trial, Treatment-Resistant Obsessive-Compulsive Disorder.

Access this article online		
Journal homepage: www.mcmed.us/journal/abs		**Quick Response code**
Received:25.07.2017	**Revised**:12.08.2017	**Accepted**:15.09.2017

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a highly prevalent psychiatric disorder [1]. With a lifetime prevalence of 2.5 percent, it is characterized by pathological obsessions and compulsions [2]. Meanwhile, OCD has a significant impact on the daily lives of patients and their families, resulting in a decrease in quality of life and frequently accompanied by anxiety and depression [3]. While serotonin and cognitive-behavioral models can help with treatment, an etiology of OCD is still unknown. 3 Selective serotonin reuptake inhibitors (SSRIs) and cognitive behavior therapy are two evidence-based treatments for OCD (CBT) [4].

Corresponding Author: **Sri Saipriya S**

In the treatment of OCD, a combination of pharmacotherapy and CBT has been found to be more effective than single treatments [5].Despite these treatment options, about 40% of patients did not respond to the drugs or CBT recommended [6, 7]. As a result, more safe and effective treatments for OCD are urgently needed. Patients with severe OCD who were unresponsive to drugs and/or behavioral therapy might benefit from different add-on stimulation techniques [8]. TMS is a type of physical therapy that uses an electric current to create a magnetic field to stimulate specific brain regions by inducing neurophysiological changes [9, 10]. Low-frequency stimulation causes long-term excitability suppression, whereas high-frequency stimulation causes long-term facilitation. 8 Abnormalities in the cortical-striatal-thalamic-cortical (CSTC) circuits have been implicated in the pathogenesis of OCD in previous neuropsychological studies [11]. 9 TMS can be used to modulate specific brain regions non-invasively and on a regular basis to alleviate OCD symptoms, and it has been found to be relatively safe and well-tolerated in clinical practice. In the short term, TMS was found to be more effective than sham TMS in a meta-analysis; however, the therapeutic effect is influenced by the target, stimulation mode, and intensity. Most previous rTMS studies on OCD used low frequency, required more than 20 minutes per session, lasted 4–6 weeks, and required outpatients to visit the hospital every day for treatment [12]. Patients have poor compliance and a high drop-out rate as a result of the long treatment period. Previous research has shown that an accelerated rTMS regimen is a safe and noninvasive way to shorten the course of treatment while also improving OCD symptoms in a short amount of time. TMS that uses continuous (cTBS) or intermittent (iTBS) stimulation of the cortex to induce excitement or inhibition is known as theta-burst stimulation (TBS). TBS can be done two or more times per day, cutting the treatment time in half. The majority of TBS studies in the treatment of OCD are currently preliminary exploratory studies. cTBS is thought to have long-term depression-like inhibitory effects that can reduce cortical excitability in specific areas and can be completed quickly. To induce longer-lasting effects, cTBS requires a shorter stimulation duration and lower intensity than other rTMS protocols, and it is also considered safer by some authors than traditional rTMS

Aims and Objective:

The aim of this study is to see how effective and safe cTBS is over the right OFC in a group of treatment-resistant OCD patients.

Material and Methods:

The subjects were all OCD patients who came to the outpatient clinic of the Department of Clinical Psychology, General Hospital of Tianjin Medical University from September 2019 to June 2020. Right-handed outpatients aged between 18 and 60 years with DSM-V OCD diagnosed using the Mini-International Neuropsychiatric Interview (MINI) were enrolled in the study. To be eligible, patients had to have a total Y-BOCS score of 16 or more, a total duration of the disease of at least 2 years, and they should have received at least two 12-week adequate sequences and dose of treatment with selective serotonin reuptake inhibitors (SSRIs) but not responding (treatment-resistant). All the psychotropic medications had to be at stable doses for at least 3 months before enrolling in the study, and the current medication regimen (included benzodiazepines) was maintained throughout the treatment and follow-up visits. Exclusion criteria were as follows: diagnosis of other psychiatric disorders (except for depressive or anxious disorders), current major depressive disorder (MDD), history of TMS, history of epilepsy or other neurological illness, pregnancy, and any contraindication to TMS. The sample size was estimated using the G*Power 3.1 software. In the previous study ,30 the effect size (Cohen's d value) for the efficacy of rTMS in OCD was 0.44 (which converts to partial eta squared value of 0.05). With modest effect size in our study, a power of 95%, alpha of 0.05, 2 groups and 3 repeated measurements, 25% dropout rate, the proposed study required 18 participants per group. The expected sample size of 40 could not be recruited due to COVID19 restrictions. We enrolled a total of 30 eligible patients, two patients (A man, a woman) withdrew before the trial began due to personal reasons. The rest of the 26 patients have fully understood this study's purpose and steps and signed informed consent forms. A researcher used a random number table, 26 patients were randomly divided into the active group and the sham group, 13 patients in each group. The numbers were written in a sealed Kraft envelope, patients were kept blind to the sequence they were assigned, and the allocation sequence was concealed from recruiters. The envelope was opened immediately before the first session's commencement by the clinician administering the cTBS for each patient. SPSS version 24.0 and STATA version 16.0 were used for statistical analysis. On categorical variables, the X2 analysis/fisher exact test was used, and on continuous variables, the t-test was used. The primary outcome variable (Y-BOCS score) and other secondary outcome variables (HAMA score and HAMD score) were compared using repeated measures analysis of variance with scores at 0, 2, and 6 weeks as a within-group factor and two active or sham levels cTBS as a between-group factor. The significance criterion was set at 0.05 for two-sided statistical testing.

Results and Discussion:

The treatment involved a total of 26 patients with OCD.They were randomly assigned to one of two groups:

active treatment or sham treatment. Two patients dropped out in the active treatment group (one due to time constraints, the other due to COVID-19 prevention and control), while three patients in the sham group (2 due to time constraints, one due to personal reasons) withdrew during the treatment period. Finally, 26 patients were included in the study, with a 17.9% drop-out rate overall. The drop-out rate did not differ significantly between the two groups. During the treatment period, two patients in the treatment group experienced scalp pain in the target area, which was relieved after rest, while the others experienced no serious adverse events or seizures. Table 1 shows the patients' general information, and the difference is not statistically significant. During the treatment period, the patient continued to take the same drug dose as before.

Antidepressants were used by 10 (90.10 percent) of the active group, antipsychotics were used by 2 (26.32 percent), and benzodiazepines were used by 1 (18.33 percent). Antidepressants were used by 11 people (100%) in the sham group, antipsychotics were used by 3 people (27.27%), and benzodiazepines were used by 2 people (18.18%). In terms of drug use, there was no significant difference between the two groups.

At the start of the study, there was no significant difference in the Y-BOCS score between the active and sham groups (p=0.275). The Y-BOCS score of the two groups decreased over time, depending on different time points. There was a significant difference (p=0.021) when compared to the baseline, but no statistical difference between the two groups (p=0.387). Despite the fact that there was no group * time interaction (F=0.584, P=0.567), repeated measures analyses revealed a significant decrease in the HAMA score compared to the baseline (F=9.509, P=0.001). Furthermore, significant differences in HAMD scores per time, group (F=16.544, P0.001), and group * time interaction (F=4.132, P=0.031) were found. We compared the two groups' effective rates, with the scale score reduced by 25% where appropriate and the total effective rate equal to improve number/total number of patients. The three outcome indicators calculated the effective rate and performed the chi-square test and the Fisher exact probability test. Following our previous findings, there was only a significant difference in the effective rate between the two groups in the depression score after two weeks (p=0.027).

The following factors may have contributed to our trial's failure: a. The subjects of this study are treatment-resistant OCD patients for whom treatment is difficult due to the disease's early onset and long course; Despite increasing the number of treatments per day, the 2-week treatment cycle may not be enough to produce significant and sustained changes in OCD symptoms; c. The intensity of stimulation is also an important factor affecting efficacy. It's unclear whether increasing the stimulation's intensity will improve efficacy. This study used an 80 percent RMT stimulus intensity, which is common in cTBS studies but may be insufficient in treatment-resistant OCD; d. We use the international 10–20 EEG system to locate the OFC target in a convenient and straightforward manner, but this method is not as accurate as neuro-navigation due to anatomical differences in each person's brain; e. We used a commonly used figure-of-8 shaped coil, which was also used in, but did not achieve clinical efficacy. It could be due to the magnetic field's shallow penetration depth, which means it can't reach the depth of the target stimulation. It found that high-frequency dTMS on the mPFC and ACC could improve OCD symptoms significantly. They used a special H-coil that allows magnetic stimulation to reach deeper and wider into the brain, resulting in therapeutic effects. Although the dTMS study yielded more promising results, there are several methodological differences (such as coil type, sample size, and symptom provocation prior to TMS application) that necessitate future research.

Table 1: Baseline Characteristics

Variables	Active Groups (n=13) Mean (SD), n (%)	Sham Group (n=13) Mean (SD), n (%)	P value
Age (Years)	28.0 (9.0)	30 (7.52)	0.296
Sex (Male/ Female)	5/8	6/7	1.00
Age at onset, y	20.0 (6.0)	20.71	0.241
Duration of illness	8.29 (7.60)	10.29	0.573
Medication in use			
Antidepressant	8 (61.53)	10.0 (90.10)	1.000
Anti-psychotics	1 (7.69)	2(26.32)	0.640
Benzodiazepines	2 (15.38)	1 (18.0)	0.590
Y-BOCS	22.5 (1.82)	21 (4.00)	0.275
HAMA	11.0 (5.26)	9.52 (5.22)	0.754
HAMD	12.0 (5.30)	8.45 (4.52)	0.100

Conclusion:

The findings suggest that two weeks of cTBS may not be the best way to improve OCD symptoms in treatment-resistant OCD, but twice-daily cTBS for OCD patients is safe, well-tolerated, and has no apparent side effects. Future research should enlist a larger sample size and look into whether treatment duration should be lengthened to help maintain treatment gains.

REFERENCES

1. Fineberg, N. A., Sivakumaran, T., Roberts, A., & Gale, T. (2005). Adding quetiapine to SRI in treatment-resistant obsessive-compulsive disorder: A randomized controlled treatment study. *International Clinical Psychopharmacology*. https://doi.org/10.1097/00004850-200507000-00005
2. Gershkovich, M., Wheaton, M. G., & Simpson, H. B. (2017). Management of Treatment-Resistant Obsessive-Compulsive Disorder. In *Current Treatment Options in Psychiatry*. https://doi.org/10.1007/s40501-017-0127-8
3. López-Alonso V, Cheeran B, Río-Rodríguez D, Fernández-del-Olmo M. Inter-individual variability in response to non-invasive brain stimulation paradigms. *Brain Stimul*. 2014;7(3):372–380.
4. Gershuny, B. S., Baer, L., Parker, H., Gentes, E. L., Infield, A. L., & Jenike, M. A. (2008). Trauma and posttraumatic stress disorder in treatment-resistant obsessive-compulsive disorder. *Depression and Anxiety*. https://doi.org/10.1002/da.20284
5. Krebs, G., & Heyman, I. (2010). Treatment-resistant obsessive-compulsive disorder in young people: Assessment and treatment strategies. In *Child and Adolescent Mental Health*. https://doi.org/10.1111/j.1475-3588.2009.00548.x
6. Yazici, K. U., & Percinel, I. (2014). The role of glutamatergic dysfunction in treatment-resistant obsessive-compulsive disorder: Treatment of an adolescent case with N-acetylcysteine augmentation. In *Journal of Child and Adolescent Psychopharmacology*. https://doi.org/10.1089/cap.2014.0053
7. Jakubovski E, Diniz JB, Valerio C, et al. Clinical predictors of long-term outcome in obsessive-compulsive disorder. *Depress Anxiety*. 2013;30(8):763–772.
8. Mondino M, Haesebaert F, Poulet E, Saoud M, Brunelin J. Efficacy of cathodal transcranial direct current stimulation over the left orbitofrontal cortex in a patient with treatment-resistant obsessive-compulsive disorder. *J Ect*. 2015;31(4):271–272.
9. Nettekoven C, Volz LJ, Leimbach M, et al. Inter-individual variability in cortical excitability and motor network connectivity following multiple blocks of rTMS. *NeuroImage*. 2015;118:209–218.
10. Pallanti S, Hollander E, Bienstock C, et al. Treatment non-response in OCD: methodological issues and operational definitions. *Int J Neuropsychopharmacol*. 2002;5(2):181–191.
11. Trevizol AP, Shiozawa P, Cook IA, et al. Transcranial magnetic stimulation for obsessive-compulsive disorder: an updated systematic review and meta-analysis. *J ECT*. 2016;32(4):262–266.
12. Suppa A, Huang YZ, Funke K, et al. Ten years of theta burst stimulation in humans: established knowledge, unknowns and prospects. *Brain Stimul*. 2016;9(3):323–335.

Cite this article:
Sri Saipriya S. Treatment of Treatment-Resistant Obsessive-Compulsive Disorder With Continuous Theta-Burst Stimulation Over The Right Orbitofrontal Cortex: A Randomized Controlled Trial. **Acta Biomedica Scientia**, 2017;4(3):158-161.