Efficacy of Repetitive Transcranial Magnetic Stimulation in the Management of Obsessive Compulsive Disorder

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ABSTRACT

Background: Obsessive-compulsive disorder (OCD) is a debilitating condition that affects approximately 1% to 3% of the world population. The primary treatments are selective serotonin reuptake inhibitors and behavioral therapy. Despite therapy, approximately 30% to 40% of patients continue to suffer from disabling OCD symptoms. Objective: is to evaluate the efficacy of repetitive transcranial magnetic stimulation (r-TMS) in management of OCD patients, either as monotherapy or as add-on treatment in patients with poor response to selective serotonin reuptake inhibitors (SSRIs). Methods: The present study included sixty OCD patients. Forty patients were none medicated; twenty of them (randomly selected), received sham stimulation as a control group and the other twenty received real r-TMS. The third group included twenty patients with poor response to SSRIs; they received real r-TMS. The results of the three groups were compared pre and post treatment. Results: While r-TMS was not effective as a single treatment for OCD patients, it was effective as add-on treatment for OCD patients. The use of r-TMS induced a statistically significant increase in the value of motor threshold (MT) in the active group of patients (both Monotherapy and add-on treatment groups) after receiving 15 sessions of real r-TMS; this means that TMS lowered the hyperexcitable circuits in OCD.

Key Words: Obsessive-compulsive disorder, transcranial magnetic stimulation

INTRODUCTION

Obsessive-compulsive disorder (OCD) is the fourth most common psychiatric disorder, affecting approximately 1% to 3% of the world population, with a life time prevalence of 2% to 3%, more than twice that of schizophrenia. Available medication and behavioral treatment, while beneficial for many patients, have limited efficacy in many others. Transcranial magnetic stimulation (TMS) is the non invasive form of physical treatment. Promising finding regarding efficacy, tolerability, reversibility and cheapness of this technique have increased interest in investigating its use in treatment of resistant OCD. However, TMS efficacy in OCD is still a matter of controversy. Few studies have explored the potential utility of TMS as a treatment in anxiety disorders in general and specifically in OCD despite the need for more effective treatments for OCD. It remains that further studies are indicated to assess the efficacy and to clarify the optimal stimulation characteristics of TMS in OCD.

The aim of the present study is to evaluate the efficacy of r-TMS in the treatment of none medicated OCD and as add-on treatment in OCD patients with poor response to medical treatment.

SUBJECTS AND METHODS

The present study was carried out at Tanta University Hospital, Neuropsychiatry department and at Psychiatry, Neurology and Neurosurgery Center from January 2008 to December 2008. It included three groups of patients. The first and the second groups included forty never medicated obsessive compulsive disorder patients. They were randomly classified into two groups and each group included twenty patients. Odd numbers of patients to receive sham stimulation (group 1) and even numbers to receive real stimulation (group 2). Group 1 included thirteen female patients and seven males. The main age of this group was 28.9±5.7. While, fifteen of them had mixed obsession and compulsions only five patients had compulsions only. Group 2 included 10 females and ten males, their mean age was 26±5.582. Thirteen patients had mixed OCD symptoms and seven patients had only compulsions. The third group included 20 obsessive compulsive disorder patients (8 females and 12 males, their mean age was 27.7±7.83) with poor response to selective serotonin reuptake inhibitors (SSRIs). The baseline score of Yale-Brown obsessive compulsive scale (YBOCS) was more than twenty. All were diagnosed as obsessive compulsive disorder according to DSM-IV criteria.

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Exclusion criteria: subjects with comorbid depression or other psychiatric disorders were excluded. Epileptic patients or history of other neurological disorders which might be epileptogenic e.g. brain tumor, history of meningitis, encephalitis or severe head trauma. Subjects with cardiac pacemaker or any other implanted electronic device, and pregnant women were excluded.

All patients were subjected to the following:

Psychiatric interview was done for each patient, using MINI International Neuropsychiatric Interview (7) to be diagnosed as OCD according to DSM-IV criteria. This interview was translated and validated into Arabic by Ghanem et al., 1999 (8). The study was explained to all patients and written consents were taken from them. Of course the patients didn’t know whether they received real or sham TMS. Also, the researchers who performed clinical assessment were blind regarding the treatment received by the patient (sham, r-TMS, or medicated groups).

YBOC S was used to assess the severity of OCD symptoms before the first r-TMS session and after completion of the 15 sessions.

Patients received real r-TMS and sham stimulation to the left dorsolateral prefrontal cortex (LDLPFC) for five sessions per week for three successive weeks.

Sham stimulation is typically applied by angling the coil off the head so that the magnetic field stimulates the superficial scalp muscles but does not enter the brain (9,10). It simulates the sensation and acoustic artifact of r-TMS (11).

After the 15 sessions had been completed, the patient should be reassessed again by YBOCS to assess the improvement of OCD symptoms. In clinical trials, a >40% reduction of YBOCS scores was considered a clinically significant improvement to a given treatment (12).

Statistical Analysis

The collected data was organized, tabulated and statistically analyzed using the Minitab computer program, for the statistical analysis. For quantitative variables, the mean and standard deviation were calculated. The difference between two means was statistically analyzed using the student (t) test. The mean values of before and after TMS were tested using the paired t test. For categorical variables, the number and percent distribution was calculated. Chi-square (X²) test was used as a test of significance and when found inappropriate Fisher exact test was used. The test of significance between two proportions (Z) test was used to compare the percentage of improvement of obsessions and compulsions. Significance was adopted when p< 0.05 for interpretation of results of tests of significance (13).

RESULTS

Patients of this study had either combined obsession and compulsion (15 of the sham group, 13 patients of the Monotherapy group and half of the add-on group) or only compulsions (5 of the sham group, 7 of the Monotherapy and half of the add-on group) (Table 1).

Use of r-TMS was effective add-on treatment for OCD. More patients of the add-on treatment group showed good response to r-TMS than the other two groups. The difference between the three groups was significant (p=0.006). The difference between the add-on group and sham group was significant (p=0.001) and also, the difference between monotherapy and add-on group was significant (p=0.05).

By the end of the fifteen sessions r-TMS induced significant reduction (p=0.001) in the YBOCS of the add-on group. Their mean score before treatment was 25.85±4.88 and after the treatment it became 20.60±4.30. Among the other two groups there was no significant change in the YBOCS before and after treatment.

The mean drop of YBOCS for obsessions was of 7.73±2.31 points and for compulsions was of 5.07±4.74 points. So, real TMS induced a 44.4% improvement of obsessions score and 57.6% improvement of compulsions score of YBOCS with no statistical significance between the two scores (z=0.36 and p=0.72).

The r-TMS significantly increased the motor threshold of the both groups of active treatment. Before treatment, the motor threshold (MT) of the monotherapy group was 71±8.8 and at the end of treatment it became 80.15±8.34 and the difference was significant (p=0.002). The mean MT of add-on group was 63.90±8.1 and then it became 69.50±7.6. The difference was statistically significant (p=0.03). The changes of MT occur mainly among patients with good response to treatment (Table 4).
Table 1. Demographic and clinical data of patients with Obsessive compulsive disorder.

<table>
<thead>
<tr>
<th></th>
<th>Sham Group</th>
<th>Monotherapy Group</th>
<th>Add-on Group</th>
<th>P3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Mean±SD)</td>
<td>28.9±5.7</td>
<td>26±5.58</td>
<td>27.7±7.83</td>
<td>0.37</td>
</tr>
<tr>
<td>Duration of illness (Mean±SD)</td>
<td>6.3±3.063</td>
<td>5.8±4.948</td>
<td>7.4±5.13</td>
<td>0.52</td>
</tr>
<tr>
<td>Sex</td>
<td>7(35%)</td>
<td>10(50%)</td>
<td>12(60%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Female</td>
<td>13(65%)</td>
<td>10(50%)</td>
<td>8(40%)</td>
<td></td>
</tr>
<tr>
<td>Clinical types:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obsession</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Compulsions</td>
<td>5(25%)</td>
<td>7 (35%)</td>
<td>10 (50%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Mixed</td>
<td>15 (75%)</td>
<td>13 (65%)</td>
<td>10 (50%)</td>
<td></td>
</tr>
<tr>
<td>Response to r-TMS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good Response</td>
<td>1 (5%)</td>
<td>5 (25%)</td>
<td>11(55%)</td>
<td>0.006*</td>
</tr>
<tr>
<td>None Response</td>
<td>19 (95%)</td>
<td>15 (75%)</td>
<td>9 (45%)</td>
<td></td>
</tr>
</tbody>
</table>

P1=0.07
P2=0.05*
P3 (Difference between sham group and add-on treatment groups) =0.001*

*Significant at p<0.05

Table 2. YBOCS score of the studied patients with Obsessive compulsive disorder before and after r-TMS.

<table>
<thead>
<tr>
<th></th>
<th>YBOCS score before TMS</th>
<th>YBOCS score after TMS</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham Group</td>
<td>22.95±3.63</td>
<td>21.65±3.01</td>
<td>0.23</td>
</tr>
<tr>
<td>Monotherapy Group</td>
<td>22.65±4.42</td>
<td>20.80±3.66</td>
<td>0.16</td>
</tr>
<tr>
<td>Add-on Group</td>
<td>25.85±4.88</td>
<td>20.60±4.30</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

*TMS transcranial magnetic stimulation, YBOCS Yale-Brown obsessive compulsive scale
*Significant at p<0.05

Table 3. Motor threshold (MT) of the studied patients with Obsessive compulsive disorder before and after r-TMS.

<table>
<thead>
<tr>
<th></th>
<th>MT before TMS (Mean±SD)</th>
<th>MT after TMS (Mean±SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham Group</td>
<td>71±8.8</td>
<td>71.6±8.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Monotherapy Group</td>
<td>71±8.8</td>
<td>80.15±8.34</td>
<td>0.002*</td>
</tr>
<tr>
<td>Add-on Group</td>
<td>63.90±8.1</td>
<td>69.50±7.6</td>
<td>0.03*</td>
</tr>
</tbody>
</table>

*r-TMS repetitive transcranial magnetic stimulation, SD standard deviation
*Significant at p<0.05

Table 4. Motor threshold (MT) of the studied patients with good response and patients with poor response to r-TMS before and after treatment.

<table>
<thead>
<tr>
<th></th>
<th>MT before TMS (Mean±SD)</th>
<th>MT after TMS (Mean±SD)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with good response to r-TMS (n=15)</td>
<td>67.13±8.71</td>
<td>79.13±8.90</td>
<td>0.001*</td>
</tr>
<tr>
<td>Patients with poor response to r-TMS (n=25)</td>
<td>67.88±9.60</td>
<td>72.24±9.12</td>
<td>0.11</td>
</tr>
</tbody>
</table>

*TMS transcranial magnetic stimulation
*Significant at p<0.05
In the present study, r-TMS of the left dorsolateral prefrontal cortex was capable to induce improvement in the score of YBOCS when added to SSRIs in the treatment of OCD, but it was not effective as a single line of treatment. It was effective in lowering the score of both obsession and compulsions without significant difference between both of them.

At our center, a previous study was conducted for evaluation of the r-TMS use in the treatment of OCD, stimulation of the right dorsolateral prefrontal cortex was found to be effective single line of treatment of OCD patients compared to sham stimulation. Greenberg and colleagues found that right prefrontal stimulation is effective in treatment of OCD. They applied left and right prefrontal and mid-occipital stimulation in 12 patients with OCD on separate days; they found that right prefrontal r-TMS decreased compulsive urges for 8 hours following the stimulation not after left prefrontal or mid-occipital stimulation. However, obsessive thoughts didn’t change significantly after any type of stimulations. Sachdev and colleagues randomly assigned 12 individuals to receive right or left dorsolateral prefrontal stimulation (10 Hz, 110% resting motor threshold, 15 minutes 5 sessions per week for 2 weeks). Two thirds of the studied subjects showed significant improvement at two weeks and 1-month follow-up with no significant difference between right or left sided stimulation. Another study of 10 patients with OCD found benefit with r-TMS applied to the supplementary motor area; approximately two thirds of the studied patients were responders.

In the present study r-TMS applied to the left dorsolateral prefrontal cortex was not effective as single line of treatment of OCD. In agreement with that, Sachdev and colleagues studied the application of r-TMS to the left side in a recent study. They found that 20 sessions of r-TMS over left dorsolateral prefrontal cortex for 2 weeks was ineffective in treatment of OCD. In contrast with the results of the present study, the results of our previous work and Greenberg et al. the right prefrontal stimulation was found to be effective in treatment of OCD. Some researchers applied TMS bilaterally for OCD patients. Mantovani and colleagues studied the effect of four daily sessions of low frequency TMS 1 Hz, 100%MT, to patients with OCD to stimulate bilaterally and simultaneously the supplementary motor areas. They reported that all the studied patients reported a clinically significant improvement in OCD symptoms lasting up to three months in almost two thirds of patients.

Frequency of stimulation: In our study we used high frequency r-TMS (20Hz) and it was effective in OCD symptoms, the same as reported by Greenberg and colleagues when they used high frequency r-TMS (20Hz/2seconds) and it was effective in OCD patients. Also Sachdev and colleagues applied high frequency stimulation (10 Hz, 110% resting motor threshold, 15 minutes 5 sessions per week for 2 weeks). Two thirds of the studied subjects showed significant improvement at two weeks and 1-month follow-up.

One opinion suggests that improvement in OCD symptoms could be secondary to the non specific antidepressant effect, but the changes in YBOCS were not reflecting changes in depression. Also, in our study, the patients with comorbid depression were excluded. Moreover, most data support that the antidepressant effect of high-frequency r-TMS can be obtained when r-TMS is applied to the left prefrontal cortex opposite to the site of stimulation used in OCD. It is more likely that the depressed mood improved secondarily to improvements in OCD.

It is reported that OCD patients have significantly decreased motor threshold compared to normal control subjects (The can be defined as the minimal TMS intensity to evoke motor response), this means that there is cortical hyperexcitability in OCD patients. In the present study, (MT) was measured at the base line and after completion of the 15th session as a measure of cortical excitability. It induced significant increase in the MT in responders of the active groups (both single line of treatment and add-on groups) while it induced non significant increase in the non responders after receiving 15 sessions of real TMS. This means that r-TMS lowered the hyperexcitable circuits in the responders group. In agreement with this study, Mantovani suggests that real repetitive TMS to the dorsolateral prefrontal cortex (DLPFC) disrupted the hyperexcitable neuronal circuits in OCD and thus improved the OCD symptoms, the same was found by Greenberg and colleagues.

**Recommendations**

The use of r-TMS in management of OCD still need further studies as regards the site of stimulation either the dorsolateral prefrontal cortex either right, left or bilateral and also, the premotor areas all these need to be further evaluated. The frequency and the rate of stimulation and number of sessions, all these factors need to be studied.

[Disclosure: Authors report no conflict of interest]
REFERENCES

الملخص العربي

فعالية التنبؤ المغناطيسي عبر الدماغ في علاج الوسواس القهري

يعتبر التنبؤ المغناطيسي عبر الدماغ أحد الوسائل العلاجية الجديدة والتي تستخدم في علاج بعض الأمراض النفسية وكذلك في العديد من الأبحاث التي تدرس فسيولوجيا الجهاز العصبي. ويعتبر التنبؤ المغناطيسي للمخ من الوسائل العلاجية الأمنة حيث أن الآثار الجانبية الناتجة عن استخدامه بسيطة ومحتملة.

وقد تم استخدامه كوسيلة ناجحة في علاج مرضى الاكتئاب النفسي وأظهر نتائج جيدة وجريئة هذه الوسيلة العلاجية في مرضى الوسواس القهري. حيث لا تزال الدراسات في هذا الموضوع محدودة.

هدف من الدراسة: تقييم التنبؤ المغناطيسي عبر الدماغ في علاج مرضى الوسواس القهري سواء كعلاج وحيد أو مضاعفا إلى العياد المستخدمة في هذه الحالة.

طريقة البحث: اشتملت الدراسة على ثلاثة مجموعات تتكون كل مجموعة من عشرة مرضى مصابين من مرضى الوسواس القهري، وتم اختيار المرضى من المجموعات الأولى والثانية بشكل عشوائي من الحالات الذين لا يتراوح أي عيادات بينما مرضى المجموعة الثالثة كانوا يتراوحون العيادات وتحدثهم لها كانت محددة. تم فحص المرضى قبل بدء العلاج وبعد اكتمال جلسات العلاج الخمسة عشر وتستخدم قياس براون لقياس الضرر في الانتظار.

نتائج البحث: أظهرت النتائج أن التنبؤ المغناطيسي كان له دور إيجابي في علاج مرضى الوسواس القهري الذين لم يستجيبوا بشكل كاف على العلاج الدوائي، أما المرضى الذين عولجوا بالتنبؤ المغناطيسي فقط لم يكن علاجهم مثاليًا بالمقارنة بالمجموعة الضابطة والمجموعة الثالثة.

بعد انتهاء العلاج وجد أن القياسات النفسية لأعراض الوسواس القهري لم Tüm المجموعة الثالثة قد انخفضت بشكله دالة إحصائية مقارنة بالمجموعتين الأخرى، وكذلك الحال بالنسبة لإحداث التنبؤ المغناطيسي في المرضى الذين استجابوا للعلاج بالتنبؤ المغناطيسي قد أنتجت بعد انتهاء العلاج مما يوضح أن هذا النوع من العلاج له القدرة على إعادة التوازن الكهربائي للخلايا العصبية في هؤلاء المرضى إلى وضع أفضل مما كان عليه قبل بدء العلاج.