NONINVASIVE BRAIN STIMULATION FOR PARKINSON’S DISEASE
Osama E. El Dib¹, Manal S. Awadh², Sabry M. Abdeldayem³, Eman awad⁴ and Mahmoud Rizk⁵

¹Department of Neurology, Menofiya University  
²Physical Medicine & Rehabilitation, Ain Shams University  
³Neurology, Tanta University  
⁴Neurology, Ain Shams University  
⁵Internal medicine, Benha University Egypt

Article History:
Received 09th September, 2018  
Received in revised form 14th October, 2018  
Accepted 23rd November, 2018  
Published online 28th December, 2018

Key Words:
Parkinson disease, Transcranial magnetic stimulation, motor cortex.

ABSTRACT
Introduction: Dopamine replacement medications are an effective current medical management of Parkinson disease (PD), particularly for motor symptoms but later, the response declines and complications develop. The efficacy of Transcranial magnetic stimulation (TMS) on motor cortex in Parkinson disease is debatable since studies have shown conflicting results. The most common adverse events are transient headaches and scalp discomfort. The aim of this work is to evaluate rTMS high frequency (15 Hz) impact on the motor functions in PD patients. Patients and Methods: 43 patients with PD (15 females and 28 males) aged between 51 and 76 years (mean 64 ± 8.2 years) were included in our study. Randomly, 31 patients were assigned to either of these two groups; Group I (16) patients on anti-parkinsonian medications only and group II (15) patients on antiparkinsonian medications and TMS. Group III (12) patients were chosen from those patient still not on medicine or stop it. 15 Hz stimulation was delivered with an intensity of 10% above the motor threshold (MT) for 10 daily sessions. Each session included the delivery of 75 stimuli for 5 sec interval then followed by a 10 sec interval. The daily total of trains and the daily number of pulses were 40 trains and 3000 pulses, respectively. The assessment before and immediately after TMS sessions included a clinical evaluation through the Unified Parkinson’s Disease Rating Scale (UPDRS) and in specific part III motor section, Schwab and England and Hoehn and Yahr scales. Reevaluation was performed after 1 months.

Results: In the present study there is significant difference (improvement) in groups II and III resulting from, between base line and immediately after rTMS course also, between base line and 1 month after rTMS. There was a slight decrease (not significant) in score at 1 month after the rTMS in correlation to immediately after it. In group I the difference between base line compared to after antiparkinsonian medications and 1 month after it were significant. The comparison between (Group I vs. Group II), revealed a statistically significant difference (improvement) between base line and after the treatment, also after 1 month. But the comparison between (Group III vs. Group I), revealed a statistically no significant difference, between base line and immediately after, and also, 1 month after rTMS. The there was no significance in the difference between directly after treatment and one month later in both Group II and group III. Conclusion: This study showed that motor symptoms in PD patients can be now treated by high-frequency TMS. Further studies are needed in this field to understand the impact of TMS on PD’s different stages, the effect of TMS on various aspects of the disease (cognition, memory, etc.), and also to optimize the stimulation parameters.

Copyright©2018 Osama E. El Dib et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Introduction
Parkinson’s disease (PD) is a progressive, neurodegenerative disease that has a fast early phase progress but slower progression in the later stages. Advances since the 1960s have mechanisms as contributing to the pathophysiology of movement disorders, such as depletion of neurotransmitters (e.g., dopamine), changes in the basal ganglia and cortical targets connecting loops, and abnormal cortical plasticity. Based on the concepts involved, a wide range of current treatment options have been developed, including medications, botulinum toxin, and deep brain stimulation (DBS). However, these current therapies are limited despite the achieved advances. Dopamine replacement medications are considered the current major medical treatment to manage motor symptoms in PD, but later, the response declines and complications develop. Although DBS procedures in PD can treat medication-induced motor fluctuations in selected patients, there has been increasing recognition of cognitive and mood side effects of DBS, in addition to risks attendant with invasive surgical options but provoke more impairment in voluntary movements (dyskinesia) in two-year follow-up interval.
Since 1985, it was safe to study the central nervous system using the noninvasive transcranial magnetic stimulation (TMS) technique that was introduced by Barker et al., and with no pain. TMS has been suggested to manage several neurological conditions, such as Parkinson disease, migraine, depression, and epilepsy. However, there is no consistent evidence regarding its efficacy on motor symptoms in PD patients. TMS is able to non-invasively alter neurons' activity and stimulate them in the cerebral cortex. When delivering series of pulses, it can act locally and at detached sites. Numerous previous studies have established the potential of repetitive TMS (rTMS) to modulate cortical neurons' excitability. The studies also demonstrated the primary parameters affecting this stimulation, including stimulation site, intensity, and frequency. After rTMS, glucose metabolism assessed using with Positron emission tomography (PET) was increased at the stimulation site and in both distant contralateral M1 and supplementary motor area (SMA), also, induce dopamine release in the ventrolateral putamen and caudate. TMS given either continuously at a low frequency (0.2-1 Hz) or in intermittent trains at higher frequencies (5-20 Hz). Circular TMS coils induce cortical currents that span at least the diameter of the coil; they are therefore less specific than focal figure-8 coils which also provide the ability to target specific cortical regions.

The Motor cortex stimulation (M1) is a key cortical target for the motor cortical subcortical loop. The prefrontal dorsolateral cortex (DLPFC) stimulation may be specific for depression, rather than for motor symptoms. Premotor cortex (SMA) stimulation as a cortical target is effective but its location makes it a difficult noninvasive cortical target.

The sham rTMS (placebo-rTMS) was applied in a similar way with the coil elevated 90° away from the head to reproduce the subjective sensation of rTMS. On the other hand, in true-rTMS (active), the coil was placed to left side from patients' head surface over the motor cortex. TMS is generally safe, noninvasive procedures with minimal adverse effects. The most common reported adverse effects are scalp pain and headaches as a result of peri-cranial muscles stimulation. However, severe adverse effects can range from mood changes and burns, to seizures associated with high frequencies and intensities of rTMS. It was suggested that TMS associated seizures result from the activation and excitation of cortical pyramidal cells and neighboring neurons, and from devastating inhibitory mechanisms.

**Patients & Methods**

Forty three patients (15 females and 28 males), aged between 51 to 76 years with a mean of 64 ± 8.2 years, were recruited in our study. Inclusion criteria depended on the following: first the UK Parkinson's Disease Brain Bank criteria for idiopathic PD and second having bilateral akinetic-rigid syndrome. Thirty one patients were randomly assigned to one of two groups; Group I (16) patient on antiparkinsonian medications only and group II (15) patients on antiparkinsonian medications and rTMS. Group III (12) patients were chosen from those patient still not on medicine or stop it, knowing that it is unethical to leave patients with no medication for several days.

The study exclusion criteria consisted of permanent rest tremor cases who cannot maintain their hand muscles completely relaxed. Patients with history of seizure or ferromagnetic metallic implants, patients with head trauma or injuries, patients with history of dementia or depressed patients with psychotic symptoms, were excluded from the study. Participating patients kept taking their original antiparkinsonian medications that were prescribed by their own doctors. They also gave their written informed consent for the study. Since anti-parkinsonian medications do not last for long time, the examination was performed 12 hours after overnight withdrawal and in 'off-drug' condition. First, we assessed their motor performance clinically. Then, dopa intake and rTMS were completed. Clinical motor evaluation was done after 20 minutes of rTMS sessions termination. Dopa intake was performed 30-60 minutes after administration drug to the patients. Part III of UPDRS; motor section, was used to clinically complete before and immediately after rTMS sessions assessments. This scale measures waking, rigidity and fast alternating movement on the upper and lower extremities. Another evaluation was conducted 1 month later.

**Repetitive transcranial magnetic stimulation (rTMS)**

Patients were randomly assigned to get different order of the rTMS interventions. The left motor cortical area was stimulated using a figure-of-eight stimulating coil. This area is analogous to the right first dorsal interosseus (FDI) muscle. The coil was placed over patient's left motor cortical area tangentially. It was pointed to the occipital lobe. This way, we ensure that the current will flow to the central sulcus. In order to determine the 'motor hot spot' that produces maximal amplitude in the right FDI muscle, the coil was continuously moved. When this spot was detected, the coil was fixed with a means device to during the whole experiment. 15-Hz frequency and 10 % above the motor threshold (MT) intensity were used to deliver stimulation. The treatment protocol consisted of 10 daily sessions during a 11-days period (start at Saturday and taking Friday off). At each session, a series of 75 stimuli was delivered during an interval of 5 seconds then followed by a 10 seconds. Each session had a daily total of 40 trains and 3000 pulses. The equipment employed in our study was the Neurostar TMS - USA.

**Unified Parkinson’s Disease Rating Scale**

Part III part: motor section of UPDRS was used. It contains 14 questions with five response options each. Option 0 = normal, Option 1 = slight, Option 2 = mild, option 3 = moderate, and option 4 = severe. Walk and hand movement tests from UPDRS were also used to holistically evaluate rTMS treatment.

**Stages II and III, Hoehn and Yahr**

This scale classified into 8 stages, from 0-5 according to distribution unilateral or bilateral and severity. Stage 0 means that there are no
signs, stage 1 refers to the unilateral disease, stage 1.5 refers to unilateral disease with axial involvement, stage 2 refers to bilateral disease, with no balance impairment, stage 2.5 refers to mild bilateral disease, with recovery on pull test, stage 3 refers mild to moderate bilateral disease with some postural instability and physically independent, stage 4 refers to severe disability but still able to walk or stand without assistance and lastly, stage 5 refers to patients on Wheelchair or bed and need assistance unless aided

VI. Schwab and England Activities of Daily Living Scale
This scale classified into 11 stages, as following: 100% = Completely independent, 90% = Completely independent but start to be aware of difficulty, 80% = Completely independent in most tasks, 70% = Not completely independent, with difficulty in some tasks, 60% = Some dependency, 50% = More dependent, 40% = Very dependent, 30% = With effort, now and then does a few chores alone, 20% = Nothing done alone, 10% = totally dependent on others and 0% = Bedridden.

Statistical Methods
The differences among the conditions were assessed for the clinical scores of motor performance such as rigidity and bradykinesia. Quantitative variables were presented as mean and SD. Kolmogrove test was done to test normality. Parametric variables were compared between the studied groups using ANOVA test, followed by Scheffe test as post-hoc test & compared within groups using repeated measures ANOVA.

Non-parametric variables were compared between the studied groups using Kruskal Wallis test, followed by Dunn test as post-hoc test & compared within groups using Friedman test. Significance level used was 0.05 SPSS statistical package version 21 was used in data analysis

Results
Forty three patient were included in this study, group I (16) patients on medical treatment only, Group II (15) patients on medical treatment plus rTMS and Group III (12) patients on rTMS only.

Table 1 Demographic and clinical characteristics of the 3 groups of the patients

<table>
<thead>
<tr>
<th>Number</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>65.47</td>
<td>65.78</td>
<td>62.63</td>
<td>NS</td>
</tr>
<tr>
<td>Sex</td>
<td>11</td>
<td>9</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>Disease Duration</td>
<td>4.48</td>
<td>5.53</td>
<td>3.42</td>
<td>NS</td>
</tr>
<tr>
<td>L. Dopa</td>
<td>524.72</td>
<td>562.35</td>
<td>-</td>
<td>NS</td>
</tr>
<tr>
<td>Hoehn and Yahr</td>
<td>1.58</td>
<td>1.95</td>
<td>1.75</td>
<td>NS</td>
</tr>
<tr>
<td>Schwab and England</td>
<td>Mean</td>
<td>75.58</td>
<td>76.53</td>
<td>72.12</td>
</tr>
</tbody>
</table>

UPDRS, Unified Parkinson’s Disease Rating Scale

There was no significant difference across the three groups of treatment (I-II-III) regarding demographic and baseline clinical characteristics.

The baseline assessment has found no difference among the groups with respect to their demographic and baseline clinical characteristics. In general, patients participated in the study were diagnosed as moderately-to-severely affected by PD. On average, Hoehn and Yahr stage calculated to be 1.9 ±1.1, and the mean UPDRS at baseline was 36.1 ±13.4, Schwab and England score was 74.32 ±14.2, with mean disease duration of 7.1±5.0 years and mean L-dopa intake was 535.0 ±201.4 mg (Group I and II). Moreover, L-dopa dose in group II was not significantly greater than that in the group I. Similarly, clinical scale stage in group II was inferior but not significant than that of group I and III. rTMS treatment was well tolerated in both group II & III and there were no major adverse effects, only occurrence of mild transient headache in two patients. Our study focused on the motor disability due to PD but also demonstrated the impact of drugs alone, drugs with rTMS or rTMS alone in disease management.

Table 2 Follow up assessment of different improvement scales

<table>
<thead>
<tr>
<th>Number</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base Line</td>
<td>56.66</td>
<td>38.53</td>
<td>35.21</td>
<td>NS</td>
</tr>
<tr>
<td>UPDRS</td>
<td>14.14</td>
<td>11.59</td>
<td>13.92</td>
<td>S</td>
</tr>
<tr>
<td>After 1 month</td>
<td>18.95*</td>
<td>11.65*</td>
<td>20.55*</td>
<td>S</td>
</tr>
<tr>
<td>Hoehn and Yahr</td>
<td>1.58</td>
<td>1.95</td>
<td>1.75</td>
<td>NS</td>
</tr>
<tr>
<td>Schwab and England</td>
<td>73.58</td>
<td>76.53</td>
<td>72.12</td>
<td>NS</td>
</tr>
</tbody>
</table>

*significant in correlation to the base line

There was a significant difference (improvement) between ”before” assessment and ”immediately after rTMS course” assessment and ”before” evaluation and ”1 month after” evaluation in the groups II and III. However, slight decline in the rTMS beneficial influence after one month was observed, in correlation to the assessment performed immediately after rTMS. In group I the difference between base line compared to after antiparkinsonian medications and 1 month after measurements were significant.
To evaluate (global assessment), we conducted ANOVA with (Group I vs. Group II), all measurements (measurements before, immediately after, and 1 month after rTMS) revealed that there is a statistically significant difference (improvement) between before and after the treatment, and before and 1 month after the treatment. ANOVA for Group III vs. Group I revealed that there is no statistically significant difference in measurements (measurements before rTMS, immediately after rTMS, and one month after rTMS). Also, there is no statistically significant difference between immediately after rTMS measurement and 1 month after rTMS measurements in both comparisons: (Group II vs. Group I) and (Group III vs. Group I).

Discussion

In the present study there is significant difference (improvement) in groups II and III resulting from 15 Hz rTMS, between base line and immediately after rTMS course also, between base line and 1 month after rTMS, although there was a slight decrease (not significant) in score at 1 month after the rTMS in correlation to immediately after it. In group I the difference between base line compared to after antiparkinsonian medications and 1 month after it were significant. The comparison between Group I vs. Group II revealed a statistically significant difference (improvement) between base line and after the treatment, also after 1 month. But the comparison between (Group III vs. Group I), revealed a statistically no significant difference, between base line and immediately after, and also,1 month after rTMS. There was no statistically significant difference between immediately after treatment and 1 month after it in both comparison groups: (Group II vs. Group I) and (Group III vs. Group I). Because it was unethical to leave patients without taking their prescribed medications, so group III (12) patients were chosen from those patient still not on medicine or stop it.

Gonzalez-Garcia et al. 20 Using High frequency 25 Hz, 80% RTM over (M1) and occipital lobe , 15 sessions over 3 months showed significant improvement in UPDRS scale. Also, Kang et al. 30 showed significant improvement on High frequency 25 Hz,100% RTM, 22 sessions over M1. Khedr et al31, using high frequency 10/25 H z , 100% RTM, total of thirty six sessions, 6 daily sessions and over six days over bilateral M1 with significant improvement. Pal et al.32 using high frequency 5 Hz , 90% RTM, 10 sessions over 10 days DLPFC with significant improvement. Also, Khedr et al. 33 using High frequency 5 Hz, 120% RTM, 10 sessions over 10 days with significant improvement.

Kodama et al. 34 using Low frequency 0.9 Hz, 110% RTM, over M1 hand and M1 leg, 8 sessions over 2 months showed significant improvement. Rектор et al. 35 10 Low frequency 1 Hz, session 10 over DLPFC, also Arias et al. 36, using Low frequency 1 Hz, 90% RTM, 10 sessions over 10 days. A significant improvement in movement and speed of walking over 10 m was reported Ikuguchi et al.37 that used 0.2 Hz frequency over six successive sessions for 2 weeks.

Our study displayed a significant clinical improvement based on UPDRS motor score assessment. These results were nearly compatible with results reported by Kumar et al. for stimulation of unilateral subthalamic nucleus38. This study also emphasized the suggestion about the idea that under activated areas in PD patients can be modulated by high-frequency rTMS. 39Cumulative improvement in bradykinesia and gait was the major result of our study, where PD patients receiving rTMS and dopaminergic drugs witnessed significant improvement in the upper extremities. There is also a difference between the measurements done before rTMS course, immediately after rTMS, and 1 month after rTMS course. The improvement due to rTMS lasted to at least one month, as indicated in the present study.

The protocol followed in this study was different in terms of stimulation site, frequency and intensity than the one used in other studies, which reported changes in gait velocity and in finger tapping. 23,33. It is worth it to note before rTMS session, motor threshold for each participant was calculated. It is possible to have variability in stimulation intensity and may not be 90% of RMT over days, which is normal to happen across different sessions ad mentioned by Wassermann40. This was not the case in the study conducted on 18 PD patients by Lomarev et al.23 who observed no changes in the RMT in a 4-week period. Furthermore, prefrontal cortex area was highly affected by 80–115% of the RMT intensity. Thus, the possible individual RMT variability remains within this range. Our study delivered less number of stimuli than that required to impact depression in PD patients.41 Interestingly, studies that proved TMS influence on motor function improvement immediately after treatment are the ones that found a significant TMS long lasting effect,33,42 whereas two studies31,43 showed no significant motor function improvement either immediately after TMS or after one month. Therefore, the immediate improvement due to TMS course can predict its long lasting influence. Studies also discovered an increase in excitability of corticospinal functions of PD patients after single TMS session .For this reason, we noted the daily possible immediate TMS effect 19,43. Some studies evaluated much longer lasting impacts of rTMS, for instance evaluating patients for 2 months as done by Fregni et al44.

In order to related the effect to the real TMS impact, placebo effect should be contributed to, because Okabe et al.43 emphasized on the placebo role in such studies. So, to distinguish between TMS real and placebo effect, sham (placebo) stimulation was employed in 5 trials used a placebo coil.19,41,43,45,46 3 trials changed stimulation angle,21,33,16 1 trial stimulated at different site; occipital region.37 However, placebo effect is considered minimal in high-frequency rTMS trials. Even the studies that recruited active and placebo groups have displaced insignificant placebo effect of TMS. Okabe et al. 43 could not able to explain motor improvement in the active group by merely the effect of placebo.

It was shown that treatment of depression could be improved and prolonged by repeating rTMS sessions.47 Nevertheless, electrode implantation determine the best way to stimulate a specific cortical region. Recent studies provided evidence about the high effectiveness of chronic and unilateral stimulation of the motor cortex using implanted extradural electrodes in PD patients 48 and in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) lesioned monkeys.49 These results aid in developing clear therapeutic strategies to manage PD patients' motor
disability through cortical stimulation, and irrespective of the good implantation outcomes.

In our study 2 patients were suffered from mild headache and no seizure. Pal et al.32 using high frequency 5 Hz, 90%, 10 sessions over 10 days, Mild transient Headache reported. Also, Khedr et al.31 High frequency 10/25 Hz, 100% MT, thirsty six sessions, six sessions daily over six days a week, transient headache in some patients. When rTMS is performed based on safety guideline, patients will not be bothered with high-frequency adverse effects,20,50 knowing that rTMS can be easily applied and can complement PD medications.

The finding that cortical rTMS can induce release of subcortical dopamine31 has raised interest in this phenomenon as a potential mechanism for clinical benefits from rTMS in PD. In PD patients, Strafella et al.52 showed that 10-Hz rTMS over the M1 can release dopamine in mild hemiparkinsonian PD patients, and that the release is greater in the more affected hemisphere. A subsequent study demonstrated that sham rTMS in moderate PD patients also showed subcortical dopamine release,32 leading to uncertainties as to the significance of dopamine release by rTMS. A significant reduction of CSF homovanillic acid (HVA) was reported in PD patients who had received weekly sessions of 0.2-Hz rTMS over 3 to 4 months.53 Because HVA is a dopamine metabolite, this effect was interpreted as inhibiting the dopamine system (despite the observation that PD symptoms improved), a finding at odds with a dopamine release hypothesis.53 Khedr et al.54 recently reported an increase in serum dopamine levels immediately after 6 days of daily 25-Hz rTMS sessions over the M1, and the increase correlated with motor UPDRS scores. More studies are needed to investigate the validity and clinical significance of the rTMS dopamine release hypothesis.

Conclusion

The present study showed that motor symptoms manifested in PD patients can now be treated by high-frequency rTMS. It in non-invasive method and it depends on cortical stimulation to manage movement disorders. It has an added value in neuromodulation without exposure to surgical risks. Further studies such as randomized controlled trial are required to specify rTMS’s role in treating PD. These studies are also needed to optimize its parameters such as intensity and frequency, rTMS various responses on the different stages of PD and clarify rTMS influence on functions rather than the motor ones, as memory, gait and cognition. It is worth noting that rTMS utility is limited due to its high cost, limited availability at specialized centers, limited personnel's skills, and lack of knowledge regarding the long-term adverse/side effects.

References


43. Okabe S, Ugawa Y, Kanazawa I. 0.2-Hz repetitive transcranial magnetic stimulation has no add-on effects as compared to a realistic sham stimulation in Parkinson’s disease. Mov Disord 2003;18(4):382–8.


How to cite this article: