International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: 6.614
Available Online at www.journalijcar.org
Volume 7; Issue 12(D); December 2018; Page No. 16600-16606
DOI: http://dx.doi.org/10.24327/ijcar.2018.16606.3074

Research Article

NONINVASIVE BRAIN STIMULATION FOR PARKINSON'S DISEASE

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A R T I C L E I N F O

Article History:
Received 06th 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.

A B S T R A C T

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 PD is controversial since subsequent studies show contradictory results. The most common adverse events are transient headaches and scalp discomfort. The aim of this work is to evaluate the effect of high frequency (15 Hz) of rTMS in the motor functions in a group of patients with PD. **Patients and Methods**: Forty three patients with Parkinson's Disease (15 women and 28 men) aged from 51 to 76 years (mean 64 ± 8.2) were included in this study. 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 TMS. Group III (12) patients were chosen from those patient still not on medicine or stop it. Stimulation was delivered using a frequency of 15 Hz and stimulation intensity of 10% above motor threshold (MT) for 10 daily sessions. At each session, a train of 75 stimuli was delivered for 5 s followed by a 10-s interval. A total of 40 trains were delivered in each session, resulting in a total number of 3000 pulses per day. The assessment before and immediately after TMS sessions included a clinical evaluation by by mean of the motor section (part III) of the Unified Parkinson's Disease Rating Scale (UPDRS) , Schwab and England and Hoehn and Yahr scales. Reevaluation was performed after1 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 difference between immediately after treatment and 1 month after it in Both (Group II vs. Group I) and (Group III vs. Group I), were not statistically significant. **Conclusion:** Our results showed that high-frequency TMS is a promising treatment of motor symptoms in PD. Future studies are also needed to clarify the optimal stimulation parameters, how the different stages of PD affect the response to TMS, and the effects of TMS on other aspects of the disease such as gait, cognition, and memory.

INTRODUCTION

Parkinson's disease (PD) is a chronic, degenerative disease that shows a fast progression rate in the early phase of PD and that slows in the later phase of the disease[1].

Advances since the 1960s have mechanisms as contributing to the pathophysiology of movement disorders, such as depletion of neurotransmitters (e.g., dopamine), altered network loops between the basal ganglia and cortical targets, and abnormal cortical plasticity[2].

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Based on the concepts involved, a wide range of current treatment options have been developed, including medications, botulinum toxin, and deep brain stimulation (DBS)[3,4]. In spite of such advances, limitations in current therapies remain. Dopamine replacement medications are an effective cornerstone of current medical management of PD, particularly for motor symptoms[5] but later, the response declines and complications develop. [6] 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 induced more dyskinesias during the 2-year follow-up.[7]

Since transcranial magnetic stimulation (TMS) was introduced by Barker *et al*. in 1985 it has become a safe, noninvasive, and painless way to study the central nervous system.[8] TMS has been investigated as a potential therapy for numerous conditions, including depression, epilepsy, migraine, and PD. [9,10,11] However, a real efficacy of TMS on motor cortex in PD is controversial since subsequent studies show contradictory results.[12] TMS a non-invasive means of stimulating neurons in the human cerebral cortex, is able to modify neuronal activity locally and at distant sites when delivered in series or trains of pulses.[13] Previous studies have demonstrated the potential modulatory effects of repetitive transcranial magnetic stimulation (rTMS) on the excitability of cortical neurons[14] and this effect depends on the parameters used in the stimulation such as intensity, frequency, site of stimulation, and can last beyond the duration of the rTMS.[15] 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),[16] also, induce dopamine release in the ventrolateral putamen and caudate.[17] 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 more focal figure-8 coils which also provide the ability to target specific cortical regions. [18]

The Motor cortex stimulation (M1) is a key cortical target for the motor cortical subcortical loop.[19,20] The prefrontal dorsolateral cortex (DLPFC) stimulation may be specific for depression, rather than for motor symptoms.[21] Premotor cortex (SMA) stimulation as a cortical target is effective butits location makes it a difficult noninvasive cortical target.[22,23]

The sham rTMS (placebo-rTMS) was applied in the same conditions with the coil elevated and angled away from the head (90 degree) to reproduce the subjective sensation of rTMS. Active or true rTMS, the coil was held tangentially to the patients' head surface over the left motor cortex with the handle of the coil pointing occipitallyl. [24]

TMS is generally safe, noninvasive procedures with minimal adverse effects. The most common are transient headaches and scalp discomfort. Scalp pain and headaches are thought to be due to activation of scalp pericranial muscles. However, more severe adverse effects may include mood changes (induction of mania), scalp burns from electrodes, and induction of seizures.[25] Because rare seizures have been associated with prolonged trains of high-frequency rTMS at high intensities. Seizures during TMS are thought to be a result of cortical pyramidal cell activation, spread of excitation to neighboring neurons, and overwhelming of inhibitory mechanisms. [26]

PATIENTS AND METHODS

Forty three patients (15 women and 28 men) aged from 51 to 76 years (mean 64 ± 8.2) were included in this study. All these patients fulfilled the UK Parkinson's Disease Brain Bank criteria for idiopathic PD.[26] and suffered from a 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 (because it was not ethical to keep patients unmedicated for several days).

Patients with permanent rest tremor were excluded from the study because of their impossibility to maintain a complete relaxation of hand muscles, precluding a reliable determination of the rest motor threshold. Other exclusion criteria were a past personal history of seizure, ferromagnetic metallic implants, major head trauma, dementia or depression with psychotic symptoms. All patients remained stable on their regular antiparkinsonian medications as prescribed by their treating physicians and gave their written informed consent for the study. Patients were examined 12 h after an overnight withdrawal of anti-parkinsonian medication, i.e. in 'off-drug' condition (no patient was treated by long-acting dopaminergic agonists). First, motor performance was assessed clinically and TMS parameters of motor cortex excitability. Second, dopa intake and rTMS, were performed. Twenty minutes after the end of the rTMS sessions, clinical motor evaluation were done. Evaluation after dopa intake was performed in the earliest best-on condition according to the patients (usually 30-60 min) after drug administration. The assessment before and immediately after rTMS sessions included a clinical evaluation by mean of the motor section (part III) of the Unified Parkinson's Disease Rating Scale (UPDRS), Schwab and England and Hoehn and Yahr scales which mainly focuses on the parameters of waking, rigidity and fast alternating movement on both the upper and lower extremities. Reevaluation was performed after1 months.

***Repetitive transcranial magnetic stimulation** (rTMS)*

The order of the rTMS interventions was randomised across patients, and a figure-of-eight stimulating coil were used to activate the left motor cortical area corresponding to the right first dorsal interosseus (FDI) muscle. The coil was held tangentially to the patients' head surface over the left motor cortex with the handle of the coil pointing occipitally. Using this orientation, the current induced in the brain flows perpendicular to the line of the central sulcus. [24] The coil was moved to determine the optimal position for eliciting of maximal amplitude in the right FDI muscle, i.e. the 'motor hot spot'. When the motor hot spot was found, the stimulation coil was fixed with a device to maintain the same location throughout the experiment. Stimulation was delivered using a frequency of 15 Hz and stimulation intensity of 10% above motor threshold (MT). The treatment protocol consisted of 10 daily sessions during a 11-days period (start at Saturday and off Friday). At each session, a train of 75 stimuli was delivered for 5 s followed by a 10-s interval. A total of 40 trains were delivered in each session, resulting in a total number of 3000 pulses per day.[28] The equipment used was a Neurostartranscranial magnetic stimulator - USA.

Unified Parkinson's Disease Rating Scale

We use III part (motor Examination), 14 questions. All items have five response options with uniform anchors of 0 = normal, 1 = slight, 2 = mild, 3 = moderate, and 4 = severe. To evaluate the whole course of rTMS treatment, the UPDRS, a walk test, and a complex hand movement test were also done.

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 = No

signs of disease. Stage 1 = Unilateral disease. Stage 1.5 = Unilateral plus axial involvement. Stage 2 = Bilateral disease, without impairment of balance. Stage 2.5 = Mild bilateral disease, with recovery on pull test. Stage 3 = Mild to moderate bilateral disease; some postural instability; physically independent. Stage 4 = Severe disability; still able to walk or stand unassisted. Stage 5 = Wheelchair bound or bedridden unless aided.

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

Statistical Methods

The variations among the conditions were assessed for the clinical scores of motor performance (rigidity and bradykinesiaquantative 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 Schefee 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 0.05SPSS 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

		Group I	GroupII	Group III	p-value
Number		**16**	**15**	**12**	
Age	Main	63.47	65.76	62.63	
	SD	4.75	8.73	6.25	*NS*
Sex	Male	11	9	8	
	Female	5	6	4	*NS*
Disease Duration	Main	6.72	8.80	5.33	
	SD	4.48	5.53	3.42	*NS*
L Dopa Use	Main	524.72	562.33	-	*NS*
	SD	193.12	174.66	-	
UPDRS	Mean	36.66	38.53	35.21	
	SD	14.54	15.10	13.92	*NS*
Hoehen and yahr	Mean	1.58	1.95	1.75	
	SD	0.89	1.02	1.13	*NS*
Schwab and England	Mean	73.58	76.53	72.12	
	SD	15.83	18.62	16.04	*NS*

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.

At the base line of our study, there was no difference between the groups in their demographic and baseline clinical characteristics. Taken as a whole, patients were moderately-to-severely affected by PD. On average, Hoehn and Yahr stage was 1.9 (±1.1), mean UPDRS baseline was 36.1 (±13.4), Schwab and England 74.32 (±14.2), mean duration of disease was 7.1 (±5.0) years and mean L-dopa use was 535.0 (±201.4) mg (Group I,II) Also, the dose of levodopa in the group II was not significantly higher than that in the group I. Similarly, Clinical scale stage of the group II was worse 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. In our study, we focused on the motor disability caused by the disease and influenced by drugs, drugs plus rTMS or rTMS alone.

Table 2 Follow up assessment of different improvement scales

		Group I	GroupII	Group III	p-value		
Number		**16**	**15**	**12**	**I& II**	**I& III**	**II& III**
UPDRS	Base Line	36.66 ± 14.54	38.53 ±15.10	35.21 ±13.92	*NS*	*Ns*	*NS*
	After session	18.41* ±11.93	13.15* ±12.34	22.35* ±10.85	*S*	*Ns*	*S*
	After 1 month	18.95* ±10.22	11.65* ±10.88	20.55* ±9.65	*S*	*Ns*	*S*
Hoehen and yahr	Base Line	1.58 ±0.98	1.95 ±1.02	1.75 ±1.13	*NS*	*Ns*	*NS*
	After session	0.82* ±0.93	0.55* ±0.98	0.95* ±0.69	*S*	*Ns*	*S*
	After 1 month	0.75* ±0.91	0.48* ±0.95	0.89* ±0.67	*S*	*Ns*	*S*
Schwab and England	Base Line	73.58 ±15.83	76.53 ±18.62	72.12 ±16.04	*NS*	*Ns*	*NS*
	After session	40.35* ±13.72	25.13* ±15.46	45.23* ±13.93	*S*	*Ns*	*S*
	After 1 month	41.60* ±12.21	26.12* ±14.93	44.33* ±12.98	*S*	*Ns*	*S*

*significant in correlation to the base line

In the groups II and III, the difference (improvement) between before and immediately after rTMS course and before and 1 month after measurements were significant Although there was a slight decrease in the rTMS beneficial effect at 1 month after the treatment measurement in correlation to 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), date factor (measurements before, immediately after, and 1 month after rTMS. revealed a statistically significant difference (improvement) between before and after the treatment, and before and 1 month after measurements. (Group III vs. Group I), revealed a statistically no significant difference, date factor (measurements before, immediately after, and 1 month after rTMS. The difference between immediately after and 1 month after measurements in Both (Group II vs. Group I) and (Group III vs. Group I), were not statistically significant.

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. The difference between immediately after treatment and 1 month after it in Both (Group II vs. Group I) and (Group III vs. Group I), were not statistically significant. Because it was not ethical to keep patients unmedicated for several days, so group III (12) patients were chosen from those patient still not on medicine or stop it.

Gonzalez-Garcia *et al*.[29] 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 al*[31]. Using high frequency 10/25 Hzs, 100% RTM, 36 sessions, 6 sessions per day for 6 days over bilateral M1with 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. Rektor *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. Ikeguchi *et al*.[37] using 0.2 Hz in 6 successive sessions for 2 weeks showed a significant improvement in pronation- supination movements, buttoning up task and a increase in speed of walking over 10 m.

As assessed on UPDRS motor score, the clinical improvement obtained by motor cortex stimulation in the present study was significant and not far from the results, which were reported for unilateral subthalamic nucleus stimulation Kumar *et al*.[38]. Our study supports the hypothesis that high-frequency rTMS can modulate underactive brain regions in PD patients.[39] The principal finding of this study was a cumulative improvement of gait and bradykinesia in the upper extremities as an apparent consequence of real rTMS in PD patients taking optimal dopaminergic medications. The difference between the measurements done before rTMS course, immediately after, and 1 month after rTMS course. This finding indicates that the rTMS effect (improvement) lasted for at least 1 month after the end of treatment.

Although other studies have reported changes in gait velocity and in finger tapping after rTMS,[23,33] the protocol of stimulation used is different in the frequency, intensity, number of delivered stimuli, and the stimulated area. We have to note that the individual motor threshold was calculated before beginning the rTMS sessions. It is possible that the intensity used for rTMS was not exactly 90% of RMT for each day, since Wassermann[40] reported important variability in the RMT in normal subjects across different sessions. However, Lomarev *et al*.[23] have not reported significant changes in the RMT in a group of 18 PD patients in a period of 4 weeks. Furthermore, intensity in the range of 80-115% of the RMT seems effective in affecting the prefrontal cortex. Thus, the possible variability of the individual RMT is not higher than the range cited. The number of delivered stimuli in our study was lower than that considered efficient in the treatment of depression in patients with PD.[23] Interestingly, the studies that showed a significant long lasting effect were those that showed a significant effect of TMS on motor function immediately after treatment,[33,42] whereas the other two studies[41,43] did not show significant motor change either immediately after TMS or at the follow up. This finding suggests that an immediate motor benefit after TMS, when present, is predictive of a long lasting effect. The daily control of a possible immediate effect of the TMS was considered since other studies show a motor improvement and increase in corticospinal excitability after a single session of rTMS over the motor cortex of parkinsonian patients[19,43] some studies evaluated the long lasting effects of rTMS, Fregni *et al*[44] which evaluated patients 2 months after treatment.

The authors attribute this improvement after TMS to the real effect of TMS although Okabe *et al*.[43] showed that this can be clearly attributed to a placebo effect. So, several different methods of sham (placebo) stimulation were used to evaluate between both real and placebo effect. Five trials used a sham coil,[19,41,43,45,46] three studies used changes in coil angle,[2133,16] one study stimulated the occipital area,[37] However, the findings from high-frequency rTMS studies are consistent and the effects of this variability are likely to be small. For the studies that used active and sham control groups, such as that by Okabe *et al*.[43] This analysis disclosed that there was a small placebo effect which was not significant, and the motor improvement observed in the active group cannot be explained by a placebo effect only.

By repeating rTMS sessions, the clinical effects could be enhanced or prolonged, as it was shown for the treatment of depression.[47] Nevertheless, the best way to stimulate a targeted cortical area remains to implant electrodes. Recently, promising clinical effects were obtained by chronic, unilateralstimulation of the motor cortex using implanted extraduralelectrodes in patients with PD.[48] and in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) lesioned monkeys, the primate model of PD.[49] Even if rTMS effects are not necessarily predictive of a good outcome of an implanted cortical procedure, the present results gave some clues to guide the development of original therapeutic strategies using cortical stimulation to control motor disability in PD.

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*.[32] High frequency 10/25 Hz, 100% MT, 36 sessions, 6 sessions per day for 6 days, transient headache in some patients. Although high-frequency rTMS has potential adverse effects, including induction of seizures, it is generally safe when used within safety guidelines.[40,50] It is well tolerated, easy to apply, and can be used as an adjunct to other treatment modalities in PD patients.

The finding that cortical rTMS can induce release of subcortical dopamine[52] 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,[52] 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

Our results showed that high-frequency rTMS is a promising treatment of motor symptoms in PD. Repetitive transcranial magnetic stimulation (rTMS)) are promising noninvasive cortical stimulation methods for adjunctive treatment of movement disorders. They avoid surgical risks and provide theoretical advantages of specific neural circuit neuromodulation. A large, randomized controlled trial with appropriate follow-up will be useful to further define its role in the treatment of PD. Future studies are also needed to clarify the optimal stimulation parameters, how the different stages of PD affect the response to rTMS, and the effects of rTMS on other aspects of the disease such as gait, cognition, and memory..Some of the factors that limit wide spread clinical use of therapeutic rTMS are the cost and limited availability of the devices to specialized centers, less knowledge of potential long-term side effects compared with drug therapies, and the requirement for skilled personnel.

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How to cite this article:

Osama E. El Dib *et al* (2018) 'Noninvasive Brain Stimulation for Parkinson's Disease', *International Journal of Current Advanced Research,* 07(12), pp. 16600-16606. DOI: http://dx.doi.org/10.24327/ijcar.2018.16606.3074

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