ISSN (Print) 1226-1750
ISSN (Online) 2233-6656
Journal of Magnetics 25(1), 105-109 (2020) https://doi.org/10.4283/JMAG.2020.25.1.105

The Effect of High Frequency Repetitive Transcranial Magnetic Stimulation on Gait and Balance in Parkinson's Patients: A Randomized Controlled Trial

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(Received 31 January 2020, Received in final form 29 February 2020, Accepted 2 March 2020)

This study was conducted to investigate the effects of high frequency repetitive transcranial magnetic stimulation (rTMS) on walking and balance in Parkinson's patients. Fifteen subjects were randomly assigned to the experimental and control groups, and high-frequency rTMS was applied to the experimental group for 20 minutes per day, 5 times a week for a total of 4 weeks. The gait speed of the subject was evaluated by 10MWT, and the dynamic and static balance was evaluated using TUG and BBS. In the experimental group, significant improvement was observed in 10MWT, TUG, and BBS after intervention ($p < 0.05$), and there was significant improvement in 10MWT and BBS compared to the control group ($p < 0.05$). The results of this study suggest that high frequency rTMS applied to primary motor cortex (M1) positively affects walking and balance in Parkinson's patients.

Keywords : balance, gait, high frequency repetitive transcranial magnetic stimulation, Parkinson

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease caused by dopamine secretion disorder, resulting in motor and non-motor symptoms [1]. It is estimated that between 6 million and 10 million PD patients worldwide, regardless of race and ethnicity, the prevalence of PD is expected to more than double by 2030 due to population growth [2].

The dyskinesia of PD is due to the degeneration of dopaminergic neurons in the substantia nigra pars compacta, which causes functional defects in several brain regions such as basal ganglia and cerebral cortex [3]. Four major symptoms of PD include resting tremor, rigidity, bradykinesia, and postural instability. In particular, gait disorder is one of the most uncomfortable symptoms of PD patients [4]. PD patients tend to have shorter stride lengths than normal adults and to increase cadence to compensate [5]. It also shortens the swing phase and causes problems with symmetry and timing of gait [6]. Mild PD patients have more physical activity and better balance than severe PD patients, but they also have a higher risk of falling. Therefore, improving balance and walking ability is an important goal in the rehabilitation of PD patients [7].

In the early stages of PD, dopamine treatment is effective for improving motor symptoms, but over time, the response to treatment decreases [8]. Since deep brain stimulation surgery is known to not improve the gait and balance disorders of PD patients, alternative therapies such as repetitive transcranial magnetic stimulation (rTMS) have attracted much attention [9].

rTMS is a non-invasive brain stimulation tool for interventional neurophysiology applications that requires no surgery or anesthesia [10]. rTMS creates a magnetic field, which passes through the skull to induce electric currents in the brain. This induced current activates neurons or causes synaptic plasticity [11]. rTMS produces an excitation or inhibition effect mainly through the regulation of frequency, which has the advantage that the effect persists even after the stimulus is finished. High frequency rTMS (≥ 5 Hz) promotes cortical excitability, while low frequency rTMS (≤ 1 Hz) reduces cortical excitability. The most common side effects reported are headaches, but they are not severe. Because seizures have often been reported as side effects, it is safer to raise the frequency

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rather than the intensity of the stimulus [12]. rTMS includes a TMS pulse train that lasts from seconds to minutes, which can sustain longer changes in neuronal activity than single pulse TMS [13]. This lasted effect of rTMS has several hours in a single session and several months in repeated sessions, and thus has an advantage as a treatment for neurological disorders [14]. rTMS has a long-term potentiation and a long-term depression action. The long-term potentiation is to change the silent synapse into an active synapse in postsynaptic membrane and long-term depression is to change an active synapse into the silent synapse. These actions cause neuroplasticity [15].

Many previous studies have reported improvements in hand and gait in PD patients after applying high frequency rTMS to primary motor cortex (M1) [16, 17]. Previous studies that applied rTMS to dorsolateral prefrontal cortex (DLPFC) in PD patients showed a positive effect on depression, and another study reported a positive improvement in motor symptoms [18, 19]. In the meta-analysis, the Unified Parkinson's Disease Rating Scale (UPDRS) scores showed significant effects when high frequency rTMS was applied to M1 and when low frequency rTMS was applied to other frontal regions [20]. Previous studies comparing the application of high frequency rTMS and low frequency rTMS to SMA showed a significant effect when applying low frequency rTMS [21].

In the previous studies, the application of rTMS for motor symptoms or non-motor symptoms was different from the brain region and rTMS application parameters. In particular, there were not many studies that applied rTMS to Parkinson's patients. Therefore, the purpose of this study was to investigate the effects of walking and balance in Parkinson's patients through the application of high frequency rTMS, which promotes the excitability of the cerebral cortex, over the area of the M1 which is selected for the improvement of motor symptoms.

2. Materials and Methods

2.1. Participants

This study was performed on 15 patients with PD admitted to a hospital. The inclusion criteria for selection were as follows: diagnosed with Parkinson's disease, without severe cognitive impairment (Mini-Mental State Examination score of 18 points or more), being at stages II–IV according to the criteria of Hoehn and Yahr during OFF periods, and independent walking with/without using aids.

The exclusion criteria for selection were as follows: previous experience with rTMS, history of seizures, implanted devices, taking antidepressant medication, and other orthopedic diseases [18]. Written informed consent according to the ethical standards of the Declaration of Helsinki was provided by all subjects prior to participation. Informed consent was obtained from all patients after sufficient explanation of the procedures.

2.2. Study design

Subjects were randomly assigned to experimental and control groups using a computer draw program. All subjects received treadmill training in common, and after treadmill training, experimental group (n = 8) received real rTMS and control group (n = 7) received sham rTMS. The rTMS intervention was conducted for 20 minutes at a time, five times a week for a total of four weeks. Until the study was completed, all subjects were blind to the group to which they were assigned.

2.3. Intervention

2.3.1. Repetitive Transcranial Magnetic Stimulation (rTMS)

Experimental group underwent 10 Hz rTMS using the Magstim Rapid2 (Magstim Co Ltd, Wales, United Kingdom) and a figure-of-eight coil with a diameter of 70 mm was used. Patients received rTMS at the same time each day, about 1 to 2 hours after dopamine, with treadmill training first followed by rTMS. rTMS was applied to the M1 area based on the International 10-20 EEG system to stimulate both lower extremities, with the handle of the coil parallel to the interhemispheric midline as used as used by Khedr *et al.* [22]. Applying the handle of the coil in parallel to the interhemispheric midline can activate the motor cortex through preferential recruitment of cortical interneurons and activating the pyramidal tract indirectly [23]. rTMS applied 10 Hz (50 magnetic pulses) with inter-train intervals of 10 s, over 20 minutes. The intensity was set at 100 % of the individual's resting motor threshold (RMT). RMT is the lowest stimulation intensity that induced 10 stimuli to induce more than 5 motor-evoked potentials, assessed in the first dorsal interosseous muscle.

Two coils were used for the sham rTMS: one coil that was not connected to the stimulator was placed over M1, and another coil that was connected to the stimulator but tilted 90 degrees above the first coil. Thus, the patient could hear the same sound of real rTMS but had no effect on the brain.

2.4. Outcome measure

In this study, the gait speed was evaluated by 10 meter walking test. The timed up and go test was used to assess the dynamic balance and mobility, and the berg balance scale was used to assess the ability to balance of subjects.

All measurements were performed before rTMS intervention and after rTMS intervention for 4 weeks.

2.4.1. 10 Meter Walking Test (10MWT)

The 10MWT was used to measure the straight walking ability, and under the measurer's observation, the subject was instructed to walk a total of 14 meters safely as faster as possible. The time taken to walk the remaining 10 m except for the first acceleration section 2 m and the last deceleration section 2 m was measured [24]. The time was recorded by a stopwatch. After repeated measurements three times, the average value was used as data.

2.4.2. Timed Up and Go (TUG) test

TUG test was used to assess dynamic balance and mobility of subjects. TUG test got up from a chair without armrests, walked 3 m, then came back and measured the time to sit on the chair. The chair used in the experiment was a chair with a backrest and moved to the less affected side for turning. Subjects could use their usual mobility aids for TUG testing. As a result of TUG test, less than 10 seconds means functional independence, and more than 30 seconds means high functional dependency [25].

2.4.3. Berg Balance Scale (BBS)

BBS was used to assess the ability of subjects to balance. It consists of static and dynamic balance tasks of varying difficulty. The BBS consists of a total of 14 functional activities, and each item can be scored from 0 to 4 points. A 0 indicates that the task cannot be performed, and a 4 indicates that the task can be performed independently. The maximum score is 56 points and the higher score means the better function [26].

Differences in general characteristics between the experimental group and the control group before intervention were compared using the Mann-Whitney tests and chi-square tests. The Wilcoxon signed-rank tests were performed to assess the before and after effects in each group. The Mann-Whitney tests were used to assess differences between real rTMS and sham rTMS. For all analyses, p values < 0.05 were considered significant. Data were expressed as the mean ± standard deviation (SD) and statistical analysis was performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA).

3. Results

Table 1 summarizes the general and medical characteristics of the subjects. There were no statistically significant differences between the 2 groups. The values of 10MWT, TUG test and BBS of the experimental and control groups are summarized in Table 2. There were significant differences between the two groups in 10MWT and BBS score ($p < 0.05$). The experimental group was significantly different before and after the test in all variances ($p < 0.05$), and the control group was significantly different before and after the test in the BBS score ($p < 0.05$).

Table 1. General and medical characteristics of subjects.

	EG (n = 8)	CG (n = 7)
Age (years)	66.8 ± 8.5[a]	67.63 ± 9.23
Sex (male/female)	4/4	4/3
Duration (month)	4.56 ± 1.21	3.89 ± 1.38
Weight (kg)	71.63 ± 7.47	68.423 ± 9.39
Height (cm)	171.93 ± 6.83	169.41 ± 8.38

[a]Mean ± SD, EG: rTMS + Treadmill training, CG: rTMS (shame Therapy + Treadmill training

Table 2. Comparison of change in characteristics of the experimental group and control group.

	EG (n = 8)	CG (n = 7)	z	p
Gait speed (m/s)				
Pre-test	.95 ± .03	.91 ± .05	1.94	0.07
Post-test	.25 ± .03	.86 ± .05	−29.83	0.00
z	39.86	1.61		
p	0.00	0.15		
Time up go test (sec)				
Pre-test	21.68 ± 2.95	22.98 ± 5.23	−0.60	0.55
Post-test	17.20 ± 1.18	21.13 ± 6.35	−1.73	0.10
z	3.98	0.67		
p	0.01	0.52		
Berg balance scale (score)				
Pre-test	36.63 ± 1.92	35.86 ± 2.91	0.61	0.55
Post-test	43.75 ± 2.38	38.71 ± 1.25	5.01	0.00
z	−7.33	−2.82		
p	0.00	0.03		

[a]Mean ± SD, EG: rTMS + Treadmill training, CG: rTMS (shame Therapy + Treadmill training

4. Discussion

This study was conducted to investigate the effect of high frequency rTMS on gait and balance in Parkinson's patients. As a result, in the gait speed test with 10MWT, the experimental group had a significant effect before and after the test and there was a significant difference between the groups. The TUG test to determine the dynamic balance and mobility had a significant effect before and after the test only in the experimental group. In addition, the BBS for evaluating the balance had a significant effect before and after the test in both the experimental group and the control group, but there was a significant difference between the groups.

In this study, we investigated the effects of motor symptoms that cause many difficulties in daily life among the problems of PD patients. Previous studies applying rTMS to PD patients have shown benefits for motor function. In particular, meta-analysis showed the effect of high-frequency rTMS on PD's motor function [27]. In addition, in a systematic review, the results of the UPDRS-III demonstrated the therapeutic effect of rTMS on motor symptoms in PD patients [28].

In this study, 10MWT was used to evaluate gait among the motor symptoms of PD patients, and the positive effect was obtained by applying rTMS. Many studies have shown positive results in gait using high frequency rTMS. Previous study applying high frequency rTMS to brain injury patients has shown significant effects on gait. In that study, 5 Hz rTMS was applied to the M1 leg and showed significant effects on gait speed and self-assessment scale [29]. Lomarev *et al.* applied high-frequency rTMS (25 Hz) to subjects bilateral M1 and DLPFC once a week for a total of 8 weeks and showed significant effects in gait and bradykinesia. These results were presumed to be the result of long-term potentiation and reformation of the circuits [30].

In this study, the results of TUG and BBS showed that the application of high frequency rTMS improves the dynamic and static balance of PD patients. In previous study, a combination of treadmill training and high-frequency rTMS in 20 patients with brain injury showed improvement in walking speed and dynamic balance [31]. Previous pilot studies that 5 Hz high frequency rTMS applied to patients with vascular parkinsonism for 5 consecutive days, showed a decrease in TUG time and improvement in UPDRS-III [32]. In addition, a pilot study of patients with atypical parkinsonism showed significant effects in turn step, TUG, and UPDRS-III after applying 10 Hz high frequency rTMS. In that study, rTMS was applied to the M1 region as in this study [33].

Although the previous studies mentioned above included subjects with both brain lesions and PD patients, high frequency rTMS was used to show positive effects on motor symptoms such as gait and balance. According to meta-analysis, most high frequency rTMS studies reported using 8-shaped coils for higher precision stimulation of target stimuli, and more than 50 % of high frequency rTMS studies selected M1 as the target area as in this study. Furthermore, after the rTMS intervention sessions, they reported an improvement in exercise for an average of six weeks [34].

rTMS enhances signaling of brain-derived neurotrophic factor (BDNF) and induces synaptic plasticity by increasing N-methyl-D-aspartate (NMDA) receptors. As a result, neural circuits are remodeled within the central motor pathway [35]. According to previous studies using functional magnetic resonance imaging, this remodeling resulted in a change in functional connectivity during the resting state. These results indicate that rTMS applied to primary motor area (PMA) reduces the connectivity between PMA and other brain regions [36]. Antczak *et al.* concluded that decreased connectivity with other brain regions increases the descending output of the motor cortex and the function of the pyramidal tract [37].

The limitation of this study is that it is difficult to generalize due to the small number of subjects, the test period is short, and the follow-up has not been followed. In future research, it is necessary to observe the effects of various brain stimulation sites and frequencies of various rTMS on motor symptoms in PD patients.

This study was conducted to investigate the effect of high frequency rTMS applied to the M1 region of the brain on gait and balance in PD patients. In order to examine the effect of rTMS, high frequency rTMS was applied to the experimental group for 4 weeks.

As a result, the experimental group showed significant difference between before and after intervention in 10MWT for evaluating gait speed and TUG and BBS for evaluating dynamic and static balance. In addition, the experimental group in 10MWT and BBS was significantly different compared to the control group.

Therefore, we suggest the application of high-frequency rTMS to the M1 region is effective in improving gait speed, dynamic and static balance in PD patients.

References

[1] J. Jankovic, J. Neurol. Neurosurg. Psychiatry. **79**, 368 (2008).

[2] E. R. Dorsey, R. Constantinescu, and J. P. Thompson, Neurology **68**, 384 (2007).

[3] A. E. Lang and A. M. Lozano, N. Engl. J. Med. **339**, 1044 (1998).

[4] G. Alves, E. B. Forsaa, and K. F. Pedersen, J. Neurol. **255**, 18 (2008).

[5] O. Henmi, Y. Shiba, and T. Saito, J. Phys. Ther. Sci. **21**, 105 (2009).

[6] R. Baltadjieva, N. Giladi, and L. Gruendlinger, Eur. J. Neurosci. **24**, 1815 (2006).

[7] H. Nakae nd H. Tsushima, J. Phys. Ther. Sci. **3**, 509 (2011).

[8] H. Braak, K. Del Tredici, U. Rub, R. A. I. De Vos, E. N. H. J. Steur, and E. Braak, Neurobiol. Dis. **24**, 197 (2003).

[9] A. Wagle Shukla and M. S. Okun, Neurotherapeutics **11**, 47 (2014).

[10] F. Fregni, S. Freedman, and A. Pascual-Leone, Lancet. Neurol. **6**, 188 (2007).
[11] A. V. Chervyakov, A. Y. Chernyavsky, D. O. Sinitsyn, and M. A. Piradov, Front. Hum. Neurosci. **9**, 303 (2005).
[12] P. M. Rossini, D. Burke, R. Chen, L. G. Cohen, Z. Daskalakis, R. Di Iorio, V. Di Lazzaro, F. Ferreri, P. B. Fitzgerald, M. S. George, M. Hallett, J. P. Lefaucheur, B. Langguth, H. Matsumoto, C. Miniussi, M. A. Nitsche, A. Pascual-Leone, W. Paulus, S. Rossi, J. C. Rothwell, H. R. Siebner, Y. Ugawa, V. Walsh, and U. Ziemann, Clin. Neurophysiol. **126**, 1071 (2015).
[13] R. Chen, D. Cros, A. Curra, V. Di Lazzaro, J. P. Lefaucheur, and M. R. Magistris, Clin. Neurophysiol. **119**, 504 (2008).
[14] N. Zhen and C. Robert, Transl. Neurodegener. **4**, 22 (2015).
[15] H. R. Siebner, N. Lang, and V. Rizzo, J. Neurosci. **24**, 3379 (2004).
[16] T. Maruo, K. Hosomi, T. Shimokawa, H. Kishima, S. Oshino, S. Morris, Y. Kageyama, M. Yokoe, T. Yoshimine, and Y. Saitoh, Brain. Stimul. **6**, 884 (2013).
[17] M. Brys, M. D. Fox, S. Agarwal, M. Biagioni, and G. Dacpano, Neurology **87**, 1907 (2016).
[18] E. Pal, F. Nagy, Z. Aschermann, E. Balazs, and N. Kovacs, Mov. Disord. **25**, 2311 (2010).
[19] M. F. del Olmo, O. Bello, and J. Cudeiro, Clin. Neurophysiol. **118**, 131 (2017).
[20] Y. H. Chou, P. T. Hickey, M. Sundman, A. W. Song, and N. K. Chen, JAMA. Neurol. **72**, 432 (2015).
[21] Y. Shirota, H. Ohtsu, M. Hamada, H. Enomoto, and Y. Ugawa, Neurology **80**, 1400 (2013).
[22] E. M. Khedr, H. M. Farweez, and H. Islam, Eur. J. Neurol. **10**, 567 (2003).
[23] J. P. Lefaucheur, N. André-Obadia, A. Antal, S. S. Ayache, C. Baeken, D. H. Benninger, R. M. Cantello, M. Cincotta, M. de Carvalho, D. De Ridder, H. Devanne, V. Di Lazzaro, S. R. Filipović, F. C. Hummel, S. K. Jääskeläinen, V. K. Kimiskidis, G. Koch, B. Langguth, T. Nyffeler, A. Oliviero, F. Padberg, E. Poulet, S. Rossi, P. M. Rossinic, J. C. Rothwell, C. Schönfeldt-Lecuona, H. R. Siebner, C. W. Slotema, C. J. Stagg, J. Valls-Sole, U. Ziemannl, W. Paulus, and L. Garcia-Larrea, Clin. Neurophysiol. **125**, 2150 (2014).
[24] K. W. Nam, J. C. Go, and Y. P. Yang, J. Korean Soc. Phys. Med. **14**, 35 (2019).
[25] D. Podsiadlo and S. Richardson, J. Am. Geriatr. Soc. **39**, 142 (1991).
[26] K. O. Berg, S. L. Wood-Dauphinée, and J. I. Williams, Physiother. Can. **41**, 304 (1989).
[27] F. Fregni, D. K. Simon, A. Wu, and A. Pascual-Leone, J. Neurol. Neurosurg. Psychiatry. **76**, 1614 (2005).
[28] Y. H. Chou, P. T. Hickey, M. Sundman, A. W. Song, and N. K. Chen, JAMA. Neurol. **72**, 432 (2015).
[29] E. M. Khedr, H. M. Farweez, and H. Islam, Eur. J. Neurol. **10**, 567 (2003).
[30] M. P. Lomarev, S. Kanchana, W. Bara-Jimenez, M. Iyer, E. M. Wassermann, and M. Hallett, Mov. Disord. **21**, 325 (2006).
[31] Y. R. Yang, C. Y. Tseng, S. Y. Chiou, K. K. Liao, S. J. Cheng, K. L. Lai, and R. Y. Wang, Neurorehabil. **27**, 79 (2013).
[32] C. W. Yip, P. W. Cheong, A. Green, P. K. Prakash, S. K. Fook-Cheong, and E. K. Tan, Clin. Neurol. Neurosurg. **115**, 887 (2013).
[33] W. H. Chang, M. S. Kim, J. W. Cho, J. Y. Youn, Y. K. Kim, S. W. Kim, A. H Lee, and Y. H. Kim, J. Rehabil. Med. **48**, 824 (2016).
[34] A. Wagle Shukla, J. J. Shuster, J. W. Chung, D. E. Vaillancourt, C. Patten, J. Ostrem, and M. S. Okun, P.M.R. **8**, 356 (2016).
[35] T. Soundara Rajan, M. F. M. Ghilardi, and H. Y. Wang, Front. Physiol. **8**, 457 (2017).
[36] T. Watanabe, R. Hanajima, and Y. Shirota, Hum. Brain. Mapp. **35**, 1896 (2014).
[37] J. Antczak, J. Pera, M. Dąąbrośś, W. Koźźmińński, M. Czyżżycki, K. Węężżyk, M. Dwojak, M. Banach, and A. Slowik, Neural. Plast. **12**, 7638675 (2019).