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SHORT COMMUNICATION

EFFECT OF CUMULATIVE REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION ON FREEZING OF GAIT IN PATIENTS WITH ATYPICAL PARKINSONISM: A PILOT STUDY

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Objective: **To investigate the potential of cumulative high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) on freezing of gait in atypical Parkinsonism.**
Design: **Randomized, single-blinded, crossover study with a blinded observer.**
Participants: **Eight patients with atypical Parkinsonism.**
Methods: **All participants received HF-rTMS over the lower leg primary motor cortex (M1-LL) for 5 consecutive days. Alternative sham stimulation was also administered with a 2-week wash-out period. Freezing of Gait Questionnaire (FOG-Q), turn steps in the modified Standing Start 180° Turn Test, the Timed Up and Go (TUG) task, and the Unified Parkinson's Disease Rating Scale part III (UPDRS-III) were performed before, after, and one week after rTMS.**
Results: **All participants completed this study without any significant adverse effects. FOG-Q and turn steps revealed significant improvements over time in the rTMS compared with the sham stimulation (χ^2=6.067, p=0.048 and χ^2=9.083, p=0.011). In addition, the TUG task and UPDRS-III showed significant improvements over time in the rTMS compared with the sham stimulation (χ^2=7.200, p=0.02 and χ^2=7.000, p=0.030).**
Conclusion: **Cumulative HF-rTMS over the M1-LL might be effective for improving freezing of gait in patients with atypical Parkinsonism. Further investigation with a large number of participants is needed to clarify the effects of HF-rTMS on freezing of gait in atypical Parkinsonism.**

Key words: atypical Parkinsonism; brain stimulation; freezing of gait; repetitive transcranial magnetic stimulation; vascular Parkinsonism.

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INTRODUCTION

Freezing of gait (FOG) is defined as a brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk (1). It is a disabling complex symptom associated with several disorders, such as advanced Parkinson's disease (PD) and atypical Parkinsonism (AP) (1, 2). In spite of the high-frequency of FOG in PD, FOG is also common in AP such as vascular Parkinsonism (VP), progressive supranuclear palsy (PSP), multiple system atrophy (MSA), and corticobasal syndrome, especially when observed early in the course of disease (2). However, few studies have reported the treatment of FOG in AP.

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation (NIBS) tool used to modulate brain activity in a specific, distributed, cortico-subcortical network (3). Many studies with rTMS have reported its beneficial effects on motor and gait function in patients with PD (4). Although the pathogenesis of FOG is not fully understood, the locomotion and postural networks, such as the frontal lobe and its connections to the basal ganglia, might be considered important regions for FOG (2). Based on these considerations, a NIBS protocol for improving gait function has been applied to modulate FOG in PD (5). In addition, our previous research showed that 10 Hz rTMS applied to the primary motor cortex of the dominant hemisphere for the lower leg (M1-LL) was effective in reducing FOG for a short time in patients with PD and AP (6). Cumulative rTMS is needed for clinical therapeutic purposes because the modulating effect of 1 session of rTMS lasts a relatively short duration of 30–60 min (7).

There is a lack of investigations regarding the effect of cumulative rTMS on FOG in AP, although cumulative high-frequency rTMS showed a positive effect improving FOG in PD (8). Therefore, the aim of this study was to investigate the efficacy of cumulative high-frequency rTMS on FOG in patients with AP. The objective of this pilot study was to assess the safety and feasibility of the design in preparation for a larger future study.

METHODS

Participants

We recruited 8 patients diagnosed with AP with FOG (5 VP, 2 PSP, and 1 MSA). Baseline characteristics of the participants are presented in Table I. All participants were right-handed. No participant had a history of receiving rTMS for treatment or research purpose. Diagnoses were made by neurologists with expertise in movement disorders (JWJ and JY) based on medical history, physical examination, and neuroimaging studies. To determine the cause of Parkinsonism, we used the PINE study as a reference (9). All participants were able to walk independently without walking devices. We excluded patients with pre-existing and active major neurological diseases other than Parkinsonism and those with a previous history of seizures or implanted metallic objects that would contraindicate rTMS (7). All study assessments took place at the same time of the day for each patient.

All study procedures were carried out with adequate understanding and written consent of the subjects involved and with the ethical approval of the authors' institutional review boards.

Study design

This study was a randomized, single-blinded, crossover design with blind observer. All patients received 5 sessions of high-frequency rTMS (real) or sham stimulation (sham) over M1-LL for a week after block randomization. The stimulation was conducted with a 2-week interval between 2 stimulations to avoid carryover effects, and the session order was counterbalanced across patients (Fig. 1). The assessment was carried out 3 times: at baseline before rTMS (T0, pre-rTMS at day 1), after rTMS (T1, post-rTMS at day 5), and 1 week after cessation of rTMS (T2, follow-up at day 12). Medication was kept constant throughout the trial, and all interventions were performed at the same time of day for each patient.

Optimal stimulating point for rTMS

The patients were seated in an armchair with a silver-silver chloride surface electrode placed over the tibialis anterior muscle contralateral to the dominant hemisphere. The hot spot was determined using a Rapid2® Stimulator TMS System (The Magstim Company Ltd, Whitland, UK) and the double cone coil. The coil was placed over the scalp and repositioned until the maximal motor-evoked potentials (MEPs) were elicited. After determining the hot spot, the resting motor threshold (RMT) was obtained by delivering single-pulse transcranial magnetic stimulation to the hot spot. The RMT was defined as the lowest transcranial magnetic stimulation intensity capable of eliciting an MEP greater than a 50 μV peak-to-peak amplitude in 5 of the 10 subsequent trials (6). In addition, 5 MEP sweeps at 120% of the RMT were performed, and the mean amplitude of the MEPs was calculated (6).

Table I. *Baseline characteristics of patients*

Patient number	Gender	Age, years	Disease duration, years	LEDD, mg/day	Diagnosis
1	M	71	6	200	VP
2	F	76	2	1,530	VP
3	M	78	6	950	MSA
4	F	81	3	500	VP
5	M	79	6	612.5	VP
6	M	64	4	487.5	VP
7	M	66	5	1,100	PSP
8	M	60	2	200	PSP
Mean (SD)		71.9 (7.8)	4.3 (1.8)	697.5 (463.6)	

LEDD: levodopa equivalent daily dose; SD: standard deviation; VP: vascular parkinsonism; PSP: progressive supranuclear palsy; MSA; multiple system atrophy.

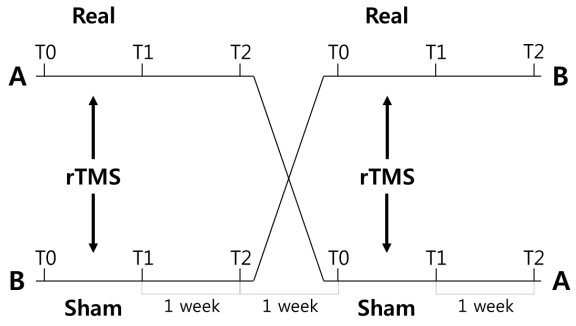

Fig. 1. Experimental sham-controlled repetitive transcranial magnetic stimulation (rTMS) crossover design. T0, pre-rTMS at day 1; T1, post-rTMS at day 5; T2, follow-up at day 12.

rTMS intervention

Pulses were delivered through a double-cone coil, and the coil was held so that the induced current was perpendicular to the midline for M1-LL stimulation. Twenty trains of 10 Hz rTMS were delivered to the target motor cortex areas of the dominant hemisphere at an intensity of 90% RMT using a Rapid® II stimulator with 2 Booster Modules (The Magstim Company Ltd). Each train lasted 5 s, with 55-s inter-train intervals, delivering a total of 1,000 pulses in 20 min. Sham stimulation was conducted with a coil held at a 90° position in order to ensure that the magnetic field did not stimulate the motor cortex (6). The stimulation paradigm was otherwise the same as that of real M1-LL rTMS. Patients were not told whether they were receiving real or sham rTMS.

Behavioural assessments

The FOG-Q (10) was used as the primary outcome measure. In addition, a modified Standing-Start 180° Turn Test was used to objectively assess FOG severity (6). Video-based analysis of the Standing-Start 180° Turn Test showed valid findings for measuring turn steps and turn time with acceptable reliability (11). We modified the Standing-Start 180° Turn Test while performing a modified Timed Up-and-Go (TUG) task (6). The TUG task was repeated twice in each direction, and the entire process was video-recorded to quantify FOG. The mean turn steps and turn time were obtained by averaging each trial. To assess locomotion and motor function, we measured the mean time to complete a standard TUG task and the Unified Parkinson's Disease Rating Scale part III (UPDRS-III) motor scale (12). All behavioural assessments were performed by one researcher who was blinded to the stimulation condition.

Statistical analysis

The Shapiro-Wilk test was used to test the normal distribution assumption for all continuous variables. This assumption was rejected for all parameters in this study ($p < 0.05$ by the Shapiro-Wilk test). Therefore, the effect of the interventions over time between 2 conditions was evaluated using the Friedman test. If there was a difference across time-points between 2 conditions, *post hoc* analysis was performed with the Wilcoxon signed-rank test to compare pairs of time-points for each condition. The significance level was set at 0.05. All statistical analyses were performed using the software package SPSS 21.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

All 8 participants completed the study including both conditions without any significant adverse effects. There were no significant differences in baseline scores on the behavioural assessments between the 2 rTMS conditions (Table II).

Table II. *Behavioural and cortical excitability assessments*

		Baseline (T0) Mean (SD)	Post-intervention (T1) Mean (SD)	Follow-up at day 12 (T2) Mean (SD)
Behavioural assessments				
FoG-Q	Real rTMS	15.3 (5.4)	13.0 (4.2)*	13.5 (3.5)*
	Sham rTMS	15.4 (4.5)	15.0 (4.5)	14.5 (4.4)
Turn steps	Real rTMS	25.3 (10.4)	20.8 (8.1)*	19.6 (8.1)*
	Sham rTMS	24.5 (9.8)	24.9 (11.3)	21.8 (9.5)
Turn time (sec)	Real rTMS	16.35 (5.77)	14.47 (4.81)	14.38 (5.56)
	Sham rTMS	15.52 (6.53)	15.27 (5.37)	16.19 (6.80)
TUG task (sec)	Real rTMS	53.75 (31.88)	46.12 (24.60)*	46.75 (26.64)
	Sham rTMS	43.75 (22.82)	44.37 (25.08)	43.62 (26.00)
UPDRS-III	Real rTMS	20.1 (12.0)	17.3 (12.8)*	16.9 (12.7)*
	Sham rTMS	19.8 (12.0)	19.1 (11.7)	20.6 (11.0)
Cortical excitability assessments				
RMT (%)	Real rTMS	42.5 (9.0)	–	–
	Sham rTMS	43.8 (10.3)	–	–
Amplitude (μV)	Real rTMS	480.2 (304.9)	–	–
	Sham rTMS	469.1 (350.1)	–	–

*$p < 0.05$ compared with baseline.
FoG-Q: Freezing of Gait Questionnaire; rTMS: repetitive transcranial magnetic stimulation; TUG: Timed Up and Go task; UPDRS-III: Unified Parkinson's Disease Rating Scale part III; RMT: resting motor threshold.

Fig. 2 (A, B) shows individual raw data of the FOG-Q and the turn steps in each rTMS condition. The FOG-Q and the turn steps showed significant differences between the conditions over time ($\chi^2 = 6.067$, $p = 0.048$ and $\chi^2 = 9.083$, $p = 0.011$). In the *post hoc* comparison, the FOG-Q and the turn step decreased significantly between T0 and T1 only in the group that received rTMS ($p = 0.049$ and $p = 0.026$). In addition, these significant effects lasted until T2 ($p = 0.028$ and $p = 0.026$). However, turn time was not significantly different between the conditions over time (Table II).

Fig. 2 (C, D) shows individual raw data of the TUG task and UPDRS-III in each rTMS condition. The results of the TUG task and UPDRS-III were significantly different between the conditions over time ($\chi^2 = 7.200$, $p = 0.02$ and $\chi^2 = 7.000$, $p = 0.030$). In the *post hoc* comparison, TUG task and UPDRS-III scores decreased significantly between T0 and T1 only in those who received rTMS ($p = 0.049$ and $p = 0.030$). In addition, the significant difference in UPDRS-III lasted only until T2 ($p = 0.028$, Table II).

DISCUSSION

This pilot study showed that 5 sessions a week of high-frequency rTMS might be effective for alleviating FOG symptoms in patients with AP without any severe adverse effects, with the effects continuing for one week. In addition, cumulative high-frequency rTMS could improve locomotion function in patients with AP. These results might suggest the potential of cumulative high-frequency rTMS for 5 days as an add-on therapy for FOG in patients with AP.

rTMS has been used widely in movement disorders such as PD, because it has the ability to modulate the activity of the distant subcortical areas in addition to the direct cortical stimulation site (4). Meta-analyses showed a significant efficacy of high-frequency rTMS over the primary motor cortex hand area on motor function in PD without significant adverse effects (13). Besides motor function, recent studies have reported that high-frequency rTMS applied over M1-LL can improve FOG symptoms in patients with PD (8). In spite of heterogeneous underlying pathophysiologies between PD and AP, attempts with similar rTMS protocols with PD have been made in patients with AP (14). In FOG in advanced PD patients, decreased neural reserve and automaticity due to dysfunctional basal ganglia are considered the major pathophysiological mechanisms (4). Under this hypothesis, our previous study showed that high-frequency rTMS over M1-LL has the potential to reduce FOG in patients with parkinsonism (6). However, the previous study could not assess long-lasting effects as only one session of rTMS was applied. For clinical therapeutic purposes, it is essential to demonstrate a long-lasting effect of NIBS. The lasting duration of the behavioural effects of rTMS relies on the number of sessions (15). Therefore, this study was designed to establish a therapeutic strategy with cumulative rTMS to reduce FOG. In this respect, it is meaningful that the effects of high-frequency rTMS on FOG were cumulative and continued for at least one week.

Because episodes of FOG are often rare or absent in the clinic, a questionnaire is often a proper assessment tool of the presence and severity of FOG (1). We used FOG-Q as the primary outcome; however, it cannot assess the immediate effect of one session of rTMS. For the objective assessment of FOG, the modified Standing-Start 180° Turn Test was also used in this study. There was no significant difference in FOG-Q immediately or one week after rTMS between the 2 conditions, although there was a statistically significant improvement over time in only real rTMS conditions. In addition, improvement in FOG-Q after cumulative rTMS was less than 20%, which suggests a lack of clinical significance. However, the turn steps in the modified Standing-Start 180° Turn Test was significantly different between the 2 conditions immediately and one week

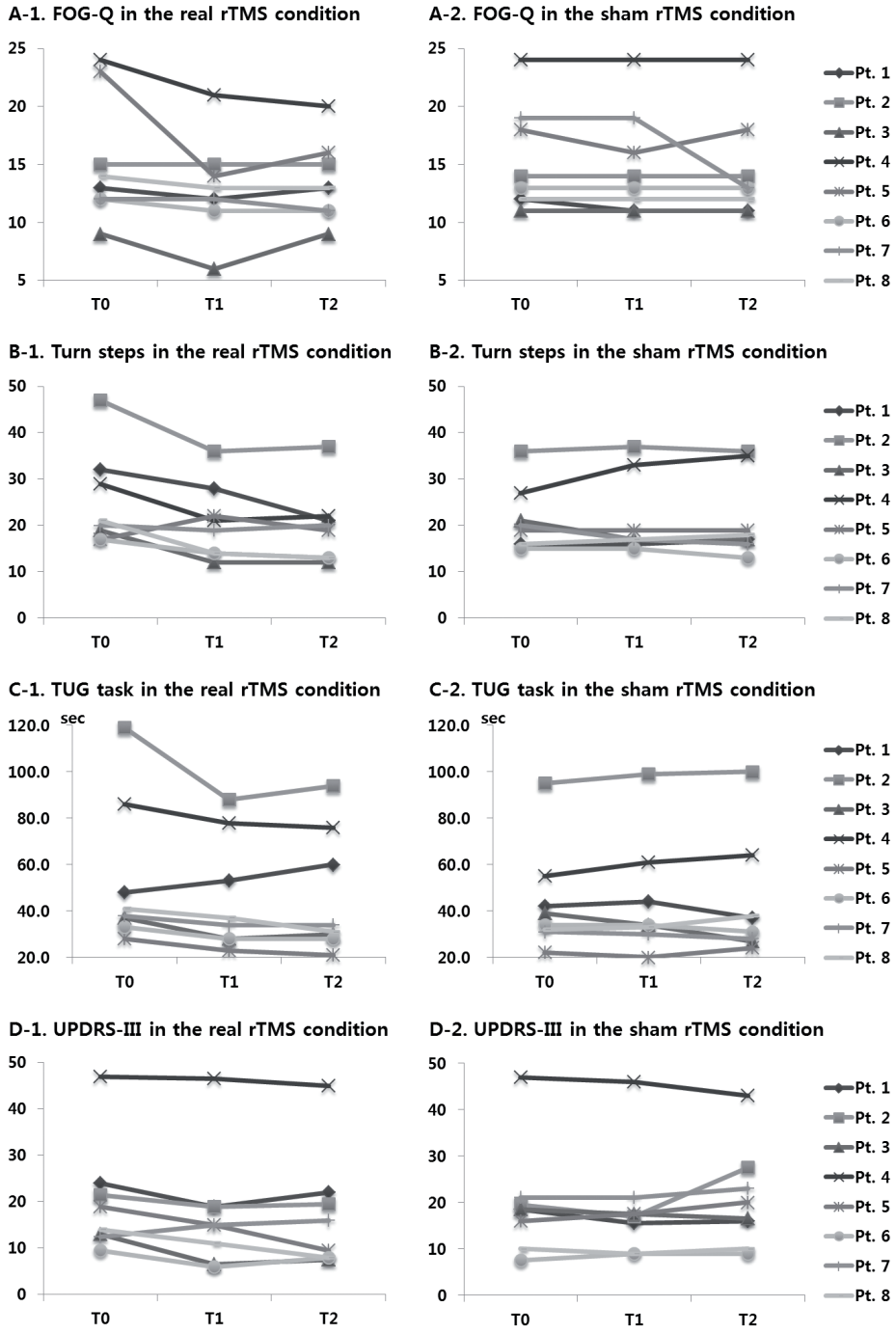

Fig. 2. Change in (A) Freezing of Gait Questionnaire (FOG-Q), (B) turn steps of the modified Standing Start 180° Turn Test, (C) Timed Up and Go (TUG) task, and Unified Parkinson's Disease Rating Scale part III (UPDRS-III) in each rTMS condition. T0, pre-rTMS at day 1; T1, post-rTMS at day 5; T2, follow-up at day 12.

after rTMS. Further study on the clinical effect of cumulative rTMS is needed to support the therapeutic potential of high-frequency rTMS for FOG in patients with AP.

A previous pilot study without a control group reported that gait function improved after 5 Hz rTMS for 5 consecutive days in patients with VP (14). In this study, the decrease in TUG task and UPDRS-III over time in real rTMS means that cumulative high-frequency rTMS could improve locomotion and motor function in patients with AP. These results were similar to those of a previous pilot study (14). Because we used a crossover study design with sham rTMS condition, the results of this study revealed stronger evidence than a previous pilot study. Therefore, cumulative high-frequency rTMS over M1-LL might be considered a potential additional therapy for

improving locomotion and motor function in patients with AP as well as with PD.

The crossover design used in this study can reduce the influence of confounding factors compared with a non-crossover longitudinal study design. In spite of this advantage, the carryover effect is the most common problem in a crossover study design (5). In this study, we used a washout period with 2 weeks and a counterbalanced session order to avoid carryover effects. However, a 2-week interval in this study was relatively short to wash out the effect of cumulative rTMS. This relatively short duration of washout is one of the limitations in this study. In addition, the duration of follow-up was relatively short in this study. The crossover design has another major limitation, in that participants could easily guess whether they received real or sham rTMS. Sham rTMS in this study, which involved tilting the TMS coil on its side, is not a true sham condition. Unfortunately, the protocol in this study did not apply the questionnaire for both real and sham conditions. To clarify these limitations, a further randomized, double-blind, parallel-group study with a longer follow-up period will be needed to investigate the effects of rTMS for FOG. Another limitation is that we included a small number of patients with VP, PSP, and MSA. The pathophysiological mechanisms responsible for FOG may differ according to each disease, despite similar clinical features. Therefore the power to draw the conclusion that high-frequency rTMS was effective on FOG in each disease may be insufficient. However, we focused on rTMS as an add-on therapy for FOG in this study. Further investigations are required to supplement these limits.

In conclusion, our results suggest that high-frequency rTMS over the M1-LL might be effective for improving FOG in AP. This pilot study warrants that further investigations with a large number of participants and better study design will be needed to clarify the effect of high-frequency rTMS on FOG in AP.

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The authors declare no conflicts of interest.

REFERENCES

1. Nutt JG, Bloem BR, Giladi N, Hallett M, Horak FB, Nieuwboer A. Freezing of gait: moving forward on a mysterious clinical phenomenon. Lancet Neurol 2011; 10: 734–744.
2. Factor SA. The clinical spectrum of freezing of gait in atypical parkinsonism. Mov Disord 2008; 23 Suppl 2: S431–S438.
3. Fregni F, Pascual-Leone A. Technology insight: noninvasive brain stimulation in neurology-perspectives on the therapeutic potential of rTMS and tDCS. Nat Clin Pract Neurol 2007; 3: 383–393.
4. Chou YH, Hickey PT, Sundman M, Song AW, Chen NK. Effects of repetitive transcranial magnetic stimulation on motor symptoms in Parkinson disease: a systematic review and meta-analysis. JAMA Neurol 2015; 72: 432–440.
5. Valentino F, Cosentino G, Brighina F, Pozzi NG, Sandrini G, Fierro B, et al. Transcranial direct current stimulation for treatment of freezing of gait: a cross-over study. Mov Disord 2014; 29: 1064–1069.
6. Lee SY, Kim MS, Chang WH, Cho JW, Youn JY, Kim YH. Effects of repetitive transcranial magnetic stimulation on freezing of gait in patients with Parkinsonism. Restor Neurol Neurosci 2014; 32: 743–753.
7. Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Safety of TMS-SCG. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 2009; 120: 2008–2039.
8. Kim MS, Chang WH, Cho JW, Youn J, Kim YK, Kim SW, et al. Efficacy of cumulative high-frequency rTMS on freezing of gait in Parkinson's disease. Restor Neurol Neurosci 2015; 33: 521–530.
9. Caslake R, Taylor K, Scott N, Harris C, Gordon J, Wilde K, et al. Age-, and gender-specific incidence of vascular parkinsonism, progressive supranuclear palsy, and parkinsonian-type multiple system atrophy in North East Scotland: the PINE study. Parkinsonism Relat Disord 2014; 20: 834–839.
10. Shine JM, Moore ST, Bolitho SJ, Morris TR, Dilda V, Naismith SL, et al. Assessing the utility of Freezing of Gait Questionnaires in Parkinson's Disease. Parkinsonism Relat Disord 2012; 18: 25–29.
11. Stack E, Ashburn A. Early development of the standing-start 180° turn test. Physiotherapy 2005; 91: 6–13.
12. Stebbins GT, Goetz CG. Factor structure of the Unified Parkinson's Disease Rating Scale: Motor Examination section. Mov Disord 1998; 13: 633–636.
13. Benninger DH. Parkinson's disease. Handb Clin Neurol 2013; 116: 469–483.
14. Yip CW, Cheong PW, Green A, Prakash PK, Fook-Cheong SK, Tan EK, et al. A prospective pilot study of repetitive transcranial magnetic stimulation for gait dysfunction in vascular parkinsonism. Clin Neurol Neurosurg 2013; 115: 887–891.
15. Alon G, Yungher DA, Shulman LM, Rogers MW. Safety and immediate effect of noninvasive transcranial pulsed current stimulation on gait and balance in Parkinson disease. Neurorehabil Neural Repair 2012; 26: 1089–1095.