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BRIEF COMMUNICATION

Effectiveness of Exercise on the Sequence Effect in Parkinson's Disease

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ABSTRACT

Objective To determine the benefits of motor training on the sequence effect (SE), an essential component of bradykinesia in Parkinson's disease (PD).

Methods Seven patients with *de novo* PD participated in this study. The patients performed regular pentagon drawing tests and exercises during four visits. The first two visits occurred before the start of medication, and the last two visits occurred at least six months after the start of medication. We assessed the severity of bradykinesia and SE at each visit and compared the results before and after exercise in both the *de novo* and treatment conditions.

Results In the *de novo* condition, the severity of bradykinesia significantly improved after motor training ($p = 0.018$), but it did not resolve and only showed a trend of improvement after treatment ($p = 0.068$). The severity of the SE decreased significantly in the drug-naïve condition ($p = 0.028$) but not after medication ($p = 0.273$).

Conclusion Our study suggests that regular motor training may be beneficial for the SE in PD.

Key Words Bradykinesia, *de novo*; Exercise; Motor training; Parkinson's disease; Sequence effect.

INTRODUCTION

The progressive reduction in the speed and amplitude of repetitive movements, which is called the sequence effect (SE), is a characteristic of Parkinson's disease (PD).[1] Festinating gait is a typical example of the SE. During walking, the step length of PD patients gradually decreases, and in turn, they take steps more quickly and may lean forward and eventually fall.[2,3] The SE may also be associated with motor arrest, such as the freezing of gait.[3,4]

Although the SE is well known, its treatment is unclear. Levodopa is a standard treatment for PD, but it is unclear whether levodopa is also beneficial for the SE.[5] It is imperative to develop effective therapies for the SE because the SE can cause several problems related to activities of daily living.[3,6]

Currently, exercise training has been reported to be beneficial in PD, and the combination of medication and exercise is used to treat PD.[7] The aim of this study was to determine whether motor training can improve symptoms of the SE.

MATERIALS & METHODS

Patients

Seven patients with *de novo* PD participated in this study. PD was diagnosed according to the UK Brain Bank criteria.[8] The Hoehn and Yahr stage, the Unified Parkinson's Disease Rating Scale score, the score of the Korean version of the Mini-Mental State Examination, years of education, disease duration, the Beck Depression Inventory score, and the Fatigue Severity Scale score were evaluated. Handedness was assessed with the Edinburgh Handedness Inventory.[9] Five patients were right-handed, and two

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patients were ambidextrous.[10] The more affected hand was determined based on the clinical features.[4] All patients provided written informed consent, and the study was approved by the Institutional Review Board of Dongtan Sacred Heart Hospital (IRB number: 2012-001).

Procedures

The patients were asked to visit the clinic four times for this study and perform the same experiment during each visit. The first two visits occurred before the start of anti-parkinsonian medications, and the remaining two visits occurred at least six months after the start of medications (Supplementary Figure 1 in the online-only Data Supplement). We planned a 2-day exercise protocol because in general, patients do not like to visit the clinic frequently, so it was expected to be challenging to recruit patients if the protocol spanned more days.

We used a repetitive pentagon drawing test, which has been previously used, to measure the severity of bradykinesia and the SE.[4] At each visit, the patients were first asked to perform the repetitive pentagon drawing test, which included drawing a pentagon ten times, with an interval of 30 seconds between each repetition. Then, patients were asked to continuously draw a pentagon ten times without a rest period between repetitions (continuous drawing test). This continuous drawing test was performed twice: with and without a dual task. The second drawing test was performed 30 seconds after the first drawing test. Then, a pentagon drawing exercise was performed. In the drawing exercise test, the patients were also requested to continuously draw a pentagon ten times without a rest period between repetitions. Then, the patients had to perform ten repetitions with a 30-second rest period between each repetition. After the training period, the patients rested their hands for one minute, and then, the continuous drawing test was performed two more times: with and without a dual task. Finally, patients performed a repetitive pentagon drawing test (Supplementary Figure 2 in the online-only Data Supplement).

Repetitive pentagon drawing test

The repetitive pentagon drawing test used was similar to that used in our previous study. We used the same equipment, and the details of the protocol are described in an earlier study.[4] In brief, the protocol was as follows. The participants were asked to trace a regular pentagon, for which each side was 17 cm, with an electronic pen. The vertices of the sides were marked with a circle of 0.5 cm in diameter. The time it took for the participant to trace each side was measured from the time the participant traced one vertex to when he or she traced the next vertex. A pause indicated an instance at which the pen deviated from the pentagon near a vertex by a distance of 1.5 cm from the vertex. The movement time for each side was defined as the tracing time excluding pauses. The severity of bradykinesia was measured as the mean value of the 10 tracing times, and the severity of the SE was measured as the progressive changes in the mean movement time from the 2nd to 5th segment, which were assessed by the slope of the linear regression. The time taken to draw the first segment was excluded from the SE analysis because there was a technical error in measuring the departure time and the pause around the first vertex. Pentagon drawing was recorded using a digitizing tablet (WACOM Intuos3 PTZ-1231W, A3 wide, 488×305 mm) with high spatial (0.05 mm) and temporal resolution (200 Hz sampling rate). The movement times were stored on a personal computer.

Dual task

In a dual task paradigm, participants perform two tasks simultaneously.[11] The dual task used in this study was serial subtraction. Each participant was asked to verbally count backward by three from 500 during the continuous drawing test. If the participant had difficulty performing the task, the test was modified to counting backward by one from 100. If he or she still had difficulty performing the task, the participant was asked to name as many animals as they could.

We used the dual task paradigm to determine whether participants performed the exercise correctly. The dual task paradigm is known to interfere with motor performance, but after motor learning, the dual task effect decreases. Therefore, we thought that if participants performed the exercise as instructed after training, the time it took them to draw pentagons with the dual task would be shorter after the completion of the pentagon drawing exercises. In addition, the dual task paradigm has been reported to increase attention and help people acquire new skills.[12,13] The dual task cost (DTC) is used to calculate the dual task effect, and the equation is as follows:[12]

$$\mathrm{DTC} = \frac{(\text{Single task} - \text{Dual task})}{\text{Single task}} \times 100.$$

Statistical analysis

The data are expressed as means ± SDs. The data were analyzed with the Wilcoxon signed-rank test. The severity of bradykinesia and the SE before exercise at the 1st visit and after exercise at the 2nd visit were compared (drug-naïve condition), and the severity of bradykinesia and the SE before exercise at the 3rd visit and after exercise at the 4th visit were also examined (treatment condition). We compared the difference in the DTC of the continuous drawing tests from before training at the 1st visit to after training at the 2nd visit. We used the single task data recorded before exercise at the 1st visit for these two DTC calcu-

lations. Likewise, we also compared the difference in the DTC before practice at the 3rd visit to after practice at the 4th visit. Values of $p < 0.05$ were regarded as significant.

RESULTS

The patient characteristics are summarized in Table 1, and data for each individual are presented in Supplementary Table 1 (in the online-only Data Supplement). The right side was more affected in five patients, and the left side was more affected in two patients. Seven patients attended the first two visits (i.e., before medication), but only four patients attended the last two visits (follow-up after medication: 10.5 ± 9 months). Before the start of medication, the severity of bradykinesia statistically significantly improved after motor training ($p = 0.018$) (Figure 1A) but only showed a trend of improvement after the start of medication ($p = 0.068$) (Figure 1A). The severity of SE significantly improved before medication ($p = 0.028$) (Figure 1B) but did not improve after medication ($p = 0.273$) (Figure 1B). The DTC significantly increased after exercise at the 2nd visit before the start of medication ($p = 0.018$), but the magnitude of improvement did not reach statistical significance after exercise at the 4th visit after the start of medication ($p = 0.068$) (Supplementary Table 2 in the online-only Data Supplement). We also analyzed the effects of medication on the SE, i.e., pre-exercise SE at the 1st visit and pre-exercise SE at the 3rd visit, but we did not find an effect of medication ($p = 1.000$) (Supplementary Table 3 in the online-only Data Supplement).

Table 1. Patient characteristics

	Results ($n = 7$)
Age (years)	57.9 ± 11.8
Sex (men:women)	6:1
Disease duration (years)	0.7 ± 0.3
K-MMSE	27.7 ± 2.2
Education (years)	11.7 ± 5.5
H&Y stage	2.0 ± 0.0
UPDRS total	31.9 ± 6.9
UPDRS I	1.3 ± 1.0
UPDRS II	6.4 ± 2.9
UPDRS III	24.1 ± 7.8
BDI	8.0 ± 5.1
FSS	2.8 ± 1.1

The values are means ± SDs. K-MMSE: the Korean version of the Mini-Mental State Examination, H&Y stage: Hoehn and Yahr stage, UPDRS: Unified Parkinson's Disease Rating Scale, BDI: Beck Depression Inventory, FSS: Fatigue Severity Scale.

DISCUSSION

Our study demonstrated that motor training improved bradykinesia and the SE before medication was started but failed to improve them after medication was started, which may be due to the small number of patients who attended follow-ups.

It is well known that motor training can reduce bradykinesia. Various types of exercise and physical therapy have been reported to be effective in treating motor and nonmotor symptoms in PD patients, even in the long term.[7,14] To increase the benefits of physical activity in PD patients, it is essential to know not only which kinds of physical activities are most helpful to patients[15] but also which symptoms improve with physical activity.

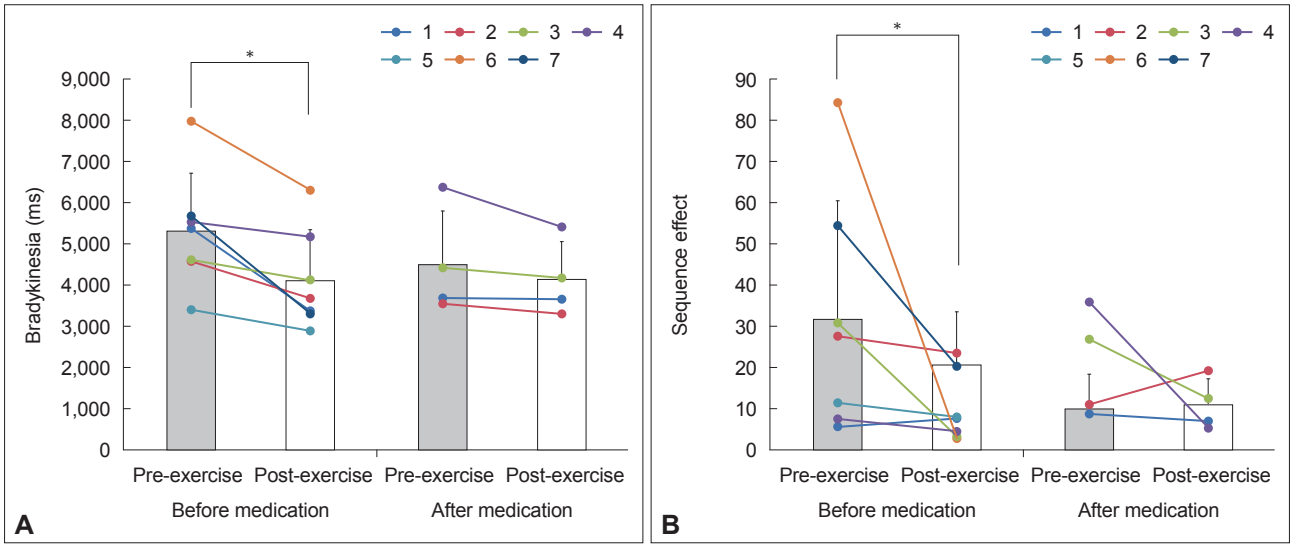

Figure 1. Changes in the severity of bradykinesia (A) and the sequence effect (B) after exercise. The left column shows the changes before treatment, and the right column shows the changes after medication. The colored lines and numbers indicate individual patients. *$p < 0.05$ indicates a significant difference.

We do not know the mechanism by which motor training improves the SE, but we think that exercise-induced neuroplasticity may be one mechanism because it was reported that the SE is associated with the anterior cingulate cortex and the cerebellum.[4] Exercise-induced neuroplastic changes in several brain regions, including the cingulate and cerebellum, have been reported in PD patients.[16] The changes in dopaminergic activity in the caudate caused by physical activity may be another mechanism,[17] considering that an association between caudate dopaminergic activity and the SE has been previously reported.[4]

Under medication, the symptoms of the SE did not improve after exercise, and there are possible explanations for this result. First, the number of patients who attended follow-ups was very small, and therefore, it is not easy to interpret the follow-up results. Second, it can be argued that because dopaminergic medication already affected the SE, there was no improvement after exercise. However, we did not find any reductions in the severity of the SE after treatment in this study (Supplementary Table 3 in the online-only Data Supplement), and as mentioned above, it is still unclear whether dopaminergic medication can improve symptoms of the SE.[5]

Because several previous studies have shown that the repetitive pentagon drawing test can be used to detect the SE, we adopted this test for our research, and this digitized repetitive pentagon drawing test yielded reliable measurements of both the training and medication effects. These kinds of computerized, objective analyses, if validated, may be useful in future large-scale studies.

Our study has some limitations. We conducted this research with a small number of participants. Additional research measuring neuroplastic changes in more patients is needed. In addition, the delayed effect of exercise on the SE remains to be explored. Second, the 2-day exercise protocol might be too short to assess motor learning. Third, we used the pentagon drawing test because previous studies have shown that the pentagon drawing test is an excellent tool for measuring the SE,[4,18,19] but it might not be a good tool to measure the effects of motor practice. Fourth, because the DTC did not improve after motor training in patients with medication, it might be possible that the participants did not practice the task properly. Nevertheless, the mean values of the DTC differed considerably between pre-exercise at visit 3 and postexercise at visit 4, but the difference was not statistically significant, perhaps due to the small number of participants.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.14802/jmd.20045.

Conflicts of Interest

The authors have no financial conflicts of interest.

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None.

Author Contributions

Conceptualization: Suk Yun Kang. Data curation: Suk Yun Kang. Formal analysis: Suk Yun Kang. Investigation: Suk Yun Kang. Methodology: Suk Yun Kang. Project administration: Suk Yun Kang. Resources: Suk Yun Kang. Software: Suk Yun Kang. Supervision: Suk Yun Kang, Young Ho Sohn. Validation: Suk Yun Kang. Visualization: Suk Yun Kang. Writing—original draft: Suk Yun Kang. Writing—review & editing: Suk Yun Kang, Young Ho Sohn.

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Ethical Standards

All procedures in studies involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1975 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all the patients included in the study.

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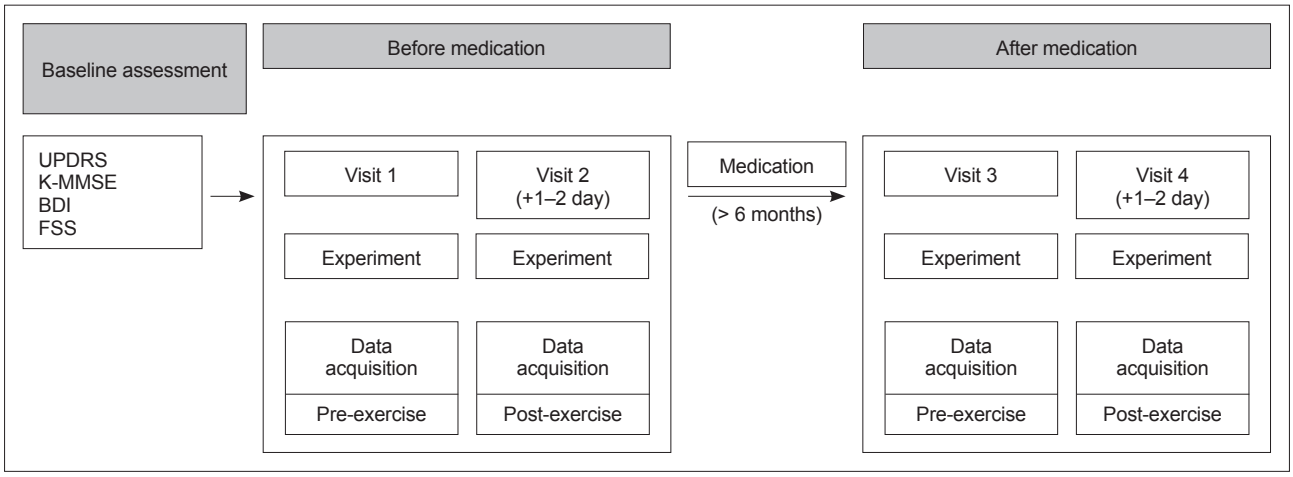
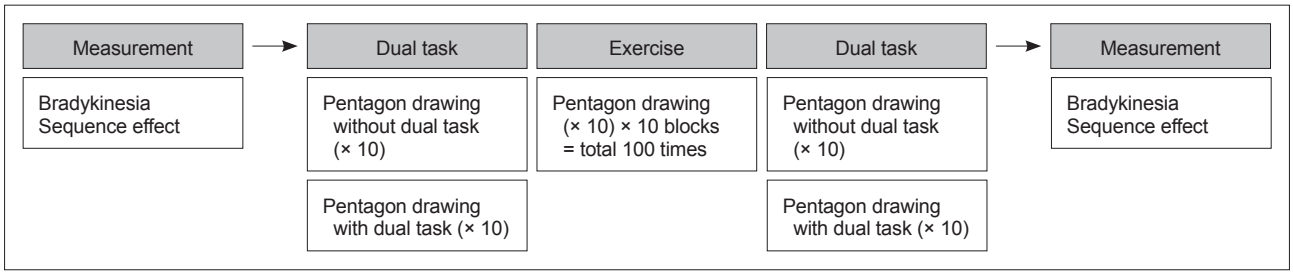


Supplementary Figure 1. Flow chart of the schedule of visits. UPDRS: Unified Parkinson's Disease Rating Scale, K-MMSE: Korean version of the Mini-Mental State Examination, BDI: Beck Depression Inventory, FSS: Fatigue Severity Scale.



Supplementary Figure 2. Experimental procedure for each visit.

Supplementary Table 1. Individual patient characteristics

Patient no	Age (yr)	Sex	Disease duration (yr)	K-MMSE	Education (yr)	H&Y stage	UPDRS total	UPDRS I	UPDRS II	UPDRS III	BDI	FSS	Medication
1	71	F	0.5	24	3	2	25	1	7	17	14	2.22	Levodopa/benserazide (100/25 mg) 1.5 tablet three times per day, trihexyphenidyl 1 mg once per day
2	45	M	1.0	30	16	2	31	0	10	21	5	3.11	Ropinirole prolonged release 12 mg once per day, amantadine 100 mg once per day
3	71	M	1.0	30	9	2	26	2	3	21	3	3.33	ropinirole prolonged release 12 mg once per day, amantadine 100 mg twice per day
4	64	M	0.6	26	6	2	39	0	2	37	0	1.33	Levodopa/carbidopa (100/25 mg) 0.75 tablet three times per day, trihexyphenidyl 1 mg once per day, rasagiline 1 mg once per day
5	38	M	0.4	28	12	2	28	3	9	16	14	4.11	
6	54	M	0.5	30	18	2	45	1	9	35	11	4.11	
7	62	M	1.0	26	18	2	29	2	5	22	9	1.33	

K-MMSE: the Korean version of the Mini-Mental State Examination, H&Y stage: Hoehn and Yahr stage, UPDRS: Unified Parkinson's Disease Rating Scale, BDI: Beck Depression Inventory, FSS: Fatigue Severity Scale.

Supplementary table 2. Dual task cost (%) used for the measurement of dual task effect

DTC in 7 patients (before treatment)			DTC in 4 patients (after treatment)		
Pre-exercise at visit 1	**Post-exercise at visit 2**	***p*-value***	**Pre-exercise at visit 3**	**Post-exercise at visit 4**	***p*-value**
- 48.8 ± 47.0	2.9 ± 41.5	0.018	-25.7 ± 15.2	-8.8 ± 12.9	0.068

The values are means ± SDs. *$p < 0.05$ indicates a significant difference. DTC: dual task cost.

Supplementary Table 3. Effect of medication on the sequence effect

	Sequence effect (4 patients)		*p*-value*
	No medication (visit 1)	Medication (visit 3)	
Pre-exercise	17.9 ± 13.2	20.5 ± 12.9	1.000

The values are means ± SDs. *$p < 0.05$ indicates a significant difference.