

Early implementation of intended exercise improves quality of life in Parkinson's disease patients

Yang Yang

Chinese PLA General Hospital

Lifeng Chen

Chinese PLA General Hospital

Jiarui Yao

Chinese PLA General Hospital

Na Wang

Chinese PLA General Hospital

Dandan Liu

Chinese PLA General Hospital

Yuliang Wang

Chinese Xiaotang Mountain Hospital

Dan Liu

Chinese PLA General Hospital

Weiping Wu

Chinese PLA General Hospital

Tianyu Jiang

Chinese PLA General Hospital

Zhenfu Wang (✉ wuwp301@163.com)

Chinese PLA General Hospital <https://orcid.org/0000-0001-8783-0338>

Research

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Abstract

Objective

Recent data have shown that regular exercise may ameliorate motor symptoms in Parkinson's disease (PD). This study aims to investigate how intended exercise impacts motor and non-movement symptoms of PD.

Methods

88 patients were randomly assigned to an early exercise group (E-EG), late exercise group (L-EG), or a control group (CG) using a randomized delayed-start design. The E-EG carried out a rigorous, formal exercise program for one hour, twice per week, for 18 months (May 2018 - November 2019). The L-EG took part in the exercise program in the final 6–12 months of the study. We assessed outcomes using the Unified Parkinson's Disease Rating Scale (UPDRS), PDQ-39 Questionnaire, Line A test, Line B test, Nine-hole column test, 30 seconds squat and stand-up test (30s SST), 10m Walk test(10mW), Balance Evaluation Systems Mini Test (MiniBESTest), FAB and Time Up and Go Test(TUG).

Results

The patients with PD in the E-EG had lower performance in the UPDRS and Line B test compared to those in the L-EG at post-exercise($p < 0.05$). Moreover, the patients with PD in the E-EG had much lower performance in the PDQ-39 and 9-Hole Peg test compared to those in the L-EG at post-exercise($p < 0.01$).

Conclusion

Implementation of an exercise regimen improved the movement abilities and quality of life in PD patients, especially in the E-EG. This data supports the idea that intended exercise should be implemented as part of the treatment strategy for PD patients as early as possible.

Introduction

Parkinson's disease (PD) is a common neurodegenerative illness worldwide and affects about 3 million people in China. The pool of at-risk patients is similarly large and the number of patients with PD is on the rise due to the increasing life expectancy of the general population[1]. Many existing PD medications only aim to slow down PD progression and the dose of these medications cannot be increased indefinitely without significant side effects. Non-pharmacologic therapies, such as rehabilitative exercise, can be implemented to avoid these side effects, with a goal of helping PD patients manage activities of daily living (ADLs), remain independent, and improve life quality[2].

As early as 1956 it was reported that after exercising, PD patients had improved initiation of motion[3, 4]. Lee Silverman Voice Treatment-LOUD (LSVT-LOUD) was one of the most widely practiced exercise programs for PD patients[5]. Initially, LSVT-LOUD was performed as a speech therapy program to treat the speech sound production difficulties observed in PD patients. LSVT® BIG was later developed to treat the motor deficits found in PD based on the neuroplasticity principle that the brain could reorganize neural synaptic connections as compensation for brain injuries[6]. LSVT® BIG aimed to promote fast, high-amplitude movements so that the typical slow movements of PD could be reversed. Multidisciplinary and intensive rehabilitation therapy has been recommended for PD patients to help improve/maintain movement ability for complex physical tasks[7, 8]. When paired with occupational therapy these two therapies helped PD patients perform ADLs and live independently as long as possible. However, prior studies have not examined such a long-term intended exercise program how to affect physical function in the PD individuals. Our study aims to fill knowledge gaps on effective implementation of an exercise regimen in these PD patient population and how timing of exercise implementation affects patient outcomes.

A recent meta-analysis from Cochrane assessed the overall effect of physiotherapy versus non-physiotherapy in PD patients [9, 10]. Notable benefits of physiotherapy were reported in key metrics such as gait speed, a freezing of gait questionnaire, two or six min walk test, Timed Up and Go Test(TUG), functional reach test, Berg-balance scale, and the Unified Parkinson's Disease Rating Scale (UPDRS).

Our study examined implantation of intended exercise regimen in early and later stages of PD therapy. All outcomes were deemed primary, given that exercise regimens have been shown to improve movement, non-movement symptoms, and quality of life in PD patients.

Methods

Participants

Eighty-eight PD patients(39 female and 49 male) admitted to the Department of Neurology in Chinese PLA General Hospital were included in this study from May 2018 to December 2019, taking or not taking anti-PD medicine. 30 patients (67 ± 9 years; 10 female and 20 male) were assigned to the early exercise group (E-EG), 30 patients (65 ± 7 years; 15 female:15 male) were assigned to the late exercise group (L-EG) and 28 patients (66 ± 4 years; 14 female:14 male) were in a control group (CG) that received only medical therapy.

Informed written consent was obtained from each patient before beginning the study and this research was approved by the ethical committee of General Hospital of Chinese PLA. Patients in the study must have had a diagnosis of PD based on the 2016 diagnostic criteria established at least six months before the study that was rated from 1.0–3.0 using Hoehn and Yahr scale criteria. Exclusion criteria included severe gait disorder unable to walk independently, other neurological, vascular, or systemic disease leading to permanent or intermittent weakness or instability, severe insufficiency of liver or kidney, cancer,

surgical history resulting in gait difficulty, chronic musculoskeletal disease leading to restricted mobility, and other exercise contraindications (such as eyes and hearing loss).

Clinical assessment

The E-EG underwent a rigorous formal exercise program for one hour, twice per week, for 18 months (May 2018 - November 2019). The L-EG participated in the exercise program in the final 6–12 months. An experienced neurologist performed the assessment of PD patient cognitive and motor function, posture, gait, balance for all groups. Patients were assessed at baseline as well as 6, 12, and 18 months after exercise. The CG only received medicinal therapy. The severity of the disease was assessed using the UPDRS and the Hoehn and Yahr scale. The assessment of attention, working memory and executive function was determined by Line A, Line B and 9-Hole Peg test.

The assessment of motor performance was determined by means of UPDRS-3 testing and a 30s Squat-Sitting Test(30sSS), and the gait assessment by means of 10m walk(10mW) at preferred speed test. Basic motor performance was assessed using stopwatch timing of the following functional tasks: sitting to standing up, lying to standing up from the treatment table, standing to sitting down, standing to lying down on the treatment table, sitting to lying down on the treatment table, and standing to lying down on the exercise mat. The time of maintaining balance in tandem stance was measured for a maximum of 30s. During the 10 m walks at a normal and preferred speed, the walking duration was recorded and numbers of steps were counted, as well as average length of steps. The balance assessment was applied by Mini-BEST test and Fullerton advanced balance scale(FAB), with higher scores indicating best balance.

PD-Specific Skill Acquisition PWR! Moves exercises procedure: (1)Warming up exercise: stride, side step, stretching exercise for 5 minutes; (2) PWR! Moves Exercises: 30 minutes, including: exercises in 5 postures, which were low floor prone, low floor supine, high floor all 4's, sitting, and standing, etc. 2 minutes break between different postures; (3) Boxing 5 minutes: Practice with each other; (4) Cooling down exercises: including: stride, side step, stretching exercise. Activities in the program included relaxation exercises, exercises of motion and stretching, trunk rotation in various body positions, exercises involving mobility and functional training, re-education of posture, gait training, balance exercises, and exercises of facial expression and hands. Verbal commands, clapping, counting, and floor markings were used to assist with exercises in different body positions. The implemented exercise program was one hour with breaks, twice per week, and lasted for 18 months.

Statistical analysis

Statistical analyses were performed using SPSS Statistical Software 14.0. Mean \pm SD is noted for descriptive statistics. Nonparametric Mann–Whitney tests were carried out to compare the pre-exercise and post-exercise assessments. Three consecutive assessments were used in Friedman's non-parametric analysis of variance for dependent tests comparing all three groups. P values of less than 0.05 were deemed statistically significant. The χ^2 independence test was carried out for the comparison of quantitative variables.

Results

Baseline PD Patient Demographics

The characteristics of patients at baseline were uniform across the E-EG, L-EG, and CG in terms of onset age, gender, disease duration, and severity of disease assessed using the H-Y scale, UPDRS, UPDRS-3, PDQ-39, Line A, Line B, 9-Hole Peg test, 30s SST, 10 m Walk, Mini-BESTest, FAB, and Timed up and Go Test (TUG) (Table 1). We didn't observe noticeable differences among the groups in terms of onset age, gender, disease duration, severity of disease, UPDRS, UPDRS-3, PDQ-39, Line A, Line B, Nine-hole column test, 30s SST, 10m Walk, Mini BESTest, FAB,TUG, levodopa-equivalent daily dose (LEDD) and Heart Rate.

Table 1
Demographic and Clinical Characteristics of the PD Patients at Baseline(pre-exercise)

Demographic and clinical parameters	Early-exercise group(n = 30)	Late-exercise group(n = 30)	Control group(n = 28)
Age-years Mean(Min Max)	67 (47–82)	65 (46–81)	66(49–80)
Female: Male	10:20	15:15	14:14
Disease duration-yr	4.88 ± 1.16	4.43 ± 1.43	4.52 ± 1.87
H&Y scale-no	21	17	15
1–2	9	13	13
2–3			
UPDRS	20 ± 8.55	21 ± 9.49	23 ± 7.65
UPDRS- III	10 ± 4.93	14 ± 5.46	13 ± 4.23
PDQ-39	29 ± 9.76	31 ± 8.92	30 ± 7.13
Line-A(s)	44.21 ± 8.43	45.53 ± 9.65	46.18 ± 6.67
Line-B(s)	129.82 ± 28.41	127.34 ± 31.24	133.02 ± 20.15
9-Hole Peg test (s)	39.56 ± 9.31	38.93 ± 12.09	42.19 ± 10.76
30'SST(n)	16 ± 4.12	15 ± 8.29	18 ± 7.45
10m Walk(s)	7.83 ± 2.49	8.32 ± 3.76	8.98 ± 3.19
Mini-BESTest	22 ± 9.47	20 ± 8.16	23 ± 9.85
FAB	31 ± 9.49	30 ± 8.48	33 ± 7.65
TUG	12.23 ± 8.87	13.93 ± 9.24	14.08 ± 8.40
levodopa-equivalent daily dose (LEDD) mg/day	352.9 ± 132.6	361.2 ± 175.9	-
Heart Rate	78 ± 29.32	82 ± 33.61	69 ± 30.68
UPDRS-III = Unified Parkinson's disease rating scale; H&Y = Hoehn and Yahr			

Pre- and post-exercise assessment of PD patients

The flow of participants throughout the study was shown in Fig. 1. There were 24 patients in E-EG group accepted pre- and post-exercise evaluation due to 5 no continuous training, 1 lack of examination; while, 14 patients in L-EG group accepted pre- and post-exercise assessments due to 11 no continuous training, 5 no examination. Changes in outcome variables were summarized in Table 2. E-EG patients showed significant improvements in pre- and post-exercise assessments as determined by the UPDRS, PDQ-39, Line B, and 9-Hole Peg test ($p < 0.05$). L-EG patients did not show these pre- and post-exercise differences

in UPDRS, PDQ-39, Line B, 9-Hole Peg test, 30sSST, 10mW and Mini-BESTest ($p > 0.05$). Changes in these scores were illustrated in Fig. 2 and figure,3. The participants with PD in the E-EG had lower performance in the PDQ-39 and 9-Hole Peg test compared to those in the L-EG at post-exercise($p < 0.01$). Meanwhile, the participants with PD in the E-EG had lower performance in the UPDRS and Line B test compared to those in the L-EG at post-exercise($p < 0.05$).

Table 2
Differences from Post-exercise and Pre-exercise in PD patients

	Differences from Post-exercise and Pre-exercise		P value
	N = 24(E-EG) N = 14 (L-EG)		
UPDRS	3.5 ± 1.27*	0.75 ± 0.21	0.025 0.09
PDQ-39	7.21 ± 2.08#	1.01 ± 0.32	0.009 0.11
Line-B(s)	15.24 ± 5.49*	6.68 ± 2.86	0.022 0.08
9-Hole Peg test(s)	6.69 ± 2.31#	1.46 ± 0.63	0.001 0.06
30sSST(n)	3.21 ± 1.34	1.50 ± 0.57	0.13 0.21
10mW(s)	0.13 ± 0.09	0.87 ± 0.26	0.73 0.94
Mini-BESTest	0.29 ± 0.11	1.25 ± 0.34	0.61 0.87
E-EG, early-exercise group; L-EG, late-exercise group. *stand for $p < 0.05$;			
#stand for $p < 0.01$			

Discussion

Exercise and physical activities have merit for improving motor manifestations of PD[2, 9–11]. Most PD rehabilitation strategies focus on relatively early stages of the disease using group exercise training programs in outpatient clinics and at-home exercise. It is important to assess the long-term benefits of rehabilitation therapy as regular programs of physical rehabilitation reported to improve PD patient motor disabilities[12], yet the improvements may not be sustained upon cessation of the program.

Implementation of intended exercise program for PD patients requires consideration of several key factors: 1) The target of the intervention should be patient-specific and address key physical limitations that disrupt ADLs. 2) The intervention has to be feasible, as patient compliance dramatically reduces when given unrealistic, time-consuming regimens. Simultaneously, the prescribed exercises should cover different areas of physical restrictions and be integrated into a session lasting no longer than an hour. 3) Exercise-related risks(such as drops) should be assessed. 4) Barriers to exercise should also be reduced by using group classes, home exercise, treatment and observation for non-movement symptoms and comorbidities, and individual goal setting to improve patient participation. Our patient-oriented intended exercise included relaxation, movement and stretching exercises, balance, gait training, and exercises of

facial expression and hands. Due to the progressive nature of PD, the present study focuses on the long-term exercise effects. We found that long-term exercise, lasting at least 18 months (E-EG), improved movement symptoms and quality of life.

Emerging evidence has suggested that exercise program may also have benefits for cognitive function in PD patients[1, 10, 13–16]. As the limited drug, non-pharmacological therapies, such as cognitive training and exercise may also play a role in improving cognitive functioning in PD[17]. Our data showed the effects of the intended exercise bring out improvement in cognitive abilities including attention, working memory and executive function. Given more time, the L-EG may have also experienced these improvements. Thus, our results suggest that exercise is an important part of the therapeutic regimen for PD patients and should be implemented as early as possible.

Physical exercise has been regarded as a practical, economic, and relatively safe neuroprotective and neuro-restorative PD therapy that can promote exercise-induced neuroplasticity[12, 15, 18, 19]. Meanwhile, it may mitochondrial energy metabolism, upregulate antioxidant mechanisms, reduce inflammation reduction, and promote angiogenesis and synaptogenesis[20]. Thus, exercise-related mechanisms of neuroplasticity are still not well understood. Observation of the relative contributions of intended exercise paired with non-invasive neuroimaging such as functional MRI (fMRI) is needed to begin understanding how the exercise we implemented may have affected brain function, connectivity, and motor behavior. It has been hypothesized that the precise exercise-induced mechanisms of neuroplasticity (namely, the ability of central nervous system cells to modify their structure and function in response to a variety of external stimuli), is that exercise improves synaptic strength and potentiates functional circuitry, leading to improved behavior in PD patients[15]. Increasing evidence also suggests that chronic oxidative stress (increased mitochondria biogenesis and autophagy up-regulation) can be reduced by physical exercise, which stimulates the synthesis of neurotransmitters and neurotrophic factors[21].

In conclusion, we found that intended exercise program implementation improved movement activities, cognitive ability, and quality of life in PD patients. These effects may be due to increased synaptic strength, functional circuitry potentiation, and decreased chronic oxidative stress. Although our data have not shown the underlying mechanism, this research provides an important foundation for future research in the area of exercise for PD patients.

Abbreviations

PD: Parkinson's disease; E-EG: early-exercise group; L-EG: late-exercise group; CG: control group; UPDRS: Unified Parkinson's Disease Rating Scale;); PDQ-39: PDQ-39 Questionnaire; 30s SST: 30 seconds squat and stand-up test; 10mW: 10m Walk test; MiniBESTest: Balance Evaluation Systems Mini Test; TUG: Time Up and Go Test; FAB: Fullerton advanced balance scale; ADLs: activities of daily living; LSVT-LOUD: Lee Silverman Voice Treatment-LOUD; H-Y scale: Hoehn and Yahr scale; LEDD: levodopa-equivalent daily dose; fMRI: functional magnetic resonance imaging.

Declarations

Statement of Ethics

This study was approved by the Ethics Committee in General Hospital of Chinese PLA (IRB No. S2020-042-02).

Disclosure Statement

The authors have no conflict of interest to report, and have consent for publication. The authors declare no financial and non-financial competing interests. All the data and materials are available.

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Author Contributions

Data analysis: Yang Yang, Jiarui Yao, Dan Liu and Na Wang. Investigation: Yang Yang, Jiarui Yao, Na Wang, Tianyu Jiang, Yuliang Wang and Dandan Liu. Methodology: Lifeng Chen and Weiping Wu. Formal design: Weiping Wu, Tianyu Jiang and Zhenfu Wang. Writing-review and editing: Yang Yang and Jiarui Yao.

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Figures

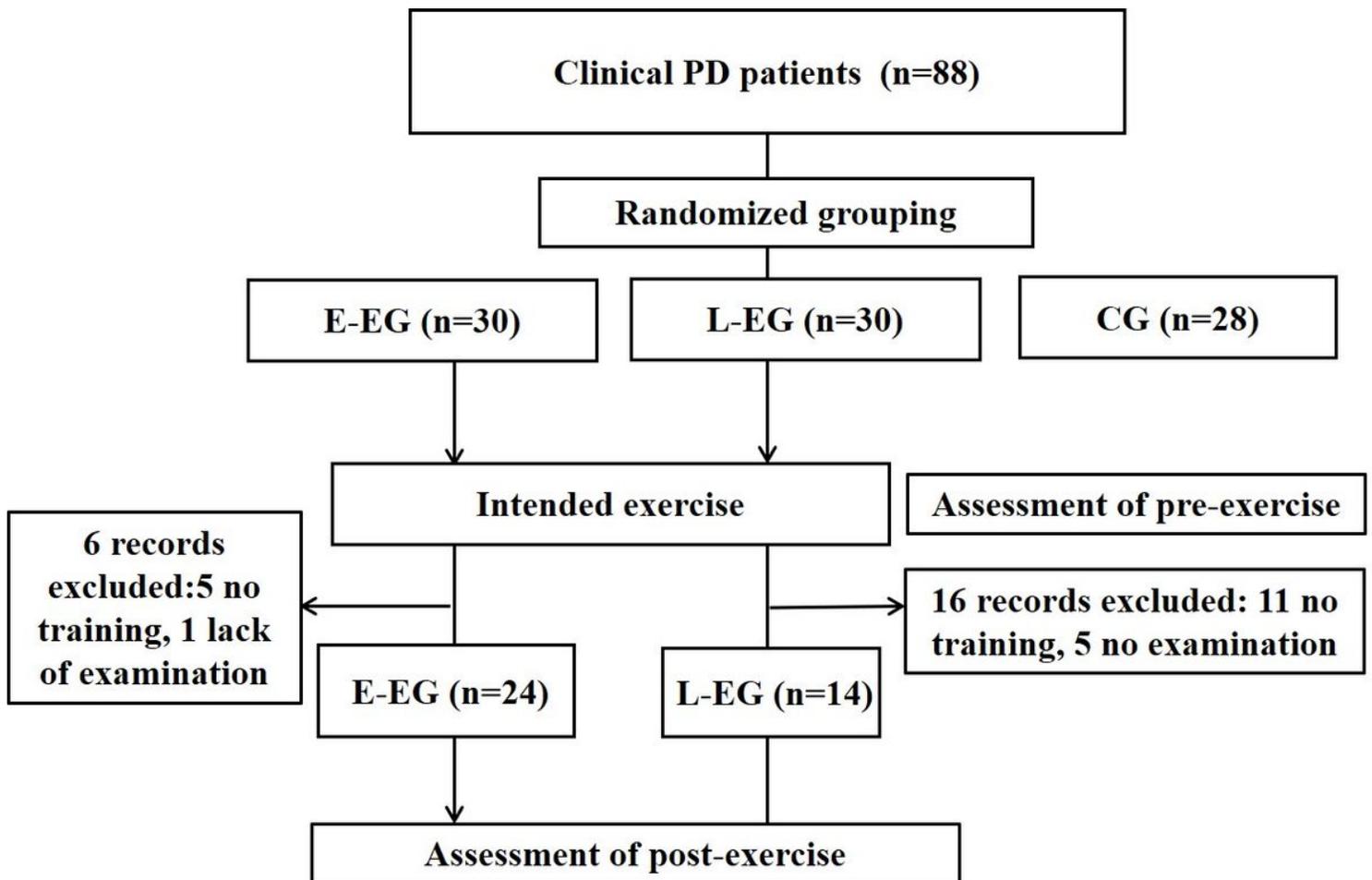


Figure 1

Flow of participants throughout the study.

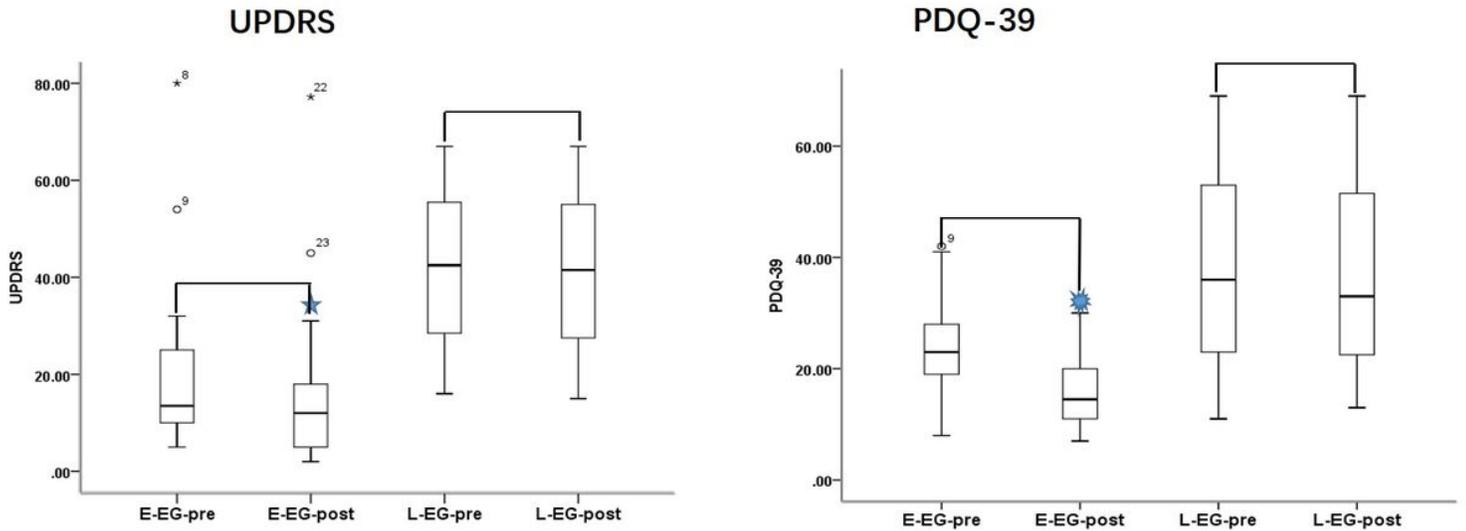


Figure 2

Participants with PD in the E-EG had lower performance in the URDRS and PDQ-39 compared to those in the L-EG at post-exercise. Error bars denote standard error. E-EG, early-exercise group; L-EG, late-exercise group. *stand for $p < 0.05$, #stand for $p < 0.01$

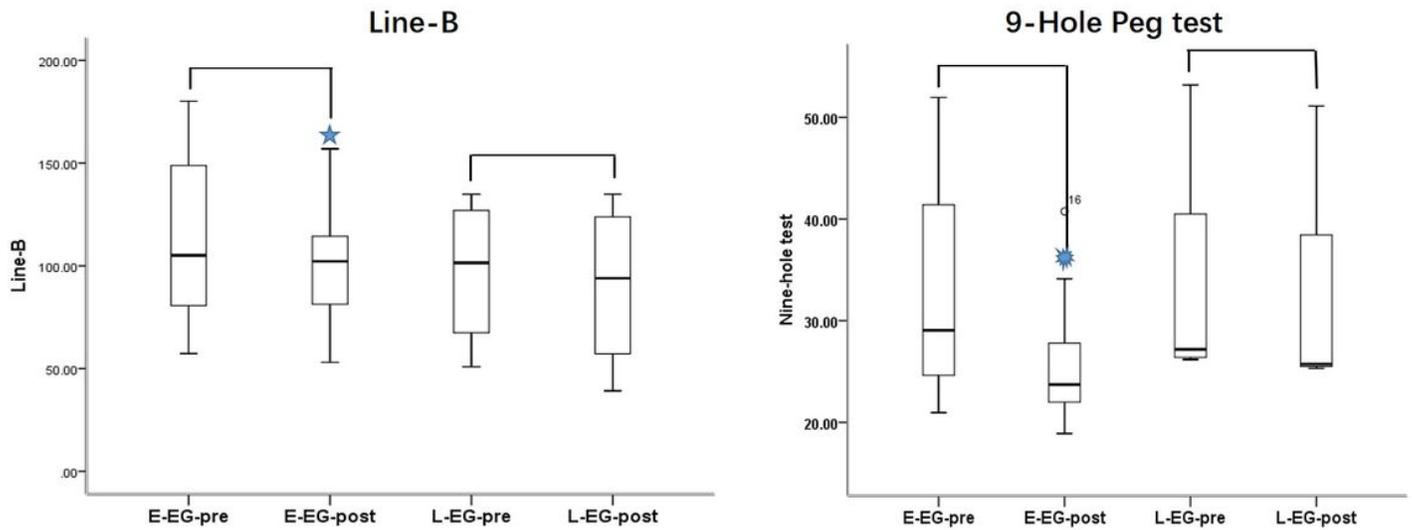


Figure 3

Participants with PD in the E-EG had lower performance in the Line B and 9-Hole Peg test compared to those in the L-EG at post-exercise. Error bars denote standard error. E-EG, early-exercise group; L-EG, late-exercise group. *stand for $p < 0.05$, #stand for $p < 0.01$