

Comparing Exercise in Parkinson's Disease—The Berlin BIG Study

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Abstract: Physiotherapy is widely used in Parkinson's disease (PD), but there are few controlled studies comparing active interventions. Recently, a technique named "Training BIG" has been introduced. Training BIG is derived from the Lee Silverman Voice Treatment and focuses on intensive exercising of high-amplitude movements. In the present comparative study, 60 patients with mild to moderate PD were randomly assigned to receive either one-to-one training of BIG, group training of Nordic Walking (WALK), or domestic nonsupervised exercises (HOME). Patients in BIG and WALK received 16 hours of supervised training within 4 (BIG) or 8 (WALK) weeks. The primary efficacy measure was difference in change in Unified Parkinson's Disease Rating Scale (UPDRS) motor score from baseline to follow-up

at 16 weeks between groups. UPDRS scores were obtained by blinded video rating. ANCOVA showed significant group differences for UPDRS-motor score at final assessment ($P < 0.001$). Mean improvement of UPDRS in BIG was -5.05 (SD 3.91) whereas there was a mild deterioration of 0.58 (SD 3.17) in WALK and of 1.68 (SD 5.95) in HOME. BIG was also superior to WALK and HOME in timed-up-and-go and timed 10 m walking. There were no significant group differences for quality of life (PDQ39). These results provide evidence that BIG is an effective technique to improve motor performance in patients with PD. © 2010 Movement Disorder Society

Key words: Parkinson's disease; BIG; Nordic walking; exercise; physiotherapy

Pharmacological and surgical treatments provide symptomatic relief in patients with Parkinson's disease (PD) but even with optimized treatment motor deficits progress during the course of disease. Exercise is an established therapeutic adjunctive and several studies evaluating different techniques have been published recently. However, few studies compare the effects of specific exercises with active control conditions.^{1,2} In addition, interpretation of trials is often limited by lack

of randomization, lack of rater-blinding, and inadequate follow up.^{3,4}

Different exercise approaches have been advocated for patients with PD, including use of attentional control,⁵ sensory cueing,^{6,7} repetitive training of specific movements,^{8,9} Nordic walking,¹⁰ domestic training programs,¹¹ and musculoskeletal exercises aiming to improve strength, range of movement, and endurance.^{12,13} High-intensity training of movement amplitude in PD was first applied in the form of the Lee Silverman Voice Treatment (LSVT[®]) to improve hypophonia. Subsequently, a controlled trial has shown that LSVT provides long-term (2 years) retention of improved loudness.¹⁴ The LSVT is now considered an evidence-based treatment for speech deficits in PD.²

Recently, a technique named "Training BIG," derived from the LSVT has been introduced.¹⁵ BIG focuses on high-amplitude movements. The training is characterized by multiple repetitions, high intensity, and increasing complexity. BIG is delivered in 16

Additional Supporting Information may be found in the online version of this article.

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Potential conflict of interest: Nothing to report.

Received 15 December 2009; Revised 25 February 2010; Accepted 30 March 2010

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.23212

(4×/week for 4 weeks) individual 1-hour therapy sessions. The goal of BIG (and LSVT) is to improve movement perception and to recalibrate disturbed scaling of movement amplitudes.

The aim of the current study was to compare the effects of BIG, Nordic walking, and unassisted home exercises. Nordic walking is a standardized approach that has been recommended for treatment of PD¹⁰ and is widely used in many countries. Subjects assigned to Nordic walking and BIG received the same total dose of therapist time. Training frequency (twice per week) and manpower (group treatment) were lower and therefore more representative of standard care situation in Nordic walking compared to BIG. The primary outcome measure was motor performance as assessed by blinded video rating of the Unified Parkinson's Disease Rating Scale (UPDRS)¹⁶ motor section.

METHODS

Patients

Sixty patients with PD referred from local outpatient clinics and office-based physicians were enrolled between June 2008 and May 2009. Participants were required to fulfill diagnostic criteria for idiopathic PD.¹⁷ Inclusion criteria comprised Hoehn & Yahr stages I–III,¹⁶ outpatient treatment, and stable medication 4 weeks prior to inclusion. Exclusion criteria were dementia (MMSE < 25), severe depression, disabling dyskinesias, and comorbidity affecting mobility or ability to exercise. Patients were randomly allocated by drawing lots to Training BIG (BIG), Nordic walking (WALK), or domestic exercise (HOME).

The study was approved by the local ethics committee and written informed consent was obtained from each subject.

Interventions

One physiotherapist (O.K.) certified as BIG-instructor and Nordic walking instructor delivered all BIG and Nordic walking sessions and also provided instructions for patients randomized to HOME. Patients assigned to BIG received 16 1-hour-sessions (4×/week for 4 weeks). Training BIG has previously been described in detail.¹⁸ Briefly, 50% of exercises consist of standardized whole-body movements with maximal amplitude, repetitive multidirectional movements (e.g., stepping and reaching), and stretching. The second half of exercise includes goal-directed activities of daily living (ADL) according to individual needs and preferences. ADL were performed using high-amplitude

“BIG-movements.” BIG is delivered one-to-one with intensive motivation and feed back. Patients are constantly encouraged to work with at least “80% of their maximal energy” on every repetition. Patients are taught to use bigger movements in routine activities to provide continuous exercise in everyday movements.

Patients assigned to WALK received 16 sessions (2×/week for 8 weeks). Each session lasted 1 hour and consisted of a standardized protocol for beginners including warming up, practicing Nordic walking, and, finally, a cooling down. Sessions were performed in a local park. All sessions were performed in groups of 4 to 6 participants and constantly supervised by the therapist.

Patients assigned to HOME received a 1-hour instruction of domestic training with practical demonstration and training. Exercises included stretching, high-amplitude movements, as well as active workouts for muscular power and posture.

Participants in all groups were encouraged to exercise regularly at home. They received a diary to document type and duration of exercise performed in addition to supervised BIG and WALK sessions. Additional information about the training programs is available in the online version of this article.

Assessment Procedures

The primary efficacy measure was the difference in change from baseline in UPDRS-III-score between treatment groups at week 16. The interval between active interventions and assessments (12 weeks in BIG and 8 weeks in WALK) was considered to be sufficient to capture sustained effects of therapy. For blinded assessment of the primary variable, patients were videotaped while performing all UPDRS part III items. Videos were then rated by an experienced rater (G.E.) blinded for group allocation and time-point of examination. Rating of rigidity was facilitated by brief comments from the person performing the physical examination.

Secondary outcome variables included differences in change from baseline for the following parameters: quality of life (PDQ-39¹⁹), timed up-and-go (TUG),²⁰ and time to walk 10 m (assessed with stopwatch). All tests were carried out during the medication “ON”-period.

Data Analysis

Differences in change from baseline to week 16 between treatment groups were assessed using analysis of covariance (ANCOVA) with the baseline values as a covariate. If the overall comparison revealed significant differences between groups, pairwise comparisons were performed. On an exploratory basis, ANCOVA with the base-

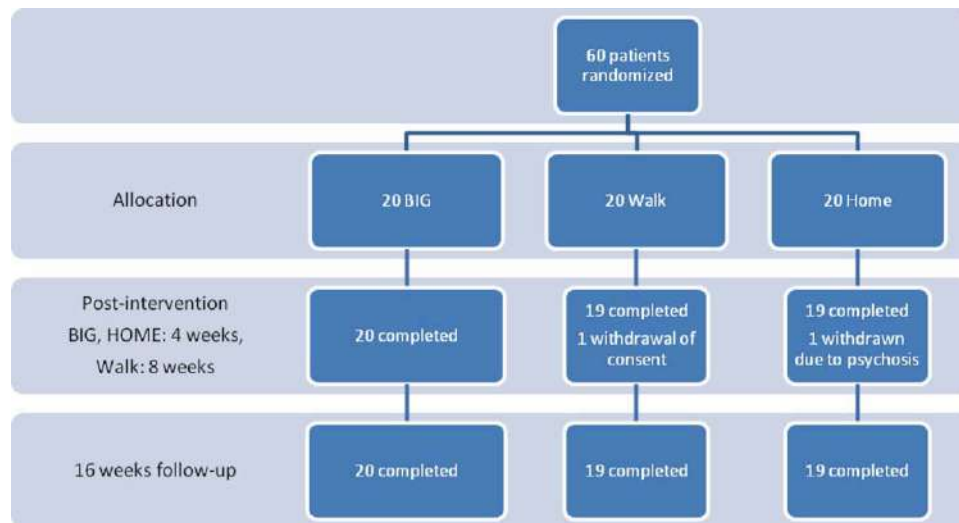


FIG. 1. Disposition of patients.

line values as a covariate was also used to analyze differences between intermediate and final assessments. α -Level was set at 0.05 and outcome analyses were conducted on a per-protocol-basis using SPSS and SAS softwares.

RESULTS

Subject Disposition (Fig. 1)

Of the sixty patients randomly assigned for treatment, 58 subjects completed the study and were available for follow up at week 16: BIG ($n = 20$), WALK ($n = 19$), and HOME ($n = 19$). One patient in WALK withdrew consent after 2 weeks, one patient in HOME dropped out before week 4 due to psychosis.

Patient Characteristics (Table 1)

Univariate ANOVA showed no significant differences between groups for age, disease duration, weekly exercise time, and L-dopa equivalence dose (LED). Adjustments of antiparkinsonian medication between baseline and week 16 occurred in 18 subjects (6 in each group). Changes of mean LED resulting from these adjustments were small (17.5 mg in BIG, 7.9 in WALK and 23.7 in HOME) and did not differ significantly between groups (Kruskal-Wallis Test, 0.437). Mean weekly exercise time (in addition to BIG or Nordic Walking) between baseline and final examination according to diary entries was 2.53 (SD = 1.19) in BIG, 2.10 (2.05) in WALK, and 2.6 (1.12) in HOME.

Efficacy (Table 2)

ANCOVA showed significant group differences for UPDRS-motor score at final assessment (Fig. 2). Mean

change from baseline was -5.05 (3.91) in BIG, 0.58 (3.17) in WALK, and 1.68 (5.95) in HOME ($P < 0.001$). In pair-wise comparisons, BIG was superior to WALK ($P < 0.001$) and HOME ($P < 0.001$). Descriptively, improvement of UPDRS in BIG was mainly related to bradykinesia items (items 18,19,23–27,29,31). Mean sum-score of these items decreased from 13.75 to 10 between baseline and week 16 in BIG. ANCOVA also showed group differences for TUG (mean change from baseline: BIG: -0.75 (1.94), WALK: 0.58 (1.72), HOME 0.44 (1.21), $P = 0.033$) and pairwise comparisons revealed a better outcome in BIG compared to WALK ($P = 0.036$) and HOME ($P = 0.024$). There was a tendency for group differences in ANCOVA for timed walking (mean change from baseline: BIG: -1.12 (0.84), WALK -0.59 (1.34), HOME: -0.45 (1.08), $P = 0.059$) with a better outcome in BIG compared to WALK ($P = 0.088$) and HOME (0.015). There were no significant group differences for PDQ39. Formal power analysis showed that the present study had a power of 27% to detect a difference of PDQ-sum-scores between the three groups. Seventy-four subjects need to be included in each group to detect a significant difference in PDQ out-

TABLE 1. Subject characteristics

	n	Age (y)	f/m	Disease duration (y)	Hoehn & Yahr	LED (mg/d)
BIG	20	67.1 (3.6)	13/7	6.1 (3.0)	2,8 (0.37)	486 (301)
WALK	19	65.5 (9.0)	12/7	7.8 (4.4)	2,6 (0.4)	530 (288)
HOME	19	69.3 (8.4)	11/8	7.4 (5.9)	2,5 (0.7)	463 (260)

Values are means (SD).

LED, L-dopa equivalence dose.

TABLE 2. Outcome measures

	Baseline, mean (SD)	Difference baseline/week 16, mean (SD)	ANCOVA between group, F/P value	ANCOVA, pairwise comparisons, F/P value
UPDRS III			11.9 / <0.001*	
BIG	21.1 (6.3)	-5.05 (3.91)		BIG vs. WALK 21.2/<0.001*
WALK	18.5 (5.8)	0.58 (3.17)		BIG vs. HOME 16.7/<0.001*
HOME	19.1 (9.7)	1.68 (5.95)		WALK vs. HOME 0.53/0.470
PDQ39			1.36 / 0.264	
BIG	31.2 (20.3)	-3.25 (11.28)		
WALK	34.3 (16.5)	-5.36 (11.34)		
HOME	35.8 (13.4)	0.21 (12.00)		
TUG (sec)			3.64 / 0.033*	
BIG	8.1 (1.6)	-0.75 (1.94)		BIG vs. WALK 4.77/0.036*
WALK	7.7 (1.4)	0.58 (1.72)		BIG vs. HOME 5.58/0.024*
HOME	7.7 (1.3)	0.44 (1.21)		WALK vs. HOME 0.08/0.784
Timed 10 m (sec)			2.97 / 0.059 [#]	
BIG	7.7 (1.1)	-1.12 (0.84)		BIG vs. WALK 3.08/0.088 [#]
WALK	7.9 (1.3)	-0.59 (1.34)		BIG vs. HOME 6.57/0.015*
HOME	7.9 (1.3)	-0.45 (1.08)		WALK vs. HOME 0.21/0.647

Changes from baseline to follow up at week 16. Pairwise post hoc comparisons between conditions (BIG/WALK/HOME) were performed when ANCOVA indicated between-group differences.

* $P < 0.05$,

[#] $P = 0.05-0.1$.

come between groups. ANCOVA did not reveal differences between intermediate and final assessments for UPDRS-rating, TUG, timed walking, and PDQ39.

DISCUSSION

In the present prospective controlled, rater-blinded study, training BIG led to improved motor performance in patients with PD. The degree of change in UPDRS motor score (mean 5.05) is considered as clinically relevant.²¹ In contrast to BIG, UPDRS motor score was not improved in patients with training in Nordic walking (WALK) with the same amount of supervised sessions and in patients receiving a single 1-hour-instruction for domestic training by a therapist (HOME). Outcome with training BIG was also superior in further assessments (TUG, 10-m walk). Our findings are in accordance with a previous non-controlled study on BIG therapy in 18 patients with PD,¹⁵ reporting a modest (12–14%) increase of velocity in walking and reaching movements after 4 weeks of training BIG.

Significant changes in quality of life (PDQ-39) were not observed but numerical improvements in PDQ-scores in patients receiving BIG and Nordic walking suggest that the present study may have been under-powered to detect moderate improvements in quality of life.

Exercise therapy in PD has recently been subject to numerous systematic reviews^{2,4,22–24} and growing interest has led to an increasing number of controlled trials.²³ Yet, there are only few studies comparing specific types of physiotherapy with both active compar-

tors and inactive controls. Sage and Almeida²⁵ reported a more pronounced improvement in UPDRS-III and other motor tasks with exercises designed to improve sensory attention and body awareness compared to lower-limb aerobic training. Mak and Chan²⁶ found better outcome in the Sit-and-Stand task when subjects received training including sensory cues compared to conventional exercise. In both studies, patients without active interventions did not improve. In the present

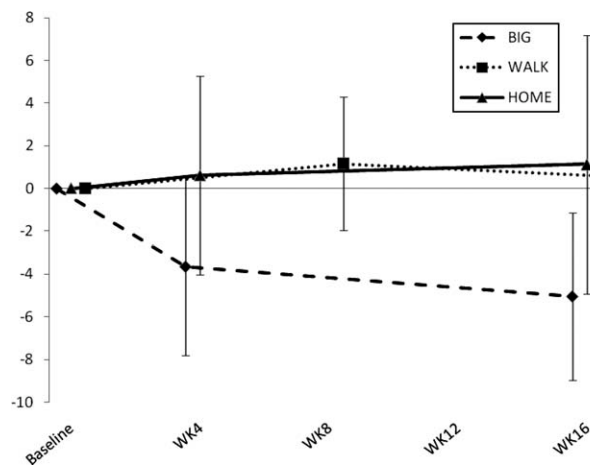


FIG. 2. UPDRS motor score (blinded rating), mean change from baseline (vertical bars = standard deviations). Change between baseline and follow up at week 16 was superior in BIG (interrupted line) compared to WALK (dotted line) and HOME (solid line), $P < 0.001$. ANCOVA did not disclose significant differences between intermediate and final assessments.

study, outcome differed clearly between the active interventions. Intensive one-to-one training (BIG) was found to be more effective than Nordic walking delivered as a group training. Differences in training techniques may have contributed to the results. In addition, it is likely that individual face-to-face interaction with the therapist was more crucial for successful outcome than total exercise-time. Further studies are needed to explore differences in cost-effectiveness between the (more expensive) individual BIG training, group treatments, and self-supervised domestic exercise.

Additional exercise and adjustments of medication in some patients during the course of the trial are methodological limitations of the present study. Yet, a more rigid protocol, requiring patients to abstain from any further exercise and any changes of medication for a 16-week observation period, was not considered feasible in the given clinical setting and would have inferred a larger number of drop outs. Since small adjustments of medication and additional exercise were equally distributed between groups it is unlikely that these factors were crucial for the superior outcome in BIG. Yet, the relatively high level of additional exercise (2.1–2.6 hr per week) may have influenced overall outcome. A recent study comparing physiotherapist-supervised and self-supervised home exercise reported equal improvements after 8 weeks of training.²⁷ Positive effects of intensive domestic exercise are likely to have contributed to relatively stable follow-up performance in the HOME group and may also have blurred effects of Nordic walking in this study. In contrast to the present results, a 6-week Nordic walking training was reported to improve timed walking tests, TUG, and quality of life (PDQ-39) in a recent study.¹⁰ Endurance and velocity in long walking distances (5–7 km) seemed to improve in patients performing Nordic walking in the present study, but this was not systematically assessed.

Most current physiotherapies in PD rely on compensatory behavior and external cueing to bypass deficient basal ganglia function.^{5,7,28–30} By contrast, other protocols do not focus on teaching compensations but rather on retraining of deficient functions. Task-specific repetitive high-intensity exercises in PD include treadmill-training,³¹ training of compensatory steps,⁹ walking,³² and muscle strengthening.^{12,33} Training of amplitude in patients with PD was first applied to treat hypophonia with Lee Silverman Voice Treatment (LSVT[®]). Training of amplitude rather than speed was chosen as the main focus in LSVT and BIG since training of velocity can induce faster movements while it does not consistently improve movement amplitude and accuracy.^{34,35}

In contrast, training of amplitude results in bigger, faster, and more precise movement.^{34–36}

In our current understanding, deficient speed-amplitude regulation leads to an underscaling of movement amplitude at any given velocity.^{35,37,38} Multiple repetitions, high intensity, and complexity are used in LSVT and BIG to restore speed-amplitude regulation. Continuous feedback on motor performance and training of movement perception is used to counteract reduced gain in motor activities resulting from disturbed sensorimotor processing.³⁹ Finally, the goal of BIG is to teach patients to use bigger movements in routine activities to provide sustained training in everyday movements. Detailed guidelines have been defined for LSVT and BIG¹⁸ to ensure standardized implementation in clinical practice.

The present study is the first randomized controlled trial comparing BIG training with another active intervention. Effects of BIG on UPDRS-motor-scores were superior compared to Nordic walking. Results from studies in speech therapy have shown that improvements of voicing achieved with LSVT are retained for up to 2 years after treatment¹⁴ and are associated with transfer to other motor symptoms including mimics and swallowing.⁴⁰ Preliminary results from a PET-study showed that reduction of hypophonia after LSVT is associated with a shift of cortical motor activation towards subcortical areas suggesting more “automatic” speech motor processing.⁴¹ Further studies are needed to evaluate whether BIG is likewise associated with long-term improvements, transfer effects (e.g. from large body movements to fine motor functions or voicing), and re-organization of brain activation patterns.

Acknowledgments: We thank Deutsche Parkinson Gesellschaft for financial and organizational support, Dr. Helge Iwersen-Schmidt and staff of Zentrum für ambulante Rehabilitation Berlin for providing rooms and technical support and Dr. Brigitte Wegner for support with statistics. We are also grateful to all patients and physicians who have contributed to the success of this study.

Financial Disclosures: Georg Ebersbach: Honoraries for presentations from Boehringer Ingelheim Pharma, Cephalon, Desitin Pharma, GlaxoSmithKline, Valeant, Novartis, Orion, and Schwarz Pharma (UCB). Honoraries for consultancy and advisory board activities from Axxonis Pharma, Boehringer Ingelheim Pharma, Cephalon, Desitin Pharma, Valeant, Orion, Grants from Deutsche Parkinson Gesellschaft (DPV) and Deutsche Forschungs-Gesellschaft (DFG). Jörg Wissel: Honoraries for presentations and advisory board activities from Allergan, Eisai, Ipsen Medtronic and Merz. Andreas Kupsch: Honoraries for presentations from Allergan, Boehringer Ingelheim Pharma, Desitin Pharma, GlaxoSmithKline, Ipsen, Lundbeck, Merz Pharma, Medtronic, Novartis, Orion, and Schwarz Pharma (UCB). Honoraries for advisory board

activities and consultancy from Novartis and Medtronic. Grants from Deutsche Forschungs-Gesellschaft (DFG) and Fresenius-Körner-Foundation.

Author Roles: Georg Ebersbach: Research project: conception and organization; Statistical analysis: design and execution; Manuscript: writing of the first draft. Almut Ebersbach: Research project: conception, organization, and execution; Statistical analysis: execution and review and critique; Manuscript: review and critique. Daniela Edler: Research project: conception, organization, and execution; Manuscript: review and critique. Matthias Kusch: Research project: execution; Manuscript: review and critique. Olaf Kaufhold: Research project: conception, organization, and execution; Manuscript: review and critique. Jörg Wissel: Research project: conception and organization; Manuscript: review and critique. Andreas Kupsch: Research project: organization; Statistical analysis: review and critique; Manuscript: review and critique.

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