Parkinsonism and Related Disorders xxx (2013) 1–6

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Effects of a formal exercise program on Parkinson's disease: A pilot study using a delayed start design

A. Park [a,*], D. Zid [b], J. Russell [b], A. Malone [a], A. Rendon [a], A. Wehr [c], X. Li [c]

[a] Department of Neurology, The Ohio State University, Columbus, OH 43210, USA
[b] Columbus Health Works, Columbus, OH 43212, USA
[c] Center for Biostatistics, The Ohio State University, Columbus, OH 43210, USA

ARTICLE INFO

Article history:
Received 18 June 2013
Received in revised form
28 September 2013
Accepted 5 October 2013

Keywords:
Parkinson's disease
Exercise
Tinetti
Neuroprotection
Depression

ABSTRACT

Introduction: Parkinson's Disease (PD) is a progressive neurodegenerative disease. Increasing evidence shows that physical exercise is beneficial for motor and non-motor symptoms of PD, and animal models suggest that it may help slow progression of disease.
Methods: Using a randomized delayed-start design, 31 patients were randomized to an early start group (ESG) or a delayed start group (DSG) exercise program. The ESG underwent a rigorous formal group exercise program for 1 h, three days/week, for 48 weeks (November 2011–October 2012). The DSG participated in this identical exercise program from weeks 24–48. Outcome measures included the Unified Parkinson's Disease Rating Scale (UPDRS), Walking Test (get-up-and-go), Tinetti Mobility Test, PDQ-39 Questionnaire, and the Beck Depression Inventory.
Results: There was minimal attrition in this study, with only one patient dropping out. Results did not show improvement in total UPDRS scores with early exercise. At week 48, the mean change from baseline total UPDRS score was 6.33 in the ESG versus 5.13 in the DSG ($p = 0.58$). However, patients randomized to the ESG scored significantly better on the Beck Depression Inventory, with a mean improvement of 1.07 points relative to those in the DSG ($p = 0.04$).
Conclusions: The findings demonstrate that long-term, group exercise programs are feasible in the Parkinson's disease population, with excellent adherence and minimal drop out. While the outcome measures used in our study did not provide strong evidence that exercise has a neuroprotective effect on motor function, earlier participation in a group exercise program had a significant effect on symptoms of depression.

1. Introduction

Parkinson's disease (PD) is the second most common progressive neurodegenerative condition in the United States, characterized by the motor symptoms of bradykinesia, rigidity, and resting tremor. It has been estimated that approximately 630,000 people in the United States had the diagnosis of PD in 2010, and prevalence of PD is expected to double by 2040, which will substantially increase the economic burden of this disease [1]. While motor symptoms and the dopaminergic system have long been the primary focus of this disease, it is now recognized that widespread involvement of various non-dopaminergic pathways also contribute to the symptoms of PD. Furthermore, it is increasingly clear that the non-motor symptoms of PD, including depression and anxiety, are often more bothersome to patients than their motor symptoms. Recently, the National Parkinson's Foundation Quality Improvement Initiative (QII) data demonstrated that the depression affects health status almost twice as much as motor impairment [2].

Countless studies have shown that a variety of exercises improve the symptoms of PD, including home based exercise [3], treadmill [4], resistance exercise [5], tango dancing [6], tai chi [7], and robot-assisted gait training [8]. The LSVT®BIG therapy is derived from the Lee Silverman Voice Treatment, and focuses on intensive exercising of high-amplitude movements. This therapy has been shown to be an effective technique for improving motor performance in patients with PD, with significant improvements seen in Unified Parkinson's Disease Rating Scale (UPDRS) motor scores [9]. At this time, there are no specific recommendations on

* Corresponding author. Madden Center for Parkinson's Disease and Related Disorders, Wexner Medical Center at The Ohio State University, 395 W. 12th Avenue, Columbus, OH 43210, USA. Tel.: +1 614 293 4969; fax: +1 614 293 6111.
E-mail address: ariane.park@osumc.edu (A. Park).

1353-8020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.parkreldis.2013.10.003

what type of exercise is most beneficial in PD, leading most clinicians to suggest any routine leading to improved physical fitness.

While there has been a strong research interest in identifying potential "neuroprotective" therapies that might slow down progression of PD, currently none have proven clinically effective. Large cohort studies have shown that vigorous exercise in midlife significantly reduces risk of developing PD [10–12]. In addition, longevity in PD has been associated with exercise [13]. Thus, if exercise may be involved in reducing the risk of PD, it is possible that it may play a role in slowing down disease progression. In 6-OH-DA rodent models of PD, studies have shown that parkinsonian deficits are attenuated by exercise [14]. Conversely, nonuse via cast immobilization of the parkinsonian side significantly exacerbates motor deficit [15], suggesting that limb disuse may lead to further neurodegeneration. In MPTP rodent models, exercise appears to have a protective effect on dopamine neurons from acute MPTP toxicity [16]. Additional findings have suggested that exercise may attenuate the hyperexcitability of striatal neurons seen after dopamine depletion, possibly via modulation of glutamatergic receptor subunit expression [17]. It is known that vigorous exercise induces brain neurotrophic factor expression [18], and both brain derived neurotrophic factor (BDNF) and glial cell line-derived neurotropic factor (GDNF) have been shown to be decreased in the substantia nigra of patients with PD [19]. It may be that neurotrophic growth factors reduce the vulnerability of DA neurons, thus conferring neuroprotective benefit.

To our knowledge, this is the first study to look at the feasibility of conducting a long-term formal group exercise program in PD, using a randomized delayed start design. This type of study design aims to separate disease modifying/neuroprotective effects from symptomatic effects. Thus, our goal was to gain information on the potential neuroprotective effects of exercise, with the primary outcome measure being total UPDRS score. Furthermore, we explored whether early exercise may confer non-motor benefit in terms of depression and quality of life.

2. Methods

Thirty-one patients with idiopathic PD were selected over a six month period. All consecutive patients referred to our movement disorder center who met inclusion criteria were approached for enrollment. The following inclusion criteria were chosen: 1) Age 40–70 years old diagnosed with PD within three years of symptom onset with a Hoehn and Yahr stage 1 or 2, 2) Participants met the UK Parkinson's Disease Brain Bank criteria [20], 3) Subjects could be on either no anti-parkinsonian medications, or could be taking amantadine, monoamine oxidase B inhibitors, and/or dopamine agonists, and 4) All subjects must have had adequate vision and English sufficient for compliance with testing and surveys. Exclusion criteria were: 1) Hoehn and Yahr stage 3 or higher, 2) Atypical or secondary parkinsonism, 3) Any other condition (other than the primary indications) which in the opinion of the investigators might contribute to gait or balance impairments or complicate its assessment, and 4) Subjects who have been or are on any formulation of levodopa.

Using a delayed start design, participants were randomized to receive either the exercise intervention for both of the 24-week phases (early start group or ESG), or to receive the exercise intervention in the second phase, weeks 24–48, only (delayed start group or DSG). The two phases were designed to capture any symptomatic benefit of the exercise intervention at the end of the first phase, and also any sustained benefit by the end of the study. Research visits were done at baseline, and at weeks 8, 16, 24, 32, 40 and 48 weeks. Attendance was taken at each exercise session, and all participants were required to participate in at least 70% of the exercise sessions in order to remain in the study. At each visit, participants provided a home exercise diary and an updated list of current PD medications. In addition, blinded clinicians conducted the Unified Parkinson's Disease Rating Scale (UPDRS) [21], Timed Walk [22] to monitor speed of movement and the Tinetti test [23], which assesses gait and balance status, and has been associated with changes in fall risk [24]. To minimize inter-rater variability, only three clinically experienced raters were used for these tests at all visits. During the baseline visit and at the 48-week visit, participants filled out the PDQ-39 questionnaire [25], which is a disease-specific measure of subjective health status, and the Beck Depression Inventory [26], an instrument to assess the severity of depression. In addition, at the baseline visit participants completed a brief demographic survey, and at week 48, participants filled out a brief post-exercise program survey.

The formal group exercise program was led by a personal trainer, and was based on two, 12-week fitness cycles as follows.

2.1. First 12-week cycle (done in a group setting)

Weeks 1–6 concentrated on each participant achieving a baseline fitness level to allow each person to safely begin the formal strength program. This portion of the fitness agenda consisted of a cardiovascular, core strength, and joint integrity plan.

During weeks 7–12, formal strength training was added with a focus on increasing weight intensity while repetitions decrease (repetition numbers from 25 decreasing to 15). The goal was that each participant came to muscle fatigue/failure with each set.

2.2. Second 12-week cycle (done in a group setting)

Weeks 13–14 consisted of cardio/core/joint integrity work without formal strength training.

During weeks 15–24, formal strength training was added, however weight intensity increased further as repetitions decreased to a smaller number (repetition numbers from 25 decreasing to 10), again with the goal of muscle fatigue/failure with each set.

All sessions lasted 1 h, and occurred three times per week for 48 weeks. These 12-week cycles were identical for both the ESG and DSG. After week 24, the ESG repeated the two, 12-week cycles over again. During cardiovascular training, attempts were made to have each participant achieve 75%–85% of their maximum heart rate for a 1-min interval. A CPR/ACLS certified RN was in attendance during each exercise session to further ensure participant safety.

Ethical permission to conduct this study was obtained from the Institutional Review Board of The Ohio State University. Written informed consent was obtained from each participant prior to enrollment. This study was conducted in full accordance with the Declaration of Helsinki.

3. Statistical analysis

For all the randomized subjects, baseline demographics and clinical characteristics were summarized between groups. For each outcome measure, group mean and standard deviation of the change in scores from baseline was reported at each post-randomization visit.

Our primary outcome was change in total UPDRS score from baseline. To assess neuroprotective effect in this delayed start design [27], we tested three endpoints simultaneously, each at the 0.05 significance level. This was done to determine whether any differences seen between the groups was enduring (as would be expected with a disease-modifying effect) and not diminishing (as would be expected with an intervention that had a prolonged

Please cite this article in press as: Park A, et al., Effects of a formal exercise program on Parkinson's disease: A pilot study using a delayed start design, Parkinsonism and Related Disorders (2013), http://dx.doi.org/10.1016/j.parkreldis.2013.10.003