Clinical Neurology and Neurosurgery 150 (2016) 117–124

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

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

Patterns and predictors of freezing of gait improvement following rasagiline therapy: A pilot study

Fariborz Rahimi[a,*], Angela C. Roberts[b], Mandar Jog[c]

[a] Department of Electrical Engineering, Bonab University, Bonab, Iran
[b] Northwestern University, Roxelyn and Richard Pepper Department of Communication Sciences and Disorders, 2240 Campus Drive, Evanston, Illinois, United States
[c] Department of Clinical Neurosciences, London Health Sciences Centre, London, Ontario, Canada

ARTICLE INFO

Article history:
Received 8 March 2016
Received in revised form 10 August 2016
Accepted 24 August 2016
Available online 30 August 2016

Keywords:
Parkinson's disease
Freezing of gait
Rasagaline
Treatment
Variability

ABSTRACT

Objectives: Freezing of gait (FoG) is a challenging clinical symptom in Parkinson's disease with variable improvements in FoG with rasagiline. In this prospective, uncontrolled, pre-/post- treatment pilot study, we explore the clinical variables that contribute to this variability and those that predict improvement.
Patients and methods: Frequency and duration of FoG, along with other standardized scales, were evaluated in 18 optimally medicated PD participants with intractable FoG, prior to and after completion of a 90-day course of 1 mg daily rasagiline. Gait tasks were video-recorded and analyzed by two independent reviewers. After evaluating the simple main effect, hierarchical cluster analysis was used to identify subgroups for treatment responsiveness. Bidirectional elimination stepwise regression analysis was conducted to identify which clinical variables predicted reduction in frequency of FoG events post-treatment.
Results: There were no overall pre-/post- treatment improvements, a result driven by a heterogeneous response to treatment. Three subgroups were identified: improved (n = 6) with a 136% and 162% reduction in FoG count and duration; worsened (n = 5) with 154% and 141% increase in FoG count and duration; and no change (n = 3). The final predictive model had good explanatory power (adjusted-R^2 = 0.9898, $p < 0.01$), explaining 99% of the variance between the improved and worsened groups. In this model, lower UPDRS gait scores, higher LEDD dose, lower anxiety scores, lower FOG-Q scores, and higher UPDRS scores for lower extremity rigidity and rise from chair, predicted FoG-related rasagiline benefit.
Conclusion: Using both objective and subjective measures for FoG, the current pilot study identified a set of clinical variables that may elucidate the heterogeneous FoG-responsiveness following rasagiline treatment and aid in predicting improvement.

1. Introduction

In Parkinson's disease (PD), health related quality of life is impacted negatively by progressive gait disturbances [1]. Gait impairments in PD lead to increased falls and reduced community mobility [2,3]. One of the more disabling gait impairments associated with PD is freezing of gait (FoG). FoG is characterized by the sudden inability to voluntarily initiate stepping movements [4]. While FoG is more commonly associated with advanced stages of the disease, it can occur at any stage and can present substantial challenges in the clinical management of gait impairment in PD.

Although dopaminergic medication improves some aspects of gait, FoG can persist even with optimal PD pharmacological management [5–7]. Fasano and Lang [8] identified four pharmacological variants of FoG that are defined by responsiveness to dopaminergic treatment. These authors, and others [9,10], have identified a subgroup of individuals whose FoG is unresponsive to oral dopaminergic treatments, despite optimizing dosing levels and medication regimes.

Adjunct pharmaceutical therapies have demonstrated variable, but promising, results in the management of FoG in PD. Studies have shown that rasagiline, a monoamine oxidase type B inhibitor (MAO-B), may provide benefit to individuals with FoG [11,12]. In the LARGO study [13], retrospective analysis showed that rasagiline improved Unified Parkinson Disease Rating Scale–postural instability and gait dysfunction scores (UPDRS-PIGD) and UPDRS-freezing scores. Similarly, both the TEMPO and the PRESTO studies showed

* Corresponding author at: Department of Electrical Engineering, University of Bonab, Velayat Highway, Engineering-305, Bonab, Iran.
E-mail addresses: frahimi@bonabu.ac.ir, fariborz.rahimi@gmail.com (F. Rahimi).

http://dx.doi.org/10.1016/j.clineuro.2016.08.025
0303-8467/

FoG-related benefits of rasagiline treatment [14,15]. However, an interesting finding from both the TEMPO and the PRESTO studies is that while some participants experienced a FoG-related benefit of rasagiline, other participants actually experienced a worsening of FoG post treatment [14,15]. These findings suggest the possibility of subgroup-specific responsiveness to rasagiline treatment. However, the specific profiles of patients that improved versus those that worsened were not delineated clearly by these study authors. Consequently, the specific clinical profile of patients that might benefit from adjunct therapy with rasagiline remains unclear.

Subtype variability in FoG-responsiveness to treatment is an emerging focus in the literature [8–10]. Previous studies have used a variety of factors to characterize these potential subgroups, including cognition [10,16,17] and pharmacological responsiveness [8,9,18]. For example, Amboni et al., reported that intractable FoG could be related to under-optimized levodopa treatment [18]. Clinically, given the variability in FoG treatment response, it is important to identify the variables that predict potential benefit not only from dopaminergic therapies but also from adjunct pharmacotherapies.

Our pilot study expands the current body of literature by identifying variables that may predict gait improvement (reduced frequency of and duration of FoG episodes) with adjunct rasagiline therapy in a group of individuals with PD and dopaminergic unresponsive FoG. Based on the existing literature, we hypothesized that global cognition (i.e., MoCA scores), LEDD, UPDRS scores and self-reported anxiety (i.e., Beck Anxiety Inventory scores) would be associated with greater responsiveness to rasagiline treatment.

2. Materials and methods

2.1. Study design

The Human Subjects Research Ethics Board (HSREB) of the University of Western Ontario approved the study. The study followed a prospective, experimental, pre-/post-treatment, uncontrolled design. Measurements were conducted at baseline (prior to starting the medication) and 3-months later, following a 90-day course of rasagiline. Since FoG is a highly variable and episodic phenomenon, participants were evaluated at the same time of day for the pre- and post- visits. Each visit was 90–120 min in duration. Rest breaks were provided between tasks and as requested by participants. Care was taken in scheduling study visits to ensure that participants remained in an optimally ON state while completing the protocol.

Participants were not remunerated for their participation. Participants did receive reimbursement for parking costs associated with the study. Rasagiline was provided to participants at no cost, for the duration of the study. Study personnel monitored participants for complications/side effects every two weeks by telephone and at the end of the study in person. Since the study was conducted within the ecological context of the existing clinical management plan, participants had unrestricted access to the clinic nurse and the movement disorders neurologist throughout the course of the study.

2.2. Recruitment

Eighteen participants were recruited from a single movement disorders clinic (London Health Sciences Centre, London, Ontario, Canada) using a convenience-sampling method. Recruitment focused on rasagiline naïve participants, who had recently been prescribed the medication as an adjunct therapy for FoG. A movement disorders neurologist (MJ) recruited and enrolled participants during routine clinic visits. To be eligible for the study, participants met the following criteria: (1) presented with Hoehn and Yahr scale scores between 2 and 4, (2) experienced intractable FoG even with optimal dopaminergic treatment, and (3) were clinically-determined to require adjunct therapy with rasagiline (i.e., physician made this decision clinically prior to recruiting).

Intractable FoG (dopaminergic unresponsive FoG) was defined as the persistence of start hesitation, gait ignition failure, and freezing during walking, despite optimization of dopaminergic medications. The movement disorders neurologist (MJ) made the diagnosis of intractable FoG using visual inspection of gait patterns during a clinical gait assessment, patient report (corroborated by a family member), clinical history, and scores from the Unified Parkinson Disease Rating Scale (UPDRS). The presence of FoG was corroborated using the FOG-Q, administered at the first study visit.

Optimal dopaminergic treatment was determined by the movement disorders neurologist (MJ) within a clinical setting. Prior to recommending adjunct therapy with rasagiline, the dosing of dopaminergic medications was optimized so as to produce dyskinesia in the patient which resulted in a measured ON. For each patient, this ON-state was then defined as the best or optimized ON. Those patients for whom adjunct therapy with rasagiline was recommended (and therefore were identified as potential participants in the current study) experienced FoG even in this stage of ON. Because of the presence of mild (but bothersome) dyskinesia, a higher dose of levodopa was not given to these patients.

Enrolled patients met the UK Brain Bank Criteria for PD [19] and were on stable, optimized, medications for at least three months prior to study enrolment. Exclusion criteria were history of neurosurgical procedures, neurological diseases other than PD (e.g., diffuse white matter disease, stroke), untreated clinical depression, clinically diagnosed generalized anxiety disorder, dementia, and use of an assistive walking device. A post-hoc review of the movement disorders clinic records indicated that no referral to physical therapy services had been made in the two years prior to study enrollment for any of the participants.

2.3. Treatment

Study participants were prescribed rasagiline 1 mg daily by their movement disorders neurologist (MJ). Participants did not begin taking rasagiline until the day after the baseline data collection. Participants were required (unless complications arose) to take the medication for a 90-day course, while taking all other medications as prescribed during the duration of the study.

2.4. Scale measures

A series of standardized scale measures were administered to all study participants along with the gait tasks, pre and post rasagiline therapy. The battery (Table 1) was designed to characterize motor severity, subjective ratings of FoG severity/frequency, global cognition, depression, and anxiety across participants. Scale measures were performed in a fixed order across participants and were administered prior to the gait tasks.

2.5. Gait tasks

Participants completed six scripted gait tasks followed by a 'free' walking task (cued navigation task) that required participants to ambulate in an open area with sudden, unpredicted turns (Table 2). Gait tasks were modeled on those described by Snijders et al. [20], in order to maximize elicitation of FoG episodes in the laboratory.