Robotic Gait Rehabilitation in Parkinson's Disease

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1.0 Background

Individuals diagnosed with Parkinson's disease (PD) often suffer from difficulties with gait initiation, maintaining a consistent kinematic gait pattern, and transitions between gait environments. Focused gait training that provides an environment that can emphasize motor control improvement in these deficits would be ideal for building a rehabilitative foundation for gait recovery for individuals with PD.

One approach that has been used to maintain and restore function in other neurological populations with severe disability is gait rehabilitation using treadmill training. This approach allows for specific and repetitive practice of walking movement and can involve therapist or electromechanical assistance. There is preliminary evidence from two small, uncontrolled studies supporting the benefits of therapist-assisted treadmill training on walking, balance, fatigue, spasticity, muscle strength, and quality of life in patients with PPMS and SPMS. Nevertheless, therapist-assisted gait training can require up to three trainers per patient making it burdensome and inefficient in the clinical setting. The intensity of manual treadmill training is low (i.e., <1.5 METs) based in part on the physical capacity and fitness level of the trainers, yet physiological adaptations for optimizing outcomes require moderate or vigorous intensity exercise.

Robotic-assisted gait training (RAGT) addresses many of the limitations of therapist-assisted gait training and can be performed using either exoskeleton or end-effector devices. Exoskeleton devices involve programmable drives or passive elements which physically move the lower limbs, whereas, end-effector approaches involve driven footplates that have trajectories that simulate the stance and swing phases. The G-EO System (Reha Technology AG: Olten, Switzerland) is a novel end-effector robotic gait training system that was developed for regaining mobility and independence in stroke survivors. This system involves minimal therapist and patient burden (e.g., quick set-up, single operate usage), there is the unique capacity for practicing walking and stair climbing movements, and the patient can receive real-time visual feedback. Gait training using the G-EO System has been applied in patients with stroke, Multiple Sclerosis (MS), and cerebral palsy (CP). These studies have established safety and feasibility, and preliminary evidence for benefits on mobility and function. For example, two studies involving 4 weeks of G-EO training with conventional physical therapy in non-ambulatory subacute stroke patients reported improved gait, stair climbing ability, leg strength, and activities of daily living (ADL) compared to physical therapy alone. There is limited RAGT studies evaluating the impact of this type of training for individuals with PD. The potential focus on improved gait kinematics may be of particular benefit for PD patients who often struggle with maintain step length and initiation.

2.0 Rationale and Specific Aims

The logistic advantages and advanced training capabilities of the G-EO System, as well as the benefits reported in other populations, support this strategy as an effective rehabilitation tool for restoring and maintaining function in Parkinson's disease. This approach represents an opportunity for improving current clinical practices for patients with Parkinson's disease. If successful, this project will provide initial evidence for increasing patient access to the G-EO System, and this could be accomplished through "regional technology centers" using a rural health-delivery approach.

The purpose of this study is to investigate the implementation of a novel gait rehabilitation stimulus (G-EO System) that could advance current clinical practices. The goal is to establish the

safety and feasibility of gait training using the G-EO System as well as investigating the impact on mobility, function, quality of life, and participatory outcomes.

Research Design: We propose a single-blinded, randomized trial of electromechanically-assisted gait training using the G-EO System in patients with Parkinson's disease with gait disability.

Specific Aim 1 will establish the safety and feasibility of gait training using the G-EO System.

Specific Aim 2 will determine the efficacy of gait training using the G-EO System for improving mobility, function, quality of life, and participatory outcomes.

3.0 Inclusion/Exclusion Criteria

Inclusion criteria

- Age $\geq$ 18years
- Confirmed diagnosis of PD (this will be confirmed by the referring neurologist)
- Hoehn and Yahr stage 1 to 3
- Stable course of disease-modifying therapy over the past 3 months
- MMSE $\geq$ 24
- Neurologist approval for exercise
- Stable deep brain stimulation setting for the past year
- Demonstrate a need for functional rehabilitation

Exclusion criteria

- Severe dyskinesia or severe on-off phenomenon
- Unstable medication regiment
- Any co-morbidity that will interfere with walking
- Conventional physical therapy or G-EO training within the past 6 months
- Height <1m or >2m
- Body weight >150 kg
- Contraindications to G-EO gait training (e.g., bone instability)

4.0 Enrollment/Randomization

A convenience sample of 30 persons with Parkinson's Disease will be enrolled for this clinical trial. Recruitment will occur through neurologists at the IU Health Neuroscience Center. Each participate will be given time to read the consent form or have it read to them and to ask questions (see Informed Consent Draft). Consent will be obtained before initial assessments and treatment randomization. The consent process will take place at the Indiana Center for Advanced Neurorehabilitation (ICAN) in the Neurorehabilitation and Robotics IU Health Neuroscience Center, 355 West 16th Street, Room 1078, Indianapolis, IN 46202 (317) 963-7050.

If found eligible for the study and agree to consent to participate, subjects will be randomized to either conventional physical therapy (CPT) group or CPT with G-EO training using a random numbers generator and concealed allocation.

5.0 Study Procedures

Screening

Potential subjects will be referred to the study via neurologists at the IU Health Neuroscience Center who specialize in the treatment and management of individuals with Parkinson's disease. A member of the research team will screen the referral by contacting the neurologist and confirming they meet the necessary inclusion and exclusion criteria. Following confirmation of criteria, potential subjects will be contacted by phone to schedule an initial visit for consent and assessment of baseline data.

Assessments

The study outcomes will be collected by treatment-blinded researchers. All participants on Day 1 who consent to be in the study will complete the following mobility outcomes:

1. Spatial and temporal gait kinematics will be assessed using a PKMAS Zeno Walkway (Protokinetics). Participants will be asked to walk over a 14-foot pressure mat that will capture their gait kinematics and speed. Comfortable and fast walking speed will be assessed. (10 minutes)
2. A 6-minute walk (6MWT) tests to determine walking endurance. Subjects will be asked to walk for 6 minutes along a 30m track. Subjects may stop and rest as often as needed. Subject walking speed will be collected during the test to evaluate rate of functional fatigue. (10 minutes)
3. Balance assessment using the Mini BESTest. Subjects will be asked to complete 14 different tasks ranging from static standing to dynamic walking. All subjects will be guarded closely for safety to prevent falling. (15 minutes)
4. The level of lower extremity functional strength combined with balance will be assessed by the five times sit to stand test. (5 minutes)
5. Performance translation of balance improvement will be measured using the self-report Activities Balance Confidence Scale. (10 minutes)
6. Their level of health-related quality of life assessed by the Parkinson's disease Questionnaire-39. (15 minutes)
7. Obstacle management while walking. Patients will be asked to walk over a flat firm surface for 14 meters. The pathway will include a box that is one foot by one foot that each person. (6 passes; 10 minute break; 6 passes; 10 minute break; 6 passes; 10 minute break) total of 40 minutes
8. Performance translation to real life activities will be measured by accelerometers. Each participate will wear an accelerometer at home to measure activity levels. (completed at home)

- After completing all of therapy, the research team will complete a short interview with the participant. The interview will focus on their experiences during therapy regardless of which group they participated in. We will also ask them to consider how valuable they think the experience was for their health. This interview will take about 15 minutes.

Participants will complete outcome assessments prior to the start of the study, at the end, and one month following completion.

Schedule

Following completion of day 1 assessments, all subjects will be scheduled for the intervention phase of the study. Regardless of group allocation, each participant will receive 12 total visits scheduled ideally two times a week for 6 weeks. Following completion of the 12 visits each subject will complete all outcome assessments. (See Table 1) If a subject cancels a treatment session, it will be rescheduled to ensure that all subjects complete the total of 12 treatment sessions prior to final testing. If a subject misses three consecutive treatment sessions, they will be dropped from the study due to inconsistency in treatment carryover. Cancellations and changes

in patient scheduling is a part of true clinical experience and represents normal clinical patient management. Therefore, the emphasis is on total number of treatments (12) and not on total number of weeks.

Pre-Intervention Phase		Intervention Phase	Post Intervention	Follow Up
Day 1	Day 2 Measurement	6 weeks intervention period	Post Assessment	Month Follow Up
• Screening of Inclusion • Informed consent obtained • Random assignment to CPT or GEO	**Outcome Measurement** 1. Comfortable & Fast Walking Speed/Mechanics ☐ Trial 1 (14') ☐ Trial 2 (14') ☐ Trial 3 (14') 2. Walking Endurance ☐ 6 MWT 3. Balance ☐ MiniBESTest 4. LE Strength ☐ 5 times sit to stand test 5. Confidence ☐ ABC Scale 6. Quality of Life ☐ PDQ-39 7. Movement agility o Obstacle Avoidance 8. Performance Assessment ☐ Accelerometer	Treatment and control group 2x a week	**Outcome Measurement** 1. Comfortable & Fast Walking Speed/Mechanics ☐ Trial 1 (14') ☐ Trial 2 (14') ☐ Trial 3 (14') 2. Walking Endurance ☐ 6 MWT 3. Balance ☐ MiniBESTest 4. LE Strength ☐ 5 times sit to stand test 5. Confidence ☐ ABC Scale 6. Quality of Life ☐ PDQ-39 7. Movement agility o Obstacle Avoidance 8. Performance Assessment ☐ Accelerometer	**Outcome Measurement** 1. Comfortable & Fast Walking Speed/Mechanics ☐ Trial 1 (14') ☐ Trial 2 (14') ☐ Trial 3 (14') 2. Walking Endurance ☐ 6 MWT 3. Balance ☐ MiniBESTest 4. LE Strength ☐ 5 times sit to stand test 5. Confidence ☐ ABC Scale 6. Quality of Life ☐ PDQ-39 7. Movement agility o Obstacle Avoidance 8. Performance Assessment o Accelerometer

Intervention

The intervention will be delivered through the Neurorehabilitation and Robotics Clinic at the IU Health Neuroscience Center. All rehabilitation training will be supplied by licensed Physical Therapists with oversight from Research Team. The clinicians involved in the delivery of the intervention will not be involved in outcome assessments. All outcome assessment will be completed by the research team. Participants in both conditions will receive conventional physical therapy (CPT) as usual care. Participants in the Robotic training condition will also receive robot-assisted gait training. The standard group will receive traditional overground walking training. This design will control for attention and social contact, total rehabilitation time, and intensity. Both conditions will be delivered at the same frequency (2x/week), duration (40 to 60 minutes), and time frame over 6-weeks. Progression will occur by increasing the session intensity weekly. Training intensity will be monitored and standardized using the Borg Rating of Perceived Exertion scale and will progress from 'fairly light' (11) to 'somewhat hard' (13). This prescription is consistent and appropriate for individuals with Parkinson's patients with mobility

impairment and low fitness levels. Total training time includes both conventional physical therapy (CPT) and gait training (i.e., 30min of CPT + 30min gait training). Training sessions will not exceed 60 minutes. We will record all training parameters. CPT sessions will involve: 3-5 minute warm-up, stretching, progressive strength training exercises, and balance training. Additional strategies for home exercises, fall prevention, and appropriate assistive devices (i.e., orthotics) will be provided universally.

Conventional physical therapy (CPT): A CPT session will involve a 3-5 minute warm-up, stretching, progressive strength training exercises, and balance training (for approximately 30 minutes). Gait training will involve traditional activities that involve overground walking activities, object avoidance, and changing speeds/directions (for approximately 30 minutes).

G-EO training: The first 30 minutes will involve a similar CPT session as outlined above. Gait training will focus on using the G-EO System, participants will be secured with the appropriate sized harness and attached to an overhead body-weight support system, with feet secured to pressure sensitive footplates. Gait training sessions will begin with a warm-up in the continuous passive mode (cadence ~40-45 steps/minute). Participants will then be transitioned into the adaptive training mode for practicing repetitive floor walking for up to 30 minutes. During this phase, the force produced by the robot is modulated to support the effort of the patient in producing a typical walking pattern. As the participants improve, intensity of gait training will be increased which will include integration of the stair stepping mode. Total training time will equal 30 minutes.

Feasibility and Safety
Feasibility outcomes will involve process, resources, management, and scientific assessment. Process metrics will include recruitment, retention, and adherence rates assessed by the movement of participants through each stage of the study and training data. Resource metrics will include evaluation of the equipment and facilities through feedback from the therapists. Time to completion relative to proposed target dates will also be reviewed. Management metrics will include data management, documentation of patient progress, record of adverse events, and compliance with approved protocols. Safety will be evaluated through assessment of recorded adverse events.

6.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

We will monitor participants for any adverse events such as muscle soreness, fatigue, temporary changes in balance/falls, and skin integrity. In the case of an adverse event, the participant's neurologist will be informed of the event. In the case of an adverse event requiring immediate/emergency attention 911 will be called.

7.0 Study Withdrawal/Discontinuation

Participants may withdraw from the study at any time by contacting the program manager (Dr. Ryan Cardinal) of Neurorehabilitation and Robotics at 317-963-7053. Additionally, participants may communicate their desire to withdraw from the study to any of the study's investigator: Dr. Peter Altenburger (317-278-0703).

8.0 Statistical Considerations

Data will be analyzed using IBM SPSS Version 25.0 (IMB Corps., Armonk, NY). Descriptive statistics will characterize the sample on demographic, clinical, safety, and feasibility metrics. We will compare safety and feasibility between groups using chi-square and *t*-tests for independent samples (*Specific Aim 1*). The efficacy of the intervention on study variables (*Specific Aim 2*) will be examined using a 2 (Group) by 2 (Time), mixed factor ANOVA. A completers analysis will be conducted (i.e., ≥75% of sessions completed). Effect sizes associated with F-statistics will be expressed as eta-squared (η^2), and effect sizes based on mean differences will be expressed as Cohen's *d*.

9.0 Privacy/Confidentiality Issues

All efforts will be taken to ensure that there is no loss of confidentiality during this study. HIPAA requirements will be observed and all patient data is coded to ensure no loss of confidentiality during dissemination of any data. The treatment environment is the Indiana Center for Advanced Neurorehabilitation (ICAN), located within Neurorehabilitation and Robotics at IU Health Neuroscience Center which is a clinical treatment site. Patient data will be secured in locked cabinets in a locked research office and access to the space is limited to researchers involved with the study and clinicians trained to provide treatment within Neurorehabilitation and Robotics.

10.0 Follow-up and Record Retention

Completion of this study is scheduled within approximately 1 year of the first subject enrollment. All patient data will remain coded and stored in locked cabinets up to 6 years following the completion of the study (7 years total). All documents related to this study will be properly shredded when appropriate. All electronic data will be stored as de-identified information in REDCap and on the Microsoft IU Secure Storage System.