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Rationale and design of a randomized controlled clinical trial of functional electrical stimulation cycling in persons with severe multiple sclerosis

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ABSTRACT

Background: This randomized controlled trial (RCT) will examine the efficacy of supervised functional electrical stimulation (FES) cycling on walking performance and physiological function among persons with multiple sclerosis (MS) with severe mobility disability.

Methods/design: This RCT will recruit 16 persons with MS that require unilateral or bilateral assistance for ambulation (i.e., Expanded Disability Status Scale (EDSS) score = 6.0–6.5). Participants will be randomized to one of two conditions: supervised FES cycling or passive cycling. The FES cycling condition will involve mild electrical stimulation that will generate an activation pattern that results in cycling the leg ergometer. The passive cycling condition will not provide any electrical stimulation, rather the movement of the pedals will be controlled by the electrical motor. Both conditions will be delivered 3 days/week for the same duration, over 6 months. Primary outcomes will include walking performance assessed as walking speed, endurance, and agility. Secondary outcomes will include physiological function assessed as cardiorespiratory fitness, muscular strength, and balance. Assessments will take place at baseline, mid-point (3-months), and immediately following the intervention (6-months).

Discussion: This study will lay the foundation for the design of a future RCT by: (1) providing effect sizes that can be included in a power analysis for optimal sample size estimation; and (2) identifying cardiorespiratory fitness, muscular strength, and balance (i.e., physiological function) as mechanisms for the beneficial effects of FES cycling on walking performance. This trial will provide important information on a novel exercise rehabilitation therapy for managing walking impairment in persons with severe MS.

1. Introduction

Multiple sclerosis (MS) affects an estimated 1 per 1000 persons in the United States [1,2]. The disease pathology initially involves immune-mediated demyelination and transection of axons within the central nervous system (CNS), and later transitions into a neurodegenerative process associated with axo-neuronal loss [3–5]. The extent and location of this damage within the CNS results in walking dysfunction [6] that can be exacerbated by physiological deconditioning or detraining brought about by physical inactivity [7,8]. Exercise training is one approach for increasing physical activity, improving physiological function, and restoring walking performance in persons with MS [7–9].

Exercise training has a variety of beneficial effects for persons with MS [10–12]; however, the majority of previous research has been conducted in samples with mild or moderate disability levels (i.e., Expanded Disability Status Scale (EDSS) scores <6.0) rather than among those with severe ambulatory impairment [10,13,14]. This is critical considering long-standing arguments that rehabilitation, including exercise training, is the only practical means of preserving and improving functional outcomes in patients with severe MS [14,15]. The provision of exercise training in persons with severe MS disability requires specialized training modalities [16,17]. One such approach involves functional electrical stimulation (FES) cycling [16,17].

FES cycling is an activity-based rehabilitation modality that involves transcutaneous electrical stimulation of leg muscles as an

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approach for producing leg-cycle ergometry. This method has been effective for improving walking performance and physiological function (e.g., cardiorespiratory fitness and muscular strength) in persons with incomplete spinal cord injury (SCI) and stroke [17–19]. Few studies, however, have examined the potential of FES cycling in persons with MS. One observational study has documented benefits of unsupervised FES cycling delivered over 6 months on walking speed and endurance, gait, and muscular strength in 5 persons with severe MS (mdn EDSS = 6.5) [20]. Two small (n = 8), uncontrolled studies involving 12–18 sessions of FES cycling demonstrated improved muscle metabolism [21] and increased thigh volume [22] in severe MS samples (EDSS > 6.0). FES cycling is an exercise rehabilitation approach that can be delivered in the home for potentially managing progressive mobility disability in severe MS. However, before home-based FES cycling can be pursued, we require high quality pilot data from a randomized trial with an appropriate control condition that demonstrates initial efficacy of this intervention.

This study involves a randomized controlled trial (RCT) for examining the efficacy of 6-months of supervised FES cycling versus a passive cycling control condition on walking performance and physiological function among persons with severe MS disability (i.e., EDSS = 6.0–6.5). This study will lay the foundation for the design of a future RCT by: (1) providing effect sizes that can be included in a power analysis for optimal sample size estimation; and (2) identifying cardiorespiratory fitness, muscular strength, and balance (i.e., physiological function) as mechanisms for the beneficial effects of FES cycling on walking performance.

2. Methods

2.1. Study design, overview and hypotheses

The proposed study will take place at the University of Illinois Urbana-Champaign campus. The study will involve a parallel group, assessor-blinded, RCT design for examining the efficacy of supervised FES cycling versus a passive cycling condition in patients with MS that require unilateral or bilateral assistance for ambulation. The primary outcome of the study will be walking performance assessed using the Timed 25-Foot Walk (T25FW), the 2-Minute Walk (2 MW), and the Timed Up-and-Go (TUG) tests. Secondary outcomes will involve measures of physiological function including cardiorespiratory fitness measured as peak oxygen consumption from an incremental exercise test, muscular strength assessed as peak torque of the knee flexors and extensors on a computerized dynamometer, and static balance assessed as center of pressure motion quantified with a force platform. We will recruit a sample of 16 persons with severe MS (i.e., EDSS score = 6.0–6.5). Participants who meet the eligibility criteria will be randomly allocated into either the FES cycling condition or the passive cycling condition. The FES cycling condition will involve mild electrical stimulation to the leg muscles that will generate an activation pattern that results in cycling the leg ergometer. The passive cycling condition will not provide any electrical stimulation to the leg muscles, rather the movement of the pedals will be controlled by the electrical motor. Both conditions will be delivered 3 days per week for the same duration, over 6 months using RT300 cycles (Restorative Therapies Inc, Baltimore, MD). Primary and secondary outcomes will be collected at baseline, 3-months, and 6-months. The effect of the intervention on primary and secondary outcomes will be examined using a Condition (FES cycling vs. Passive cycling) × Time (Baseline, 3-months, 6-months) mixed model analysis of variance (ANOVA). The role of physiological function as a mediator of the effect of FES cycling on mobility will be examined using bivariate correlation and multiple linear regression analyses. We hypothesize that there will be an improvement in walking performance and physiological function among individuals who receive FES cycling compared to those who receive passive cycling. We expect FES cycling will have a positive effect on walking performance through its influence on physiological function (i.e., cardiorespiratory fitness, muscular strength, and balance).

2.2. Participants

We plan to enroll a sample of 16 persons with MS to this trial. Participants will be recruited through advertisements in local media outlets. We will further distribute study information to individuals who have participated in previous research with our laboratory or who have inquired about previous exercise training studies, but were disqualified based on disability status (i.e., EDSS ≥ 6.0). The study will be described as an opportunity to participate in one of two leg cycling exercise programs. Participants will be asked to contact the Clinical Exercise Physiology Laboratory for information on study participation and screening for inclusion. The criteria for study inclusion are listed in Table 1. We will include participants irrespective of disease-modifying or symptomatic therapies, but will record this information at each testing session to control for potential covariates in data analysis.

2.3. Sample size

We estimated the sample size for detecting a Condition [2 levels of between-subjects factor: FES cycling vs. Passive cycling] × Time [3 levels of within-subjects factor: 0, 3, and 6 months] interaction using the effect size [$d = 0.73$] from a published observational study of FES cycling on mobility in advanced MS [20] and assumptions of $\alpha = 0.05$, $\beta = 0.20$, ICC = 0.50, and $\varepsilon = 1.0$. These parameters were selected based on the pilot nature of this investigation and the population that will be targeted. The minimal sample for testing the interaction should be 14 participants, and we will recruit 16 individuals with severe MS to account for potential attrition (~10–15%).

2.4. Measures

2.4.1. Disability

A clinically-administered EDSS [23] examination will be conducted to confirm self-reported disability status and to describe the disability level of the sample. The EDSS will be performed by a member of the research team who is Neurostatus certified.

2.4.2. Timed 25-Foot Walk (T25FW)

The T25FW will be administered as a measure of walking speed, and will be administered according to standardized instructions [24]. Participants will be instructed to walk 25 feet as quickly as possible, but safely. An average of two walking trials in seconds will be computed and also converted to walking speed in m/s.

2.4.3. 2-Minute Walk (2MW)

The 2MW test will be administered as a measure of walking endurance and will be performed according to standardized instructions [25]. Participants will be asked to walk as fast and as far as possible for the duration of 2 min in an accessible corridor that is free of obstructions. A member of the research team will follow 1–3 m behind the participant with a measuring wheel to record the total distance traveled in meters. Based on the target disability level of the sample, the 2WM was selected as a measure of walking endurance to ensure that all participants will be able to complete the test.