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Pilot randomized controlled trial of functional electrical stimulation cycling exercise in people with multiple sclerosis with mobility disability☆

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ABSTRACT

Background: Exercise training has been shown to be beneficial for persons with multiple sclerosis (MS). Adapted exercise modalities are needed to accommodate those with severe mobility impairment (Expanded Disability Status Scale [EDSS] scores 5.5–6.5). Functional electrical stimulation (FES) cycling is one such exercise modality; however, few studies have examined the feasibility and potential benefits of FES cycling for people with MS with severe mobility impairment.
Objective: Determine the feasibility of FES cycling exercise for people with MS with severe mobility impairment, and the efficacy of FES cycling exercise for improving mobility and physiological fitness.
Methods: 11 participants with MS with mobility impairment (EDSS = 5.5–6.5) were randomly allocated to FES cycling exercise ($n = 6$) or passive leg cycling (PLC; $n = 5$). Feasibility metrics included participant recruitment, retention, adherence, safety, and satisfaction. The primary mobility outcome was walking speed assessed by the Timed 25-Foot Walk (T25FW) test. The primary physiological fitness outcome was peak oxygen consumption (VO_{2peak}), assessed using a cardiopulmonary exercise test.
Results: Eight participants completed the intervention (FES $n = 4$; PLC $n = 4$) with an adherence rate ≥80%. Three participants (FES $n = 2$, PLC $n = 1$) withdrew due to a lack of time. Six Grade 1 (i.e., mild) adverse events were experienced by participants in the FES group. Participants in the FES cycling condition demonstrated small-to-moderate improvements on T25FW performance (Cohen's $d = 0.40$; 22.9%) and VO_{2peak} (Cohen's $d = 0.34$; 13.8%) compared to participants in the PLC condition.
Conclusions: We provide evidence that FES cycling exercise is feasible for individuals with MS with severe mobility impairment, and might have positive effects on mobility and physiological decondition. These results will inform the design of future efficacy trials of FES cycling exercise for persons with MS with mobility disability.

1. Introduction

Multiple sclerosis (MS) is an immune-mediated disorder of the central nervous system characterized by accumulation of progressive neurological impairment (Frohman et al., 2006). Such impairment is commonly reflected as the loss of mobility, one of the most common and poorly-managed consequences of MS (Larocca, 2011). Mobility impairment increases with disease progression and has negative consequences for employment, participation in everyday activities, and overall quality of life (QOL) (Larocca, 2011). Furthermore, the

Abbreviations: 2MW, 2-minute walk; AE, adverse event; BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; EDSS, expanded disability status scale; FES, functional electrical stimulation; FM, fat mass; FFM, fat-free mass; MSM, multiple sclerosis; MSWS-12, Multiple Sclerosis Walking Scale-12; PLC, passive leg cycling; RCT, randomized control trial; T25FW, Timed 25-Foot Walk; TUG, Timed Up-and-Go; VO2peak, peak oxygen consumption; QOL, quality of life; WR, work rate

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progression of mobility disability has been associated with substantial socioeconomic costs (Karampampa et al., 2012; Grima, 2000), highlighting the need for therapeutic strategies for managing mobility loss.

Mobility disability in MS is further impacted by physiological deconditioning (i.e., reduced physiological fitness) (Sandroff et al., 2013; Sandroff et al., 2015). There is substantial evidence for physiological deconditioning among persons with MS, including reduced cardiorespiratory and muscular fitness, and these measures have been associated with mobility outcomes (Sandroff et al., 2013; Motl and Goldman, 2011; Pilutti et al., 2015). Physiological fitness declines with disease progression in MS, further exacerbating mobility impairment (Pilutti et al., 2015; Motl and Learmonth, 2014). Exercise training is an effective strategy for improving physiological fitness in persons with MS (Platta et al., 2016) and has been reported to improve mobility outcomes (Pearson et al., 2015). Unfortunately, this evidence has primarily been established in people with mild-to-moderate disability, rather than among those with severe mobility impairment, and the greatest need for exercise rehabilitation (Latimer-Cheung et al., 2013a; Edwards and Pilutti, 2017).

Traditional exercise modalities have limited the study and application of exercise training for people with MS with mobility disability (Pilutti and Hicks, 2013). One advanced exercise-rehabilitation modality that was originally developed for individuals with spinal cord injury, and may also be beneficial for those with MS is functional electrical stimulation (FES) cycling (Baldi et al., 1998). FES cycling uses mild electrical stimulation delivered though surface electrodes to initiate involuntary muscle contraction. The addition of FES enhances the capacity for muscle recruitment during exercise, and consequently, the potential for physiological and functional adaptations to exercise training. There is support for the application of FES cycling in persons with MS (Ratchford et al., 2010; Reynolds et al., 2015; Backus et al., 2016; Szecsi et al., 2009), but none of the current evidence derives from a randomized controlled trial (RCT) design, potentially limiting the applicability of the findings.

We conducted the first pilot, RCT of supervised FES cycling exercise compared with passive leg cycling (PLC) as a placebo-control condition in individuals with MS with severe mobility impairment. The objectives of this study were to: (1) assess the feasibility of 24-weeks of supervised FES cycling exercise based on metrics of participant recruitment, retention, adherence, compliance, safety, and satisfaction; and (2) examine the efficacy of FES cycling exercise for improving mobility and physiological fitness. This pilot trial will provide critical information to design and deliver future efficacy trials of FES cycling exercise in persons with MS with mobility impairment.

2. Methods

2.1. Trial design and participants

The detailed protocol for this trial has been previously published (Pilutti et al., 2016). The trial design involved a parallel group, assessor-blinded, pilot randomized placebo-controlled trial. Participants were randomly allocated to receive FES cycling exercise or PLC for 24 weeks, using an allocation ratio of 1:1. Reporting of the trial follows the CONSORT guidelines for pilot and feasibility trials (Eldridge et al., 2016). Inclusion criteria for participants have previously been reported (Pilutti et al., 2016).

2.2. Outcome measures

2.2.1. Demographic/clinical characteristics

Height and weight were measured in the laboratory using a scale with a stadiometer (Detecto, Webb City, MO). Disability status was confirmed through a clinically-administered EDSS (Ratzker et al., 1997) examination by a Neurostatus-certified assessor. Clinical and demographic characteristics were collected using a self-report questionnaire.

Table 1
The demographic and clinical characteristics of participant who completed the FES cycling exercise and PLC interventions. Values are reported as means (SD), unless specified otherwise.

Characteristic	Overall (n = 8)	FES (n = 4)	PLC (n = 4)	p-value
Age, y	52.9 (7.9)	57.3 (6.0)	48.5 (7.7)	0.12
Sex, n				0.29
Female	7	3	4	–
Male	1	1	0	–
Height, cm	160.8 (9.1)	161.1 (10.4)	160.5 (9.2)	0.93
Weight, kg	78.2 (33.7)	70.6 (19.5)	85.8 (46.0)	0.56
BMI, kg/m^2	29.7 (10.7)	27.2 (7.4)	32.1 (13.9)	0.56
EDSS (mdn, IQR)	6.3 (0.5)	6.3 (0.5)	6.3 (0.9)	0.67
Disease duration, y	21.5 (6.6)	22.3 (5.3)	20.8(8.5)	0.77
MS type, n				1.0
Relapsing MS	4	2	2	–
Progressive MS	4	2	2	–

Anthropometric, clinical, and demographic characteristics were collected for descriptive purposes.

2.2.2. Feasibility

Feasibility included metrics of participant recruitment, retention, adherence, compliance, safety, and satisfaction with the intervention. Recruitment and retention were described as the number of participants during each phase of the trial. Adherence was characterized as participants' attendance at the prescribed exercise sessions, and quantified as the percentage of completed sessions out of a possible 72. Compliance was characterized as participants' completion of the prescribed exercise at a specified intensity and duration, and was quantified with training variables recorded at each session (i.e., pedaling distance, resistance, work rate, and heart rate). Safety was assessed as adverse events (AEs), which were defined as any unfavorable change in health that occurred during the trial period (Requirements, 2018). Each AE was characterized based on severity (Grade 1 [mild] through 5 [death]), expectedness (expected or unexpected), and potential relation to study participation (not related, possibly related, or study-related) using the National Institutes of Health Terminology and Classification scheme (Chen et al., 2012). Participant satisfaction was assessed using a 7-item feedback questionnaire quantifying the level of satisfaction with various characteristics of the leg-cycling programs (i.e., overall, trainers, equipment, training intensity, and likeliness to recommend to others or to use the cycle at home). Each item was rated on a 5-point scale that ranged from 1 (Not at all) to 5 (Extremely), with higher scores indicating greater satisfaction with the intervention. Feasibility metrics were selected based on recommendations for feasibility trials and previous studies examining the feasibility of exercise training interventions in people with MS (Adamson et al., 2016; Tickle-Degnen, 2013).

2.2.3. Mobility

The primary mobility outcome was walking speed, assessed using the Timed 25-Foot Walk (T25FW) test. An average of two walking trials in seconds was calculated and converted to a walking speed in m/s. Walking endurance and agility were assessed with the 2-Minute Walk (2MW)(m) and the Timed Up-and-Go (TUG) tests (sec), respectively. All mobility tests were performed according to standard protocols (Coleman et al., 2012; Goldman et al., 2008; Nilsagard et al., 2007). The 12-item MS Walking Scale (MSWS-12) was used to capture self-reported mobility impairment. The total MSWS-12 score ranges from 0 to 100, where higher scores indicate greater walking impairment (Hobart et al. 2003).

2.2.4. Physiological fitness

Physiological fitness was assessed as cardiorespiratory fitness (CRF), muscular strength, and body composition using previously reported protocols in persons with MS (Sandroff et al., 2013; Pilutti et al., 2015;