The effect of cycling using active-passive trainers on spasticity, cardiovascular fitness, function and quality of life in people with moderate to severe Multiple Sclerosis (MS): a feasibility study

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The effect of cycling using active-passive trainers on spasticity, cardiovascular fitness, function and quality of life in people with moderate to severe Multiple Sclerosis (MS); a feasibility study.

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Key words; cycling, active-passive trainers, MS, exercise, spasticity

Abstract

Background; Exercise options for those with moderate to high levels of disability are limited. The aim of the study was to evaluate the feasibility of a progressive, four week lower limb cycling programme using active-passive trainers (APT's) on spasticity, cardiovascular fitness, function and quality of life in people with moderate to severe MS.

Methods; Participants were in-patients in the Physical Disability Rehabilitation Unit, Queen Elizabeth University Hospital, Glasgow, UK and randomised to APT + usual care or usual care only. The APT group received 30 minutes of APT (2 minutes passive warm up, 26 minutes active cycling, 2 minutes passive cool down), five days per week for 4 weeks. Outcome measures; Oxygen Uptake Efficiency Slope, Modified Ashworth Scale, Multiple Sclerosis Spasticity Scale, Functional Independence Measure, Timed 25 foot walk test and the MSQOL-54, were taken before and after the intervention period. Symmetry, distance cycled and active participation were also recorded for each cycling session.

Results; 24 participants were recruited, 15 to the intervention and 9 to the control group. There was a 100% adherence to the intervention and a significant increase in average speed, power output and distance cycled ($p < 0.001$ for each) over the four weeks. There were no adverse events and both groups improved in average scores for all outcome measures.

Conclusions; APT cycling was well tolerated, while the cycling parameters improved it was difficult to separate the effects of the therapy programme and APT cycling. A longer duration, fully powered trial in a community setting is merited.

Introduction

Multiple sclerosis (MS) is the most common disabling neurological condition [1-3]. People with MS are less physically active than the general population [4] which leads to de-conditioning, a downward spiral of loss of functional capacity and reduced ability to perform activities and exercise. It is widely agreed that exercise brings many benefits for people with MS including increased cardio-respiratory fitness, muscle strength and endurance, improved mood and enhanced ability to complete activities of daily living [5-7]. Other studies have shown improved cognition and executive functioning with periods of regular exercise in people with MS (pwMS) [8-9] which were associated with improved mood and quality of life. Secondary benefits of exercise include reduced risk of co-morbidities such as heart disease, increased cholesterol and osteoporosis [10-12].

Exercise is therefore a fundamental component of the treatment strategy of pwMS. The mode of exercise people choose is driven by personal preference and capability [7]. However, exercise can be difficult for many pwMS due to e.g. symptoms, accessibility and transport. The evidence base to support the benefits of exercise for pwMS with moderate to severe MS remains limited [13,14] and exercise options are especially limited [14,15].

Cycling is an exercise often adopted by people with neurological conditions as it is a safe, feasible option and improves aerobic endurance, muscle and bone strength, spasticity and function [15-20]. Cycling is similar to walking; they are both cyclical activities, involve reciprocal contraction and relaxation of major muscle groups of the lower limb and share sensori-motor control mechanisms [17,18,21].

Lower limb active passive trainers (APT's) are an alternative to ergometers. They can be used by people with all levels of disability as they provide cycling from a chair or wheelchair and the speed, resistance and type of exercise (active, active assisted or passive) can be adjusted depending on the user's level of ability. Users receive visual feedback on their speed, distance cycled actively and passively, power output and symmetry of cycling which increases motivation, facilitates motor learning/control and improves rehabilitation outcomes [16-18].

Although APTs are used clinically, with anecdotal benefits, there is a paucity of evidence for their use in people with MS, especially those with higher levels of disability. The aim of this randomised controlled study was to evaluate the feasibility and potential effectiveness of a progressive, four week programme of exercise using lower limb APT (Motomed) in terms of lower limb spasticity, cardiovascular fitness, function and quality of life, in people with moderate to severe MS.

Methods

All those admitted to the Physical Disability Rehabilitation Unit at the Queen Elizabeth University Hospital, Glasgow, UK who fulfilled the inclusion and exclusion criteria were invited to take part. To be included participants had to have a confirmed diagnosis of MS, be aged over 18 years and have an Expanded Disability Status Scale (EDSS) of between 6.0 and 8.5. Participants were excluded if they had significant cognitive impairment such that they could not understand instructions, co-morbidities which would preclude them taking part in exercise, visual impairment meaning they could not see the screen on the APT or were unable to be seated appropriately in a wheelchair for 30 minutes. All participants gave written, informed

consent and were randomly assigned to the intervention or control group, by choosing a sealed envelope which contained a piece of paper stating either control or intervention. Ethical approval was granted by the West of Scotland Research Ethics Committee (reference 16/WS/0084) and research and development approval was obtained through NHS Greater Glasgow and Clyde (reference GN15PY148).

Those in the APT group (intervention) were positioned on a chair or their wheelchair and received 30 minutes of APT cycling (2 minutes passive warm up, 26 minutes active cycling and 2 minutes passive cool down), five days per week for four weeks in addition to usual care (described below). Each participant started the intervention at resistance level one, and the aim was to cycle at a speed that maintained a moderate intensity of exercise such that the exertion RPE score was between 12 and 14 [22-24]. If the RPE, averaged over the exercise period, was 11 or below then the resistance level was increased at the next session, and if it was 15 or above then the resistance level was reduced. Participants were encouraged to actively cycle however if they were unable to maintain this throughout the session the APT reverted to passive mode and continued.

Those in the control group continued with usual care which was an individualised therapy programme, delivered Monday to Friday, and could include PT, OT, SLT and Psychology.

For both groups at baseline, demographic details were recorded which included age, sex, type of MS, time since diagnosis, EDSS, past medical history, social circumstances, and mobility status. Medication was recorded at the start and end of the study period and any changes in medications or relevant medical interventions throughout the study period were noted.

Outcome measures were assessed the day before and after the four week study period by a research assistant who was blind to the group allocation. The primary outcome measure was spasticity and was assessed using the MS spasticity scale (MSSS-88) and Modified Ashworth Scale (MAS). The MSSS-88 is a self reported questionnaire which examines the effect of spasticity on aspects of daily life [25,26]. The MAS is a six point ordinal scale (0-4) which grades the resistance during passive muscle stretching [25,27,28]. In this scale zero represents no increase in tone and four is graded where the affected part is rigid and unable to be moved. MAS scores were recorded for hip flexors, hip extensors, hip adductors, quadriceps, hamstrings, plantarflexors and invertors in both lower limbs of each participant.

Secondary outcome measures were cardiovascular fitness measured using the Oxygen Uptake Efficiency Slope (OUES), Functional Independence Measure (FIM), Timed 25 Foot Walk Test (T25FW) and MS Quality of Life 54 (MSQOL-54). Cardiovascular fitness, measured using the OUES, has previously been validated as a sub-maximal test to gauge fitness in patients with MS [24-25]. Pulmonary gas exchange data was obtained during a fixed duration protocol using the Motomed APT; gas exchange data was collected at rest, during unloaded 'passive' cycling and then during 'active' cycling for eight minutes (all started at resistance level 0 and progressed every two minutes with progression based on the investigator's clinical perception of the participants ability to maintain RPE between 12 and 14).

Function was assessed by the FIM and T25FW. The FIM consists of 18 items, 13 motor tasks and five cognitive tasks required for daily living [31]. Each task is rated from one- requiring full assistance, to seven- independence in completing the task. Total scores range from 18 to 126 with higher scores indicating higher levels of independence. The FIM has been shown to be valid, reliable and responsive in MS

[32-34]. The T25FW was assessed in those who could walk. In this test the time taken for the participant to walk along a 25 foot course as fast as they were able, using walking aids as required, was recorded [35]. Two metres were added at the start and end of the course for acceleration and deceleration.

Quality of life was measured with the MSQOL-54, a condition specific, multi-dimensional health-related quality of life measure [36]. The measure consists of 54 questions and the two summary scores of physical and mental health were recorded. Participants who were unable to complete questionnaires on their own were assisted to complete them orally with the assessor.

After each exercise session the following data were recorded from the APT: symmetry, distance cycled, power, average speed and resistance level. It has been reported that an increase of one grade of resistance is equivalent to an increase of 1kg [16]. The inpatient therapy programme (usual care) each patient received within the study period was also recorded.

Analysis

Descriptive statistics were performed with estimates of effect size and an over view of the possible main effects observed from the outcome measures using repeated measures. Demographics and outcome variables were summarised with group differences being tested using chi-square tests for categorical variables, two independent sample t-tests or Mann-Whitney tests where appropriate. Simple linear regression was used to assess if any significant increases occurred from cycling

outcomes variables (total distance, average rpm and power). A 5% level of significance was used and all analysis was performed using IBM SPSSv24.

Results

Over the recruitment period 36 people with MS were admitted to PDRU, 33 met the inclusion criteria and were therefore invited to participate. Eight patients declined to participate for various reasons which included being unable to commit to the study time period, concerns about managing the intensity of the intervention and the effect on fatigue (Figure 1). Twenty five people were recruited to the study. One participant dropped out due to a relapse therefore results are given for 24 participants, 15 in the intervention and 9 in the control group.

Figure 1 Near Here

There was no significant difference between the groups at baseline for gender, age, EDSS or years since diagnosis (see Table 1).

Table 1 Near Here

There was 100% adherence rate to the cycling intervention (Table 2) with no adverse effects reported. Simple linear regression was used to assess the relationship between the cycling variables and time and three were shown to be statistically significant, average speed cycled (R^2 = 0.888, p= 0.026), power (R^2 = 0.866, p= 0.006) and the total distance cycled (R^2 = 0.878, p= 0.032). For each day cycling there was an average increase in distance of 0.04 miles, speed of 0.42 rpm and power of 0.32 watts. There were no notably change in relation to leg symmetry

however the median resistance level at start of the study was 1, by end was 2 (range of 0-7) (Table 2).

Table 2 Near Here

Participants received a therapy programme as standard care during the study and could include PT, OT, SLT and Psychology. The average number of therapy sessions for each discipline was calculated for each participant in each group during the study period (see Table 3).

Table 3 Near Here

Following the intervention there were improvements in average scores for all outcome measures (see Table 4), but there were no significant difference between the intervention and control groups over time.

Table 4 Near Here

From the results of the MSSS-88 scores (Table 4) there was no significant group effect ($p= 0.336$). On average both groups reported a reduction in perceived spasticity which was shown to be significant over time ($p= 0.010$). The MSSS-88 scores of the control group demonstrated a large size effect (0.76) while the intervention group showed a medium effect size (0.50) although there was no interaction effect ($p= 0.699$).

Table 5 & 6 Near here

In terms of MAS spasticity levels were, on average, low and, in the intervention group, spasticity reduced from 1 to 0 in the right hip adductor muscles and increased from 0 to 1 in right and left soleus muscle. In the control group spasticity reduced in

the right and left hip adductor muscles and left gastrocnemius muscle changing from 1 to 0 in both groups. There were no changes in any of the other muscle groups for either intervention or control groups.

Of the 24 participants only 11 were able to complete the T25FW at baseline, 8 from the intervention group and 3 from the control group (Table 4). However an additional 4 participants were able to complete the test post-intervention, 3 from the intervention group and 1 from the control group. The results in Table 4 however are from the 11 subjects who completed both pre and post-intervention 25FTW. From these 11 participants there was no significant group effect ($p= 0.302$). Furthermore, no overall time or interaction effects were detected ($p= 0.586$ and 0.345 respectively). Calculating effect sizes for the T25FW was inappropriate given so few participants completed the test at both time points and the unequal number of participants in the groups (control n= 3 and intervention n= 8).

There was no significant group effect for the FIM scores ($p= 0.290$). However there was a significant increase in total score over time ($p < 0.001$) with the control group demonstrating a large effect size (0.73) and the intervention group a medium effect size (0.31). There was no interaction effect ($p= 0.149$).

Improvements were shown across both physical health (PH) and mental health (MH) domains in the MSQOL-54. There was no significant group effect for either PH ($p= 0.631$) or MH ($p= 0.838$) domains. Overall, there was a significant time effect for both domains, PH ($p= 0.007$) and MH ($p= 0.029$). In addition a large effect size was demonstrated for the intervention group (0.93) and medium effect size in the control group (0.46). Again there was no interaction effect for PH ($p= 0.385$) or MH ($p= 0.986$).

There was no significant group effect for the OUES scores (p = 0.838) (Table 4). Overall there was no significant time effect (p = 0.535) nor interaction effect (p = 0.325). The control effect size was negligible (0.07) whilst the intervention group yielded medium effect size (0.36).

Discussion

The study demonstrated that an APT exercise programme is feasible option for people with moderate to severe MS who are in-patients in a rehabilitation ward. In addition the results suggested that most people (33/36) fulfilled the inclusion criteria and of those around 75% (25/33) agreed to take part. These figures help to determine the recruitment strategy of any subsequent study in this area.

Improvements were noted in the majority of outcome measures, although no statistically significant group differences were found. The average power output, distance cycled and speed improved in the intervention group this did not translate to statistical changes in the outcome measures. There was also 100% adherence to the cycling intervention, with no adverse effects reported, showing it to be a safe and acceptable treatment option.

Spasticity

There were minimal changes in spasticity for both groups, although participants in both groups perceived spasticity changed from the MSSS-88 results, which was shown to be significant over time (p= 0.010). The median MAS scores were also found to be much lower in both groups than anticipated and were considered minimal with no patterns found. This may have resulted in a floor effect of the MAS.

Overall there was no difference between groups, although the study was not powered detect a difference.

From the previous studies that have considered the effect of cycling on lower limb spasticity in pwMS [15,19,20,37,38], only two have used APTs [15,19] and only one considered the effects of a cycling programme [38], the other examined a single session of exercise [15]. A further study with a group of participants with various neurological conditions, also included pwMS [19]. In the study by Sosnoff et al (2009) participants cycled on an ergometer for 30 minutes, three times a week for a month. Like the current study, Sosnoff et al (2009) found no objective change in spasticity after the cycling intervention when measured by either neurophysiology or MAS scores. In comparison Szecsi et al (2009) showed significant reduction in MAS scores ($p= 0.05$) after six APT sessions. Rosche et al (1997) showed reduction in mean F wave/M response ratio ($p< 0.001$) immediately after a single session of 30 minutes of cycling using an APT, however as mentioned previously, this study included participants with other neurological conditions in addition to pwMS. Other studies have also demonstrated spasticity to be significantly reduced for up to one hour after a single session of ergometer cycling, as opposed to APT cycling in pwMS [20,37].

The lack of objective change in spasticity within this study could be due to the outcome measures used and the study design. While the MAS is the most universally used measure of spasticity it only quantifies passive resistance or limb stiffness, it does not measure the neural components that contribute to spasticity [39-41]. Other studies have found neurophysiology tests to be more sensitive in the detection of spasticity compared to the MAS [38,41-44].

Function

During this study only 11 participants completed the pre and post T25FW test, eight from the intervention group and three from the control. However at the end of the study a further three participants in the intervention group and one from the control group were able to complete the T25FW.

The minimal clinically important difference (MCID) for the T25FW in pwMS is reported to be 17.2% [46]. Seven participants in the intervention group and two in the control group improved their walking speed by more than the MCID, thus representing an important change in function for these participants.

Although the T25FW test is one of the most used clinically, no other study has used it as an outcome measure when considering the effects of cycling in pwMS. Several studies have used alternative walking measures such as the 6MWT, 10MWT or other timed motor tests. The majority of these studies showed significant improvement in walking performance after a cycling intervention [16,47-49]. While the results of this study did not show statistically significant improvements this was likely down to the small numbers of participants who were able to complete both pre and post assessments.

Health Related Quality Of Life (HRQOL)

In relation to quality of life, the results of this study showed improvements across both physical health (PH) and mental health (MH) domains in the MSQOL-54. However, the MCID has not been established [50].

Few studies have used quality of life measures when considering the effects of a programme of cycling on pwMS [51-53]. Rampello et al (2007) used the MSQOL-54

to investigate the effects of an eight week cycling programme and showed significant improvements in three subgroups of the MSQOL-54 (emotional well being, energy and health distress). Other studies have used the SF-36 [51-53], the measure from which the MSQOL-54 was developed. While Cakit et al (2010) found significant improvements in physical functioning and role-physical functioning, from the SF-36, over an eight week intervention, Mostert et al (2010) found significant improvements in social functioning and vitality after a four week intervention. All of these studies however used ergometers to cycle, and no studies of APTs in pwMS included HRQOL measures.

Cardiovascular fitness

This study showed a small improvement in OUES scores in the intervention group however there were no significant differences between groups demonstrated. Fitness is improved due to peripheral and central adaptations, thus the training must be at a sufficient dose in terms of intensity, duration and frequency. Endurance training leads to peripheral adaptations first, with increases in the concentration of oxidative enzymes and mitochondria within the muscle fibres [54,55], and an increase in number of capillaries around these fibres. These permit increased muscle blood flow and venous return an in combination these changes make the muscle more efficient and resistant to fatigue [55,56]. Central adaptations take longer to occur studies; suggesting 6-12 months of cycling intervention at 60-70% VO_{2peak} or 60-80% of HR_{max} is required [13,57]. However, another study demonstrated cardiac and skeletal muscles changes as early as 3 weeks which continued during a 12 week trial [58]. Their training programme consisted of 3 x week cycling sessions for 45 minutes at power output that elicited 70% of $VO_{2max.}$ In the current study the improvements in the average total distance cycled, speed and

power output would suggest peripheral adaptations may have occurred due to cycling. However given the disability levels of the participants, a longer study would perhaps be needed to elicit the central changes required to show a change in cardiovascular fitness.

Limitations

There were several limitations to this study. The study included only in-patients who were receiving an intensive period of therapy as 'usual care', making it difficult to separate the effects of the in-patient therapy programme from any effects of the cycling intervention. Whilst previous studies have exercised participants up to 90% of maximal heart rate (REF) we did not feel this was appropriate for our participant already undergoing an intense rehabilitation programme. In addition, participants in both groups underwent medication changes or procedures that could have influenced clinical measures. The outcome measures were assessed the day before and the day after completion of the study period, and for several participants their last exercise session was a Friday and the assessment was on Monday. This may have resulted in the treatment effects from cycling may have been lost, as studies have shown the antispasticity effects of cycling to be present immediately after the exercise period [15,20,37]. Lastly with 24 participants this study had a small sample and was not powered to show statistically significant changes. Based on the data generated from the MSSS-88, it was estimated that groups of 38 participants would be required to detect significant group differences with an 80% power.

Conclusion

This study has demonstrated that daily cycling for 30 minutes is a feasible and safe exercise option for people moderately to severely affected by MS. It produced no adverse effects or increase in symptoms in any participants, and participants were able to tolerate the intensity of treatment as demonstrated by 100% adherence to the intervention programme. Although the majority of outcome measures improved, this was not statistically significant, however pwMS were able to cycle for longer and with a higher power output. A fully powered, study of APT cycling over a longer of period of time and using community dwelling people, who would not be receiving concurrent intensive therapy, is merited to further determine the effects of APT cycling in people moderately to severely affected by MS.

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Conflicts of interest

There were no conflicts of interest for any of the authors whilst completing this research study.

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Figures/Tables to add in

Figure 1 Consort diagram

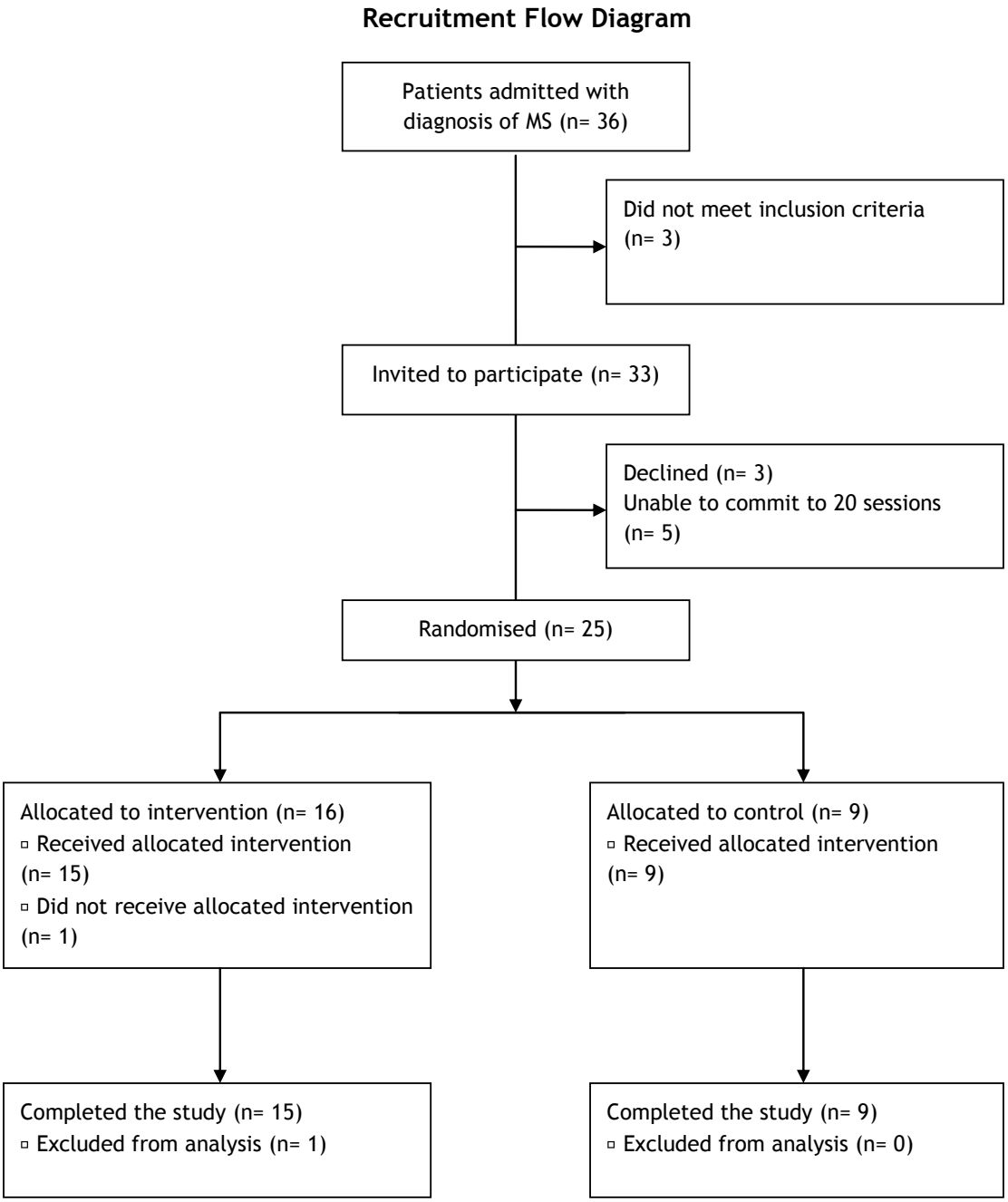

Table 1 Summary of participant demographic variables

	Intervention Group (n = 15)	**Control Group (n = 9)**	**Significance of Group Factor**
Gender (M/F)	6/9 (40%/60%)	3/6 (33%/67%)	1.000[c]
Age (yrs) (mean ± SE)	54.9 ± 2.6	53.6 ± 2.7	0.739[a]
Type of MS: n (%) PPMS SPMS RRMS	 3 (20.0%) 10 (66.7%) 2 (13.3%)	 2 (22%) 6 (67%) 1 (11%)	0.982[b]
Years since diagnosis (mean ± SE)	14.6 ± 2.3	16.9 ± 4.5	0.609[a]
EDSS score (mean ± SE)	7.2 ± 0.2	7.3 ± 0.2	0.665[a]
Marital status: n (%) Married/co habit Single Other	 11 (73.3%) 2 (13.3%) 2 (13.3%)	 8 (89%) 1 (11%) 0	0.824[b]
Education status: n(%) University College Employed from school	 5 (33.3%) 2 (13.3%) 8 (53.3%)	 3 (33.3%) 3 (33.3%) 3 (33.3%)	0.456[b]
Smoker: n(%) Yes No	 6 (40%) 9 (60%)	 2 (22%) 7 (78%)	0.470[c]

[a] two-sample t-test; [b] chi-square test; [c] Fisher's Exact test; PPMS (primary progressive MS); SPMS (secondary progressive MS); RRMS (relapsing and remitting MS); EDSS (Extended disability status scale).

Table 2 Cycling variables - Day 1 and Day 20

	1st session (Day 1)	20th session (Day 20)	p-value*
Duration active (min)	25.9 ± 0.0	25.8 ± 0.2	0.446[a]
Duration passive (min)	4.0 ± 0.0	4.1 ± 0.2	0.446[a]
Distance active (miles)	3.4 ± 0.3	3.9 ± 0.5	0.145[b]
Total distance (miles)	3.5 ± 0.3	4.2 ± 0.4	0.032[b]
Revolutions per minute (rpm)	42.2 ± 3.5	50.5 ± 4.3	0.026[b]
Power (W) (n=13)	7.2 ± 1.1	13.6 ± 2.8	0.006[a]

All values mean ± SE; * data analysed with [a] wilcoxon test; [b] paired t-test

Table 3 Summary of usual care

Therapy	Average no of therapy sessions - Intervention group	Average no of therapy sessions – Control group
PT	29 ± 3	29 ± 6
OT	9 ± 6	15 ± 8
SLT	1 ± 1	1 ± 1
Psychology	1 ± 2	1 ± 1

Table 4 Summary of Outcome Measures

Outcome measure	Intervention pre	Intervention post	Control pre	Control post	Significance of Group Factor
MSSS 88	238 ± 17	204 ± 16	220 ± 22	176 ± 21	p= 0.336
T25FW(s)	60 ± 14 (n=8)	64 ±18 (n=8)	39 ± 22 (n=3)	23 ± 29 (n=3)	p= 0.302
FIM	98 ± 5	104 ± 5	88 ± 6	98 ± 6	p= 0.290
MSQOL-54; PH MH	28 ± 4 52 ± 7	43 ± 4 63 ± 7	34 ± 5 54 ± 9	42 ± 6 65 ± 9	p= 0.631 p= 0.838
OUES (L/min)	0.734 ± 0.074	0.829 ± 0.063	0.768 ± 0.123	0.746 ± 0.111	p= 0.838

All values mean ± SE

Table 5 Intervention group median MAS scores

Intervention group	Right Leg		Left Leg	
	Pre	Post	Pre	Post
Hip flexors	0	0	0	0
Hip extensors	0	0	0	0
Adductors	1	0	0	0
Quadriceps	1	1	0	0
Hamstrings	0	0	0	0
Gastrocnemius	1	1	1	1
Soleus	0	1	0	1
Invertors	0	0	0	0

Table 6 Control group median MAS score

Control group	Right Leg		Left Leg	
	Pre	Post	Pre	Post
Hip flexors	0	0	0	0
Hip extensors	0	0	0	0
Adductors	1	0	1	0
Quadriceps	0	0	0	0
Hamstrings	0	0	0	0
Gastrocnemius	1	1	1	0
Soleus	1	1	1	1
Invertors	0	0	0	0