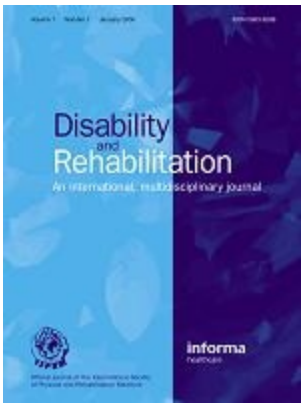

MSTOCT: Combining a supervised and home-based task-oriented circuit training improves walking endurance in patients with multiple sclerosis. A randomized-controlled trial.

Journal:	*Disability and Rehabilitation*
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Keywords:	multiple sclerosis, endurance, home rehabilitation, task-oriented circuit, muscle oxygen comsumption

MSTOCT: Combining a supervised and home-based task-oriented circuit training improves walking endurance in patients with multiple sclerosis. A randomized-controlled trial.

Abstract

Background

Gait impairments and physical deconditioning are very common in people with multiple sclerosis (PwMS).

Objectives

The effects of a supervised 2-weeks task-oriented circuit training (TOCT) followed by a monthly-supervised, progressive 12-weeks home exercise program were tested,

Methods

36 PwMS have been randomly assigned to 10 TOCT sessions over 2 weeks followed by a 12-weeks home exercise program or a delayed-treatment group. Six Minute Walk Test (6MWT), Timed 25-foot walk test (T25FW), Timed Up and Go test (TUG), Dynamic Gait Index (DGI), Modified Fatigue Impact Scale (MFIS), Multiple Sclerosis Walking Scale – 12 (MSWS-12), Multiple Sclerosis Impact Scale–29 (MSIS-29) and resting muscle oxygen consumption ($rmVO_2$) were delivered at baseline (T0), after TOCT (T1), 12-weeks of home-based exercise program (T2) and other 3 months (T3).

Results

A superiority of TOCT was verified for the 6MWT ($F_{2,88} = 7.80$; $p<0.001$). Between-group differences were highlighted for T25FW, TUG and MSWS-12 after the 12-weeks home-exercise programme. $RmVO_2$ was significantly reduced in the experimental group. Positive effects on 6MWT were retained after 3 months ($p<0.001$).

Conclusions

The combination of a supervised and self-managed task-oriented program enhances walking endurance with positive effects on disability, quality of life and resting muscle oxygen consumption in PwMs.

Trial registration: NCT02421744

Keywords: Task oriented circuit, multiple sclerosis, endurance, home rehabilitation, muscle oxygen consumption

Introduction

Gait impairments, balance disorders and fatigue are common in person with Multiple Sclerosis (PwMS) with negative consequences on disability and quality of life (QoL) [1]. Moreover, the majority of PwMS are less physically active, especially those with higher disability[2] and this can further deteriorate their mobility status[3]. Physical deconditioning, that reflects skeletal muscle dysfunction and poor exercise tolerance, can be measured by the near-infrared spectroscopy (NIRS) resting muscle oxygen consumption ($rmVO_2$). This is a parameter that reveal the muscle's capacity to extract oxygen from the blood in a resting condition and that was found to be increased in PwMS compared to healthy controls[4]. Exercise training is considered a valuable option to reverse the sedentary life behaviour of PwMS [5]-[6]; furthermore, task-specific practice seems also need to facilitate activity-dependent neuroplasticity and inducing functional recovery[7]. Recently, exercise has been considered as a medicine, with three main functions in the MS management: as a symptomatic treatment (i.e. tertiary prevention), for the disease-modifying effects (i.e. secondary prevention) and for its possible impact on the risk of developing MS (i.e. primary prevention)[8]. Resistance and endurance training has been found to be effective in improving physical fitness and muscle strength, even if in progressive MS[9]. Moreover, interventions that promote physical fitness are strongly recommended in PwMS by existing guidelines[10].

Task-oriented circuit training (TOCT) is an high-intensity, progressive, motor learning intervention, where a small group of peers exercise in functional motor tasks on different workstations. Even though previous review[11] [12] highlighted positive effects on mobility in stroke patients, scarce evidence are available for MS population [13]-[14]. So far, pilot studies, revealed promising effects on walking competency[15], knee kinematics[16], balance[17] and QoL[13]. A task-oriented approach has been successfully tested also in combination with balance training to treat gait ataxia[18] or in PwMS who needs walking aids[19]. However, the application of exercise to PwMS presents several barriers and difficulty in adhering to the training[20]. Moreover, positive effects are usually lost at follow-up, probably because they stop participating in exercise once the study is concluded. In our feasibility study[13] several limitations have been underlined (i.e. a low adherence to home-based exercise with poor retention at 3 months follow-up). Our primary hypothesis is that a supervised 2-weeks high-intensity task-oriented circuit training (Phase 1) followed by a monthly-supervised, tailored, progressive 12-weeks home exercise program (Phase 2) would have higher benefits compared to a delayed treatment group in people with multiple sclerosis and mild gait impairment. Our secondary hypothesis is that this intervention can induce long-lasting effects on motor function.

Methods

The Multiple Sclerosis Task Oriented Circuit Training (MSTOCT) trial is an assessor-blinded randomized controlled trial approved by the Ferrara Ethics Committee (registration number 140489) and registered on the ClinicalTrials.gov database (NCT02421744). Patients with multiple sclerosis (PwMS) have been recruited at Ferrara University Hospital and signed an informed consent before any evaluation or treatment. The inclusion criteria were: males and females; age 18 to 70; diagnosis of MS (primary or secondary progressive, relapsing-remitting), without relapses in the preceding 3 months; gait impairments referred to Expanded Disability Status Scale (EDSS) score between 4 and 5.5. The exclusion criteria were: other conditions that may affect motor function, impaired cognitive

functioning that interfere with the acquisition of the consent to the study. Eligible patients have been randomized to Task Oriented Circuit Training (TOCT) (experimental group) or delayed-treatment group (control), through a block randomization approach (1:1 ratio). The randomization scheme has been generated by using the web site Randomization.com (http://www.randomization.com). Treatment allocation occurred when a participant was eligible for the intervention, the informed consent had been obtained and baseline assessments were complete. Allocation was concealed from the outcome assessor and from the physiotherapist until the point of treatment.

Task Oriented Circuit Training (TOCT) (experimental group)

TOCT include six workstations with five levels of complexity each one (step, slalom, tandem exercise, goals, obstacles, long step) in which PwMS exercised for 5 minutes in each one (3 of exercises and 2 of rest)[13]. They were encouraged to increase their level of functioning among sessions. During each session, PwMS underwent 2 laps that take about 60 minutes (6 workstation x 5 minutes x 2 laps), with 10 minutes of rest after each lap. In addition, walking endurance was trained by 30 minutes walking on the treadmill including rests if necessary. During the circuit PwMS received feedbacks (visual and auditory) by the physiotherapist. One session included up to 3 patients and last 120 minutes, 5 days/week for 2 weeks. After the supervised 2 weeks (Phase 1), a tailored home-exercise illustrated brochure and the training material (i.e. stepper, stop-watch, small obstacles) has been delivered to subjects so that they can independently train for the following 12 weeks (Phase 2). At home, we recommended 60 minute sessions, 3 times/week. The home-based program includes exercises with similar modalities and difficulty as learnt during the Phase 1. Patients recorded the frequency and duration of the exercise in a diary and in case of need they could have called the hospital for further information and feedback. Adherence to treatment was monitored through the monthly visit to the hospital, scheduled to verify adherence to treatment to provide further feedback and adapt the exercises on the subjects' skills: the accuracy and the number of repetitions achieved during a session were assessed; the difficulty of the exercises was modified in the case in which the patients improved.

Delayed-TOCT (control group)

The control group did not receive any specific rehabilitation treatment for gait performance and improved mobility. However, they were allowed, at will, to exercise in non-rehabilitative settings for the 14 weeks waiting time. After this period they also received the TOCT with home exercise programme.

The outcome measures used are functional tests (gait speed, gait resistance, mobility, balance), self-reported questionnaires (fatigue, health-related quality of life and walking ability) and instrumental measures. Furthermore, adherence were assessed. Blind evaluators performed functional tests, questionnaires and instrumental measurements the week before treatment (T0), the week after the end of TOCT (T1), after the 12-weeks home training program (T2) and at 12 weeks follow-up (T3). Adherence to the home-based programme, repetitions performed for each workstation and level of difficulty was assessed each month during the home training program (M1, M2 and M3). The primary outcome measure was the 6-minute walking test (6MWT). Subjects have been instructed to walk up and down a 20m walkway as far as possible in 6 minute. As secondary outcomes we selected: i) Timed 25-Foot Walk (T25FW) ; ii) Timed Up and Go Test (TUG) ; iii) Dynamic Gait Index (DGI); iv) Modified Fatigue Impact Scale (MFIS); Multiple Sclerosis Walking Scale–12 (MSWS-12); Multiple Sclerosis Impact Scale–29 (MSIS-29). Adherence to the 3 months home-based programme has been assessed through Visual Analogue Scale (VAS).

Resting muscle oxygen consumption

Resting muscle oxygen consumption ($rmVO_2$) was measured by near-infrared spectroscopy (NIRS) using a continuous wave system (Oxymon-MK III, Artinis Medical Systems, Elst, Netherlands). With the patient lying in the supine position, NIRS optodes with an interoptode distance of 3.5 cm were placed along the medial gastrocnemius muscle. $RmVO_2$ was assessed by rapidly inflating a cuff placed around the thigh to a pressure of 60 mmHg to obtain venous occlusion for 30 seconds. The absolute $rmVO_2$ value was calculated by the rate of increase in concentrations once the venous outflow was blocked, as previously reported [21] [4] [22]. For this study, the value of the mean of the

two limbs was considered. Data collection and calculation were performed using the software Oxysoft 2.0.47 (Artinis Medical Systems, Netherlands).

Statistical analysis

Baseline characteristics were reported as mean and standard deviation and compared among groups to confirm the quality of randomization (unpaired t-test, Wilcoxon rank test or Pearson's Chi-Square test). To test the primary hypothesis an analyses of variance with one between factor (TOCT/delayed-treatment group) and one within factor (time interval: T0,T1,T2) was performed. The un-paired t-test was used to underline between-group differences. Moreover, to investigate time effects within groups, the ANOVA repeated measures analysis with Bonferroni post-hoc correction when $p<0.05$ was done. An intention-to-treat analysis was carried out on all outcome measures, handling missing data with the last observation carried forward approach. Statistical analysis was performed using STATA 13.1 software. Significance was recognized when $p < 0.05$.

Results

36 patients with MS were enrolled in the study (mean age 50.82, 13 males, 11.6 MS years). One patient in the TOCT group and one patient in the delayed-TOCT group did not receive the allocated treatment due to a post-randomization drop-out. Five patients in the TOCT group did not complete the 12-weeks home-exercise training (1 due to MS worsening, 3 for personal issues, 1 discontinued the intervention), while three patients in the delayed-TOCT group did not return for the 12-weeks follow-up visit (1 for MS worsening, 2 for personal reason). The study flow diagram is reported in Figure 1.

INSERT FIGURE 1 ABOUT HERE

The two groups were similar in demographic and clinical characteristics, as summarized in Table 1.

INSERT TABLE 1

Primary outcome (walking endurance)

A superiority of TOCT on delayed-TOCT was verified by the significant interaction time-treatment ($F_{2,88} = 7.80$; $p<0.001$) for the primary outcome measure. Analysis of variance results were reported in Table 2.

INSERT TABLE 2 ABOUT HERE

The experimental group increased by 29.80 (42.55) m after the 2-weeks supervised training, with a further gain of 44.07 (55.35) m after the 12-weeks home-exercise programme. Conversely the control group reported a 4.04 (33.82) m changes at T1 and -19.80 (60.63) m at T2. Between-group differences for the 6MWT was highlighted at the end of the home-exercise programme ($p<0.01$). See Table 3.

INSERT TABLE 3 ABOUT HERE

Within-group analysis revealed how walking endurance significantly improved only in the experimental group and specifically after the entire training period ($p<0.001$). See Table 4.

INSERT TABLE 4 ABOUT HERE

Secondary outcome results

No interactions time-treatment were found for the secondary outcome measures. However, between-group differences were highlighted for gait speed (T25FW), mobility (TUG) and walking disability (MSWS-12) after the 3 months home-exercise programme. Psychosocial component of fatigue (MFIS-P) was significantly lower after the 2-weeks supervised training compared with the delayed-TOCT group ($p<0.05$). Positive effects on gait speed (T25FW), mobility (TUG), balance (DGI), fatigue (MFIS-F and MFIS-P), walking disability (MSWS-12) and quality of life (MSIS-29 motor and psychological domain) were found after the experimental intervention; whereas the control group reported positive effects only for the quality of life (MSIS-29 motor and psychological domain). Muscle oxygen consumption, measured by NIRS, was significantly reduced only in the experimental group.

Task-oriented circuit training long-term effects

The retention of this intervention was tested in the entire population (n=36) confirming how the positive effects on the primary outcome measure were long-lasting after 3 months ($p<0.001$).

INSERT FIGURE 2 ABOUT HERE

Home Exercise adherence, progression and repetitions

A mean adherence of 6.2 out of 10 was reported for the home-exercise programme. The mean task repetitions on each workstation significantly increased linearly ($p<0.01$), as the mean level of difficulty of each task ($p=0.03$) after every timepoints.

Power calculation

Considering an alpha of 0.05, the estimated power of this study is 0.89. This value has been calculated given that walking endurance improvement after the 14-weeks program was 44.07 ± 55.35 m compared to -19.80 ± 60.63 m in the control group.

Discussion

This study corroborates the hypothesis that combining a supervised motor learning approach with a self-managed home-based training can produce long-lasting effects on walking function in PwMS with moderate gait disability (EDSS 4-5.5). After the 14-weeks program, patients improved their walking endurance, gait speed, mobility and walking abilities compared with controls. Walking endurance, the primary outcome, was significantly increased after the 14- weeks by 44m during the 6MWT, that is a clinically meaningful value for PwMS [23]. This effect was more pronounced than in previous pilot studies[15] [13] that were more focused on the in-hospital, supervised high-intensity training.

Conversely, dynamic balance that is commonly impaired in PwMS with higher risk of falls [24] was not improved after MSTOCT with a DGI change within the standard error of measurement [25].

As previously reported [13] [15] [17], a positive effects of motor training on health-related quality of life has been confirmed. Patient-reported Outcome (PRO) measures, such as MSWS-12 or MSIS-29, are essential because they capture the impact of MS on everyday life according to the patients' prospective [26]. Regarding fatigue, that represents a major disabling symptom in PwMS [27], no overall effects were reported through the exercise period, except for a significant reduction of physical fatigue after the 2-weeks intensive, in-hospital, supervised training, superior to the 19.3% of

Minimally Detectable Change (MDC)[28]. We can hypothesized that fatigue are more sensitive to change during an high-intensity exercise (120 minute/session, 5 times/week over 2 weeks), rather than a less intensive home-based program (60 minute/session, 3 times/week over 12 weeks). Moreover, exercise with peers can contribute to alleviating this multidimensional symptom, as previously reported[29]. This preliminary data can help to design future trials that address fatigue as primary outcome.

In addition to behavioral gains that can be due to activity-dependent neuroplasticity mechanisms aiming at restoring motor function, in MSTOCT study we observed values of muscle oxygen consumption higher compared to the reference values collected in healthy subjects [21] [30], and consistent with previous observation in patients with MS at higher or similar disability[21]. We noted in this trial that in a sample of patients a reduced value of $rmVO_2$ occurred after training, despite without any significant difference with the control group. The reported return of $rmVO_2$ values into a normality range after training have been yet observed in MS patients at higher disability, who received a robot-assisted gait training, with variability according to the individual training intensity[30]. This non-invasive, physiological parameter reflects a biological function of the skeletal muscle and can be considered a biomarker of physical deconditioning in PwMS that is potentially reversible after rehabilitation. Three major determinants of this intervention can be responsible of the aforementioned functional gains: i) motor learning components (intensity, specificity and salience of training); ii) working with peers and iii) the adoption of strategies to increase adherence and favoring self-management.

During the 2-weeks in-hospital supervised training, PwMS received an high dose of gait practice both on the treadmill and in different contexts that mimic everyday life motor tasks as slalom, passing small obstacles, stair steps and achieving goals. Throughout each session, they can make several thousands of steps as previously observed in community-dwelling chronic stroke survivors[31] and practice hundreds of task repetitions. Other than intensity and specificity, a key component of motor learning is salience[7] and having the chance to exercise at progressive difficult level of activity can

help maintaining participants motivating and active. Even during the 12-weeks self-managed training, intensity, progression and salience has been maintained, leading to a significant improvement of the number of task repetitions and difficulty level compared to the beginning.

Exercising with peers represent a fundamental key factor of MSTOCT with the aim of increasing motivation, good competition, self-esteem and general counseling[32]. An alternative to the task-oriented circuit training is the group exercise training where a standardized program can determine positive effects on balance, fatigue and QoL[29].

In our feasibility study[13], after the 2-weeks supervised TOCT, we asked patients to exercise on functional tasks and gait practice at their home, returning a compiled brochures with their activity after 12-weeks. This methods had several limits, only 58% of patients returned the booklet, revealing a poor adherence to the proposed home-based training. Moreover, outcomes achieved during the in-hospital training were minimally retained after the home-based protocol. These findings were consistent with the fact that several social and physical barriers exist on the adoption of physical activity among PwMS[20]. Compared with our previous study, a series of adjustments were adopted to increase both adherence and outcomes. Firstly, we planned a progressive exercise program which was tailored on patients' abilities and preferences. Moreover, in-hospital monthly visits were scheduled in order to adjust the dose and difficulty of exercises, register patients' feedbacks and provide counselling for maintaining high motivation and engagement. Indeed, the integration of self-help with professional-help has been shown to favour health promotion and community-based physical activity participation[33]. Furthermore, strategies for promoting communication between patients and physical therapists beyond the initial period of supervision have positive effects on self-management behaviour, quality of life and fatigue with long-lasting impact on outcomes[34].

This study has some limitations. Firstly, this results cannot be generalized to a wide spectrum of MS-related disability. Secondly, we did not address the possible barriers for the implementation of this intervention into a public health clinical setting. For this aim, a transferability analysis including national stakeholders should be performed, as planned in others European countries [35].

Conclusions

The combination of a supervised and self-managed task-oriented program enhances walking endurance in PwMS (EDSS 4-5.5) with positive effects on disability and perceived quality of life. In addition to behavioral and functional effects, it helps ameliorating physical deconditioning directly acting on the skeletal muscle metabolism, measured by the resting muscle oxygen consumption. Walking endurance beneficial effect was long-lasting, hypothesizing that this intervention lead to a life style modification, promoting successful self-management in PwMS.

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Conflict of Interest

None declared.

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Figure Legend

Figure 1. CONSORT study flow diagram.

Figure 2. Walking endurance changes after MSTOCT at follow-up (T3).

Table 1. Baseline characteristics of the two study groups.

	TOCT group (n = 18)	**Delayed group (n = 18)**	**Total (n=36)**	**P value**
Age (years)	49.65 (13.56)	52.6 (12.60)	50.82 (12.96)	0.59
Sex (M/F)	7/11	6/12	13/23	0.72
MS duration (years)	12.4 (11.36)	9.64 (5.59)	11.06 (9.0)	0.42
EDSS	4.55 (0.70)	4.79 (0.56)	4.67 (0.64)	0.27
MS Type (PP/SP/RR)	5/5/8	6/5/7	11/10/15	0.88
Primary outcome				
6MWT, m	316.99 (102.46)	372.63 (81.81)	344.81 (95.63)	0.094
Secondary outcomes				
T25FW speed, ms^{-1}	1.34 (0.38)	1.47 (0.31)	1.41 (0.35)	0.248
TUG, s	10.34 (4.24)	9.65 (2.13)	10.00 (3.33)	0.962
Dynamic Gait Index	16.89 (4.60)	18.39 (3.53)	17.64 (4.11)	0.316
MFIS physical	20.83 (7.91)	19.50 (6.18)	20.16 (7.03)	0.495
MFIS cognitive	11.78 (9.35)	8.95 (9.34)	10.36 (9.31)	0.317
MFIS psychosocial	3.67 (2.20)	3.00 (2.03)	3.33 (2.11)	0.299
MSIS-29 motor component	50.72 (15.52)	49.33 (11.64)	50.03 (13.54)	0.776
MSIS-29 psychological component	50.00 (17.10)	50.86 (16.24)	50.43 (16.44)	0.975
MSWS12 (%)	65.37 (20.00)	63.52 (13.33)	64.44 (16.78)	0.727
$rmVo_2$	0.06 (0.03)	0.06 (0.04)	0.06 (0.03)	0.667

Abbreviations: TOCT-group, Task oriented circuit training group; Delayed-group: patients who received TOCT at the end of the study; T25FW, timed 25-foot walk test; 6MWT, 6-minute walking test; TUG, timed up and go; MFIS, modified fatigue impact scale; MSWS12, multiple sclerosis walking scale; MSIS, multiple sclerosis impact scale-29; $rmVO_2$, resting muscle oxygen consumption.

Table 2 – Analysis of variance results for outcome variables

	Group Effect		Time Effect		Interaction (Time x Group)	
	F (1, 34)	*p*	F (2, 68)	*p*	F (2, 68)	*p*
6MWT, m	0.75	0.393	2.30	0.107	7.80	<0.001
T25FW, m/s	1.49	0.230	69.79	<0.001	0.30	0.739
TUG, s	0.00	0.978	7.10	0.001	2.72	0.073
DGI	0.34	0.563	4.36	0.016	1.53	0.223
MFISphy	0.00	0.986	6.94	0.001	0.96	0.388
MFISc	0.66	0.422	3.06	0.053	0.18	0.831
MFISpsy	0.05	0.823	1.56	0.217	2.46	0.092
MSIS-29m	0.11	0.746	7.90	<0.001	0.22	0.800
MSIS-29psy	0.09	0.765	14.43	<0.001	1.28	0.284
MSWS-12 (%)	0.36	0.552	10.06	<0.001	2.06	0.135
$rmVO_2$	1.19	0.282	4.51	0.014	0.01	0.993

Abbreviations: T25FW, timed 25-foot walk test; 6MWT, 6-minute walking test; TUG, timed up and go; MFIS, modified fatigue impact scale; MSWS12, multiple sclerosis walking scale; MSIS, multiple sclerosis impact scale-29; rmVO2, resting muscle oxygen consumption.

Table 3. Changes in outcome measurements

	Δ T0-T1		Δ T0-T2	
	TOCT group	Delayed group	TOCT group	Delayed group
6MWT, m	29.80 (42.55)	4.04 (33.82)	44.07 (55.35)**	-19.80 (60.63)
T25FW speed, ms^{-1}	0.13 (0.19)	0.03 (0.22)	0.13 (0.28)*	-0.06 (0.20)
TUG, s	-1.35 (2.31)	-0.54 (1.37)	-1.57 (2.31)*	-0.26 (1.42)
Dynamic Gait Index	1.72 (3.21)	0.72 (2.19)	1.56 (3.22)	0.11 (2.14)
MFIS physical	-4.22 (5.48)	-1.66 (5.66)	-3.83 (5.36)	-2.28 (5.95)
MFIS cognitive	-2.39 (4.55)	-1.67 (3.36)	-2.50 (5.44)	-1.39 (6.90)
MFIS psychosocial	-1.06 (1.80)*	0.11 (1.28)	-0.44 (1.34)	-0.06 (2.01)
MSIS-29 motor component	-5.56 (9.62)	-4.50 (7.82)	-4.00 (8.57)	-4.77 (10.53)
MSIS-29 psychological component	-7.28 (9.70)	-3.70 (11.88)	-8.02 (9.21)	-9.62 (12.87)
MSWS12 (%)	-12.59 (15.25)	-5.46 (12.83)	-9.81 (10.78)*	-2.5 (10.58)
$rmVO_2$	0.00 (0.03)	- 0.01 (0.03)	0.00 (0.04)	- 0.01 (0.03)

* $p < 0.05$ for the comparison between treatments; ** $p < 0.01$ for the comparison between treatments;

Abbreviations: TOCT-group, Task oriented circuit training group; Delayed-group: patients who received TOCT at the end of the study; T0, baseline evaluation; T1, after the 2-weeks supervised training; T2, after the 12-weeks self-managed training; T25FW, timed 25-foot walk test; 6MWT, 6-minute walking test; TUG, timed up and go; MFIS, modified fatigue impact scale; MSWS12, multiple sclerosis walking scale; MSIS, multiple sclerosis impact scale-29; $rmVO_2$, resting muscle oxygen consumption

Table 4. Effects of TOCT on primary and secondary outcome measures.

	TOCT-group				Delayed-group			
	T0	T1	T2	RM-ANOVA	T0	T1	T2	RM-ANOVA
6MWT, m	316.99 (102.46)	346.79 (90.33)	361.06 ± 111.61**	<0.001	372.63 (81.81)	376.68 ± 75.31	352.84 (96.73)	0.12
T25FW speed, ms^{-1}	1.34 (0.38)	1.47 (0.35)	1.47 (0.33)	0.02	1.47 (0.31)	1.50 (0.28)	1.41 (0.36)	0.29
TUG, s	10.34 (4.24)	8.99 (2.31)	8.77 (2.44)*	<0.01	9.65 (2.13)	9.12 (2.01)	9.40 (2.74)	0.28
Dynamic Gait Index	16.89 (4.60)	18.61 (3.62)	18.44 (3.68)	0.03	18.39 (3.53)	19.11 (3.38)	18.50 (3.97)	0.29
MFIS physical	20.83 (7.91)	16.61 (7.21)*	17.00 (7.59)	<0.01	19.50 (6.18)	17.83 (7.37)	17.22 (7.24)	0.24
MFIS cognitive	11.78 (9.35)	9.39 (9.29)	9.28 (8.53)	0.13	8.95 (9.34)	7.28 (8.24)	7.56 (8.05)	0.37
MFIS psychosocial	3.67 ± 2.20	2.61 (2.06)	3.22 (2.29)	0.02	3.00 (2.03)	3.11 (2.25)	2.94 (2.24)	0.90
MSIS-29 motor component	50.72 ± 15.52	45.17 (12.53)	46.72 (13.66)	0.01	49.33 (11.64)	44.83 (10.83)	44.56 (12.40)	0.03
MSIS-29 psychological component	50.00 ± 17.10	42.71 (15.20)*	41.98 (15.49)*	<0.001	50.86 (16.24)	47.16 (16.62)	41.23 (16.69)*	<0.01
MSWS12 (%)	65.37 (20.00)	52.78 (16.52)**	55.56 (15.71)*	<0.001	63.52 (13.33)	58.06 (16.36)	61.02 (15.93)	0.14
$rmVO_2$	0.06 (0.03)	0.06 (0.03)	0.04 ± 0.01)	0.04	0.06 (0.04)	0.06 (0.03)	0.05 (0.02)	0.19

* $p < 0.01$ for the comparison at T0

** $p < 0.001$ for the comparison at T0

Abbreviations: TOCT group, Task oriented circuit training group; Delayed group: patients who received TOCT at the end of the study; T0, baseline evaluation; T1, after the 2-weeks supervised training; T2, after the 12-weeks self-managed training; T25FW, timed 25-foot walk test; 6MWT, 6-minute walking test; TUG, timed up and go; MFIS, modified fatigue impact scale; MSWS12, multiple sclerosis walking scale; MSIS, multiple sclerosis impact scale-29; rmVO2, resting muscle oxygen consumption.

- People with multiple sclerosis (PwMS) suffers from gait impairments and physical deconditioning during their life
- Task-oriented circuit training can induce positive effects on mobility, balance and Quality of Life
- The combination of an in-hospital supervised with an home-based intervention is feasible an
- Long-lasting effects on walking endurance were found at 3 months follow-up

Assessed for eligibility (n=42)

Enrollment

Excluded (n =6)
- Not meeting inclusion criteria (n=6)

Randomized (n= 36)

First visit:
- Clinical and demographic data
- Clinical and instrumental assessments (Baseline)

First visit:
- Clinical and demographic data
- Clinical and instrumental assessments (Baseline)

Allocation

Allocated to TOCT group (n= 18): 2-weeks task - oriented circuit training (Phase 1)
- Received allocated intervention (n= 17)
- Did not start rehabilitation after randomization: Organization or personal reasons (n = 1)

Allocated to Delayed-TOCT group (n= 18): Clinical and instrumental assessments after two weeks without intervention
- Received allocated intervention (n= 17)
- Self-excluded from the study for organization or personal reasons (n = 1)

Home-based 12-weeks training with monthly in-hospital visits (Phase 2):

Clinical and instrumental assessment

Clinical and instrumental assessments after 12-weeks without intervention

Follow-Up

Modified Intention-To-Treat analysis (n= 18)

Lost to 12-weeks follow-up (n= 5):

MS worsening (n=1)

Personal issues (n=3)

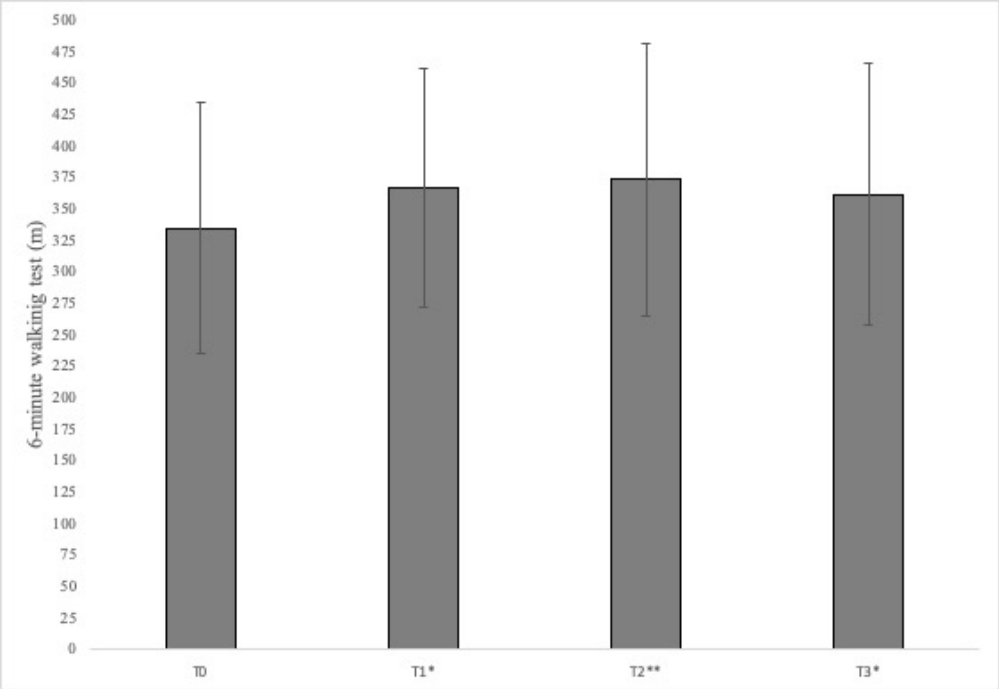
Discontinued intervention (n= 1)

Modified Intention-To-Treat analysis (n= 18)

Lost to 12-weeks follow-up (n= 3):

MS worsening (n=1)

Personal issues (n=2)



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