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ORIGINAL REPORT

INTENSIVE CIRCUIT CLASS THERAPY IN PATIENTS WITH RELAPSING-REMITTING MULTIPLE SCLEROSIS

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Objective: **Long-term physiotherapy is of considerable benefit to patients with multiple sclerosis (MS) who have motor dysfunction or gait impairment. The aim of this study was to determine the effectiveness of a 12-week intensive circuit class therapy for patients with MS, with a wider focus on fatigue and gait ability.**

Methods: **A total of 46 patients with relapsing-remitting MS were divided randomly into 2 groups: 23 patients (mean Expanded Disability Status Scale (EDSS) 2.33 ± 0.74) participated in an intensive 12-week course of intensive circuit class therapy, and 23 patients (mean EDSS 2.04 ± 0.63) served as a control group. The EDSS, Timed Up and Go (TUG) test and Four-Stage Balance Test (FSBT) made up the physical testing part, supplemented by questionnaires such as the Modified Fatigue Impact Scale (MFIS), 12-Item Multiple Sclerosis Walking Scale (MSWS-12), Beck Depression Inventory (BDI) and 36-Item Short Form Survey (SF-36).**

Results: **Significant improvements were found among intensive circuit class therapy-exercising patients in FSBT ($p < 0.05$), TUG test ($p < 0.01$), MFIS ($p < 0.01$), BDI ($p < 0.05$), MSWS-12 ($p < 0.05$) and the 3 subscales of SF-36 after 12 weeks of intensive circuit class therapy, while there were no significant changes in the control group.**

Conclusion: **Intensive circuit class therapy is an effective therapeutic approach for improving gait and balance problems in patients with MS. It has also proved to alleviate fatigue and symptoms of depression.**

Key words: multiple sclerosis; physical therapy modalities; rehabilitation; gait; fatigue; circuit-based exercise.

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LAY ABSTRACT

Gait impairment and fatigue are among the most common manifestations of multiple sclerosis (MS). In this study we aimed to test the effect of 12-week intensive circuit class therapy (ICT) on motor skills and fatigue in MS patients. Forty-six MS patients with mild to moderate disability were randomly assigned to those who underwent the ICT, or to the control group. The ICT patients exercised intensively one day per week on nine different stations with two experienced physiotherapists, the control group patients continued their routine daily exercise. Intensively exercising MS patients then improved significantly in the overall balance, gait and fatigue parameters, while there was no significant improvement in the control group. These findings indicate that ICT is an effective therapy for MS patients with gait, balance or fatigue problems.

Multiple sclerosis (MS) is an inflammatory, immune system-mediated, chronic demyelinating disease of the central nervous system. MS is currently one of the main causes of disability in young adults, with an estimated incidence ranging from 1.1 to 4 per 100,000 globally (1). Furthermore, MS features significant inter-individual variability in presentation and prognosis and is frequently associated with complex disability (2). Since a clinical relapse treated even with the best of protocols may be followed by incomplete remission, there is an essential need for physical therapy. Patients with MS exhibit substantially lower physical activity than the general population (3). Over 40% of patients with MS experience problems with activities of daily living, leading, together with fatigue and depression, to decreased functional independence and quality of life (4).

Several recent studies have shown that patients with motor dysfunction and/or gait impairment may benefit hugely from long-term physical therapy (5, 6). Moreover, properly managed physical therapy has been shown to alleviate fatigue (5). A variety of physical therapy techniques, among them yoga and aqua-therapy (7), exergaming, conventional balance training, single-task exercises (8), progressive resistance training on a bicycle ergometer and balance exercise (9), have been shown to improve overall mobility, decrease risk of falls, and ameliorate depression, in patients with MS. Circuit class therapy can be defined as therapy provided to more than 2 participants; involving a tailored intervention programme, with a focus on practice of functional tasks received within a group setting. In practice, this can involve participants physically moving between work-stations set up in specific locations within each class, or participants performing a set of core activities adapted to suit individual needs within a group setting, but without the need to physically move between work-stations. Optimally, the intervention is targeted at multiple levels, such as strength and balance and walking practice and range of movement. Participant's progress is continuously monitored and the activities are adapted as required (10, 11).

There is moderate evidence that circuit class therapy is effective in improving mobility for people after stroke; they may be able to walk further, faster, and with more independence and confidence in their balance. The effectiveness of circuit class therapy on walking ability in patients with MS has been demonstrated in a small number of patients (12, 13, 14, 15). In addition, circuit class therapy reduces the high demands on physiotherapists in conventional one-on-one exercise, and may therefore be made available to more patients. The aim of this study was to determine the effectiveness of a 12-week intensive circuit class therapy (ICT) on patients with MS, through evaluating the efficacy of ICT, mainly its impacts on gait competency and fatigue. In addition, the feasibility of such treatment and its overall effects on quality of life and depression were assessed.

METHODS

Study design

A dedicated programme of ICT was designed for this controlled trial. The study included 46 patients with relapsing-remitting MS (RRMS), treated with a disease-modifying therapy (DMT, 26 treated with interferon beta-1a(b), 9 with glatiramer-acetate, 4 with dimethyl fumarate, 2 with teriflunomide, 3 with fingolimod, and 2 with natalizumab) with a lower disability (maximal Expanded Disability Status Scale (EDSS) 4.0) in the large multiple sclerosis centre of a university hospital. Subjects were randomized into 2 groups (using stratified block randomization with block size randomly assigned to 4 or 6 patients):

(i) an intensive 12-week ICT group of 23 patients with MS (19 women and 4 men, mean age 41.86±8.87 years, mean EDSS 2.33±0.74, mean duration of disease 5.22±4.25 years); and *(ii)* a control group of 23 patients with MS (19 women and 4 men, mean age 37.43±7.14 years, mean EDSS 2.04±0.63, mean duration of disease 8.69 ± 3.83 years). The control group received no specific physical therapy rehabilitation exercise or treatment, and the patients were instructed to continue with their routine physical activities. The control group was sex-matched with the ICT group, and the age and EDSS were not different between both groups. Demographic and clinical characteristics are summarized in Table I, and the study design is shown in Fig. 1.

Inclusion and exclusion criteria

Inclusion criteria were:

- adult patients with RRMS who met the revised 2017 McDonald's criteria (14) and were treated with a disease-modifying therapy;
- EDSS (16) of maximum 4.0, willingness to train both at home and in a hospital setting; and
- clinical stability with no relapses or disability worsening for at least 3 months;

Exclusion criteria were:

- occurrence of comorbid neurological or other (e.g. orthopaedic) diseases with a possible effect on gait or balance;
- unstable cardiovascular condition; and
- impaired cognitive functioning (Mini-Mental State Examination score less than 24).

Examination

Each patient was assessed 1 week before and 1 week after the ICT (ICT group) or at the same interval before and after a corresponding period of 12 weeks (control group) (Fig. 1). Physical testing incorporated the EDSS (16), the Timed Up and Go (TUG) test (17), and the Four-Stage Balance Test (FSBT) (18). Estimation of fatigue and overall impact on quality of life were investigated with self-reported questionnaires, such as the Modified Fatigue Impact Scale (MFIS) (19), the 12-Item Multiple Sclerosis

Table I. Demographic and clinical characteristics

	All subjects	ICT	Controls	*p*-value
Total, *n*	46	23	23	1*
Sex (female/male), *n*	38/8	19/4	19/4	1*
Age (years), mean (SD)	39.65 (8.27)	41.86 (8.87)	37.43 (7.14)	0.31**
EDSS score (before ICT), mean (SD)	2.18 (0.70)	2.33 (0.74)	2.04 (0.63)	0.17**
MS duration (years), mean (SD)	6.95 (4.37)	5.22 (4.25)	8.69 (3.83)	**0.006****

Significant values are marked in **bold**.

ICT: intensive circuit class therapy; EDSS: Expanded Disability Status Scale; SD: standard deviation; MS: multiple sclerosis. *Comparison between ICT and control group using the χ^2 test. **Comparison between ICT and control group using the parametric Student's *t*-test for independent samples.

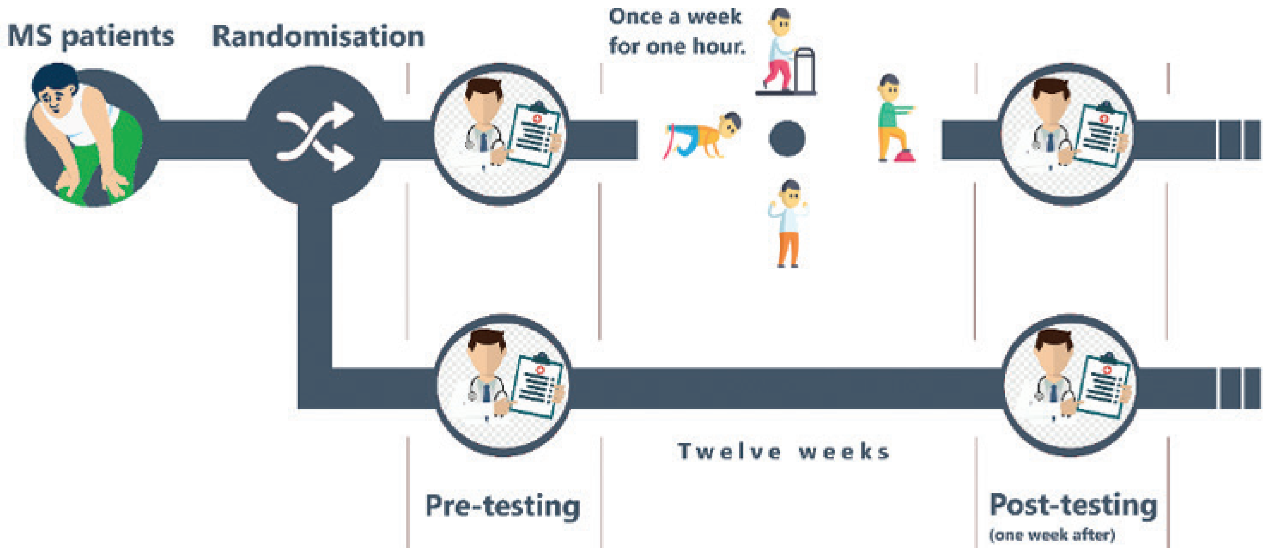


Fig. 1. Study flow diagram. MS: multiple sclerosis.

Walking Scale (MSWS-12) (20), and the Beck Depression Inventory (BDI) (21, 22), together with a 36-Item Short Form Survey (SF-36) (23). These constituted the main test batteries.

Timed Up and Go test. The TUG test focuses on mobility, balance and walking ability and is in widespread use to determine the risk of accidental falls. The patient is given a verbal instruction to stand up from a chair, walk 3 m, turn around, walk back, and sit down again. The time taken is recorded. A patient with a TUG time > 12 s is at higher risk of accidental falls (17).

Four-Stage Balance Test. The FSBT helps to indicate whether a patient is at risk of falling, and may be helpful in combination with other balance tests (such as the TUG test, above) in assessing postural hypotension. The patient is instructed to maintain 4 challenging positions without any assisting device (e.g. crutch or stick); each successive position becomes more difficult to hold. The position is changed every 10 s, and the test ends when the subject can no longer maintain a position (18). Not being able to hold the tandem stance (task number 3) for 10 s is an indication of increased risk of falls (24).

21-Item-Modified Fatigue Impact Scale. The MFIS is a questionnaire that concentrates largely on physical tiredness and any lack of energy experienced by the patient in the course of the previous 4 weeks. This scale was created during the development of the Multiple Sclerosis Quality of Life Inventory, by shortening its 40-item questionnaire. The patient reads 21 statements and chooses from 5 options, scoring from 0 (never) to 4 (almost always) points. The total MFIS score can range from 0 to 84 points; the higher the score, the greater the impact of fatigue on the subject's activities. Furthermore, the MFIS items may be divided into 3 subscales, reflecting the impact of fatigue in the physical, cognitive, and psychosocial domains (19).

Multiple Sclerosis Walking Scale-12. The MSWS-12 is a self-reported questionnaire consisting of 12 items (arranged in terms of gait speed, running, confidence of balance, stair-climbing and fatigue) to assess the overall impact of MS on gait. The total score is the sum of all items (each worth 0–5 points), totalling 0–60. The higher the patient's score, the more his or her walking is handicapped (20).

Beck Depression Inventory. The BDI is a dedicated, self-reported inventory that is widely used for measuring the severity of depression. It consists of 21 multiple-choice questions concerning the subject's feelings in the course of the previous week. The total score represents the current level of patient's depression (0–10 is considered normal, 11–16 mild mood disturbance, 17–20 borderline clinical depression, 21–30 moderate clinical depression, 31–40 severe clinical depression, and over 40 extreme clinical depression) (21, 22).

36-Item Short Form Survey. The SF-36 is a self-administered questionnaire containing 36 items, taking approximately 5 min to complete. It provides a measure of health in 8 multi-item dimensions, covering functional status, well-being, and overall evaluation of health. For each dimension, item scores are coded, summed, and transformed into a scale from 0 (worst health) to 100 (best health) (23). The study herein focussed largely on the 3 main parts of this questionnaire, which assess fatigue and mental health. Stated in its own terms,

Table II. Training description

Training protocol	
Patients per group, *n*	5–6
Therapists, *n*	2 physiotherapists
Intensity	12 weeks, 1 day per week, 60 min
Progression	More difficult exercise options, using heavier weights, using balance pads
Exercises	Work-stations (A – Easiest, B – Moderate, C – Most difficult)
1.	A) Four-point kneeling position
	B) High plank
	C) High plank with hands on a Bosu ball
2.	A) Step on low stepper
	B) Step on higher stepper
	C) Step on higher stepper with 1 kg weight
3.	A) Shadow-boxing
	B) Shadow-boxing with 2×0.5-kg dumb-bells
	C) Shadow-boxing with dumb-bells. With a balance pad underfoot
4.	A) Squat
	B) Squat on a balance pad
	C) Squat on a Bosu ball
5.	A) "Three-month-old child" supine position
	B) "Three-month-old child" supine position with upper extremity movement
	C) "Three-month-old child" supine position with upper and lower extremity movement
6.	A) Lunge exercise
	B) Lunge exercise with 1-kg weight
	C) Lunge exercise with 1-kg weight on a balance pad;
7.	A) Triceps push-ups against the wall
	B) Triceps push-ups with hands on a box
	C) Triceps push-ups with hands on a fit-ball
8.	A) Bridging
	B) Bridging with 1-leg lift
	C) Bridging on a balance pad with 1-leg lift
9.	A) Four-point kneeling on a Flow-in pad and upper limb movement;
	B) High plank on a Flow-in pad and upper limb movement;
	C) High plank on a Flow-in pad, upper limb movement against TheraBand resistance.

these are: Energy/Fatigue; Role Limitations due to Emotional Problems; and Emotional Well-being.

Intensive circuit class therapy

All 23 exercising subjects were divided into smaller groups of 5 or 6 patients with MS. They exercised for 1 h a week at 9 different work-stations designed to strengthen the whole body, especially through movement activities and by using particular tools (e.g. Bosu ball, Flow-in or Fitball) to improve balance. The 1-h exercise unit always consisted of an aerobic warm-up (15 min), the main ICT (30 min), and final stretching and relaxation (15 min). The warm-up included repetitive step variations and dynamic stretching to improve coordination, in order to prepare each patient for greater loads (25). Subjects then exercised for 1 min at each station and were given approximately 30 s to shift between stations. The session consisted of 2 laps with 4 min rest between them. The ICT was regularly adjusted according to the capabilities of the group, and supervised by 2 expert physiotherapists at 3 levels of difficulty. The level of difficulty was modified according to the patient's individual condition. Further details of the protocol are shown in Table II. Patients were instructed to interrupt the exercise if it felt unpleasant or fatigue was excessive. The final part of the training unit was devoted to stretching and relaxation in order to calm the heart rate. Elements of yoga, which has been proven to reduce stress, fatigue and pain, were employed. The calm down part of training included poses from yoga, such as child's pose, cat pose, melting heart pose, pigeon pose, downward facing dog pose, garland pose, etc.

Study analyses

Power analysis. A power analysis was performed after the first group of ICT ($n=6$). Student's *t*-test power analysis (significance level 0.05; statistical power 0.90) was performed for the pre-ICT and post-ICT difference of main outcome measures of the study (FSBT, TUG, MFIS, BID, and MSWS-12) (Table III). The estimated minimum number of patients for significance of expected results was 22.

Biostatistical analysis. Descriptive statistics (mean, median, standard deviation (SD), percentiles and confidence intervals) were employed to describe samples before and after ICT. Baseline characteristics (sex, age, EDSS score) and pre-testing clinical tests and questionnaires (TUG, FSBT, MSWS-12, MFIS, SF-36) were compared between the ICT and control group using Student's *t*-test for independent samples and χ^2 test to assess the quality of randomization. Pre-testing and post-testing values of all the tests were compared in particular groups using Student's *t*-test for dependent samples to demonstrate the effect of ICT on measurable outcomes in the training group (or its absence in the control group). For the same purpose, changes in parameters/test (non-normally distributed) were compared between the groups using the Mann–Whitney *U* test. More detailed test specifications are shown in the Tables. Statistical analysis was performed within STATISTICA software v12.1 (Developed by StatSoft, Czech republic, http://www.statsoft.cz/). The significance level was set at 0.05.

Table III. Power analysis for the pre-intensive circuit class therapy (pre-ICT) and post-ICT difference of main outcomes

	FSBT	TUG	MFIS	BID	MSWS-12
Estimated number of samples	7	19	22	19	19
Significance power	0.9	0.9	0.9	0.9	0.9

ICT: intensive circuit class therapy; MFIS: Modified Fatigue Impact Scale; BDI: Beck Depression Inventory; MSWS-12: Twelve-Item Multiple Sclerosis Walking Scale; FSBT: Four-Stage Balance Test; TUG test: Timed Up and Go test.

Table IV. Comparison of clinical and questionnaire pre-tests in intensive circuit class therapy (ICT) and control groups

	Median (25th–75th percentile)	*p*-value*
EDSS		
ICT	2.50 (2.00–2.50)	0.18
Control	2.00 (1.50–2.50)	
FSBT (s)		
ICT	40.00 (37.00–40.00)	0.48
Control	40.00 (39.28–40.00)	
TUG test (ms)		
ICT	848.00 (793.50–995.00)	0.90
Control	911.00 (803.50–995.00)	
MFIS		
ICT	28.00 (16.50–38.50)	0.79
Control	28.00 (9.50–41.00)	
BDI		
ICT	7.00 (2.50–11.00)	0.86
Control	7.00 (2.00–9.50)	
MSWS-12		
ICT	15.00 (13.50–20.00)	0.87
Control	18.00 (12.00–20.00)	
SF-36-RLEP (%)		
ICT	100.00 (67.00–100.00)	0.87
Control	100.00 (67.00–100.00)	
SF-36-E (%)		
ICT	50.00 (40.00–65.00)	0.89
Control	45.00 (35.00–70.00)	
SF-36-EWB (%)		
ICT	80.00 (64.00–88.00)	0.56
Control	72.00 (64.00–88.00)	

ICT: intensive circuit class therapy; EDSS: Expanded Disability Status Scale; FSBT: Four-Stage Balance Test; TUG test: Timed Up and Go test; MFIS: Modified Fatigue Impact Scale; BDI: Beck Depression Inventory; MSWS-12: Twelve-Item Multiple Sclerosis Walking Scale; SF-36-E: Energy/fatigue; SF-36-RLEP: Role limitations due to emotional problems; SF-36-EWB: Emotional well-being

*Student's *t*-test for independent samples to compare parameters between particular groups.

RESULTS

Functional tests results (walking endurance, speed, balance, mobility)

Pre-ICT testing did not reveal any significant difference between the 2 groups (see Table IV), which confirms the quality of the randomization. Postural stability was not obviously impaired in either group prior to the treatment intervention. The results of both FSBT and TUG pre-ICT tests were mostly normal. Only 3 out of 46 subjects with MS (2 from the ICT group and 1 from the control group) had a time of <30 s in FSBT and 2 out of 46 (both from the ICT group) had a time >12 s in TUG testing, which is considered a correlate of a high risk of falling according to the published data (18).

Despite mostly normal pre-testing values, significant improvements were evident in both FSBT ($p<0.05$) and TUG test ($p<0.01$) after 12 weeks of ICT in the training group, in contrast with the control group, who maintained their usual status. There was no significant change in EDSS in either group during follow-up. Descriptive statistics are shown in Table V and Fig. 2.

Patient-reported questionnaires (fatigue, walking ability, health-related quality of life)

No significant differences between the 2 groups were found during pre-testing (pre-ICT), which further confirms the quality of randomization. Among the questionnaires, ICT-exercising patients reported improvement in MFIS ($p < 0.01$), BDI ($p < 0.05$), MSWS-12 ($p<0.05$), SF-36/RLEP ($p<0.05$), SF-36/E ($p<0.05$), SF-36/EWB ($p < 0.01$) after 12 weeks of ICT, while there were no significant changes in the control group. Descriptive statistics are shown in Table VI and Fig. 2.

DISCUSSION

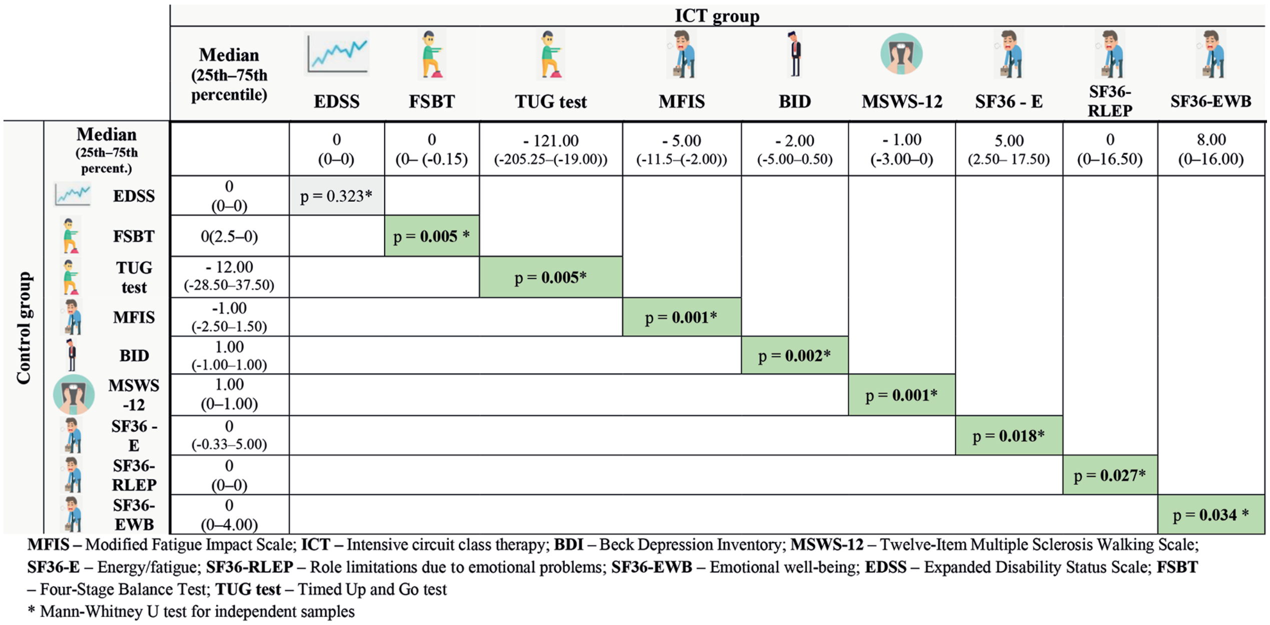
This study demonstrated the efficacy of ICT in treatment gait and balance problems in patients with MS with mild-to-moderate disability. Furthermore, highly significant positive effects of ICT were found for several important MS comorbidities, i.e. fatigue and symptoms of depression. The results thus broaden evidence-based knowledge concerning physiotherapy as an important part of the treatment provided to patients with MS, adding to its many already-proven benefits, including the effect on cognitive functions (12, 26). This study also provides new evidence of the benefits of ICT for social connectivity. Furthermore, use of ICT

Table V. Clinical outcomes

	ICT (*n*=23)			Controls (*n*=23)		
	Mean (SD)	Median(25th–75th percentile)	95% CI	Mean (SD)	Median(25th–75th percentile)	95% CI
EDSS						
Pre-ICT	2.33 (0.74)	2.50 (2.00–2.50)	2.02–2.63	2.04 (0.64)	2.00 (1.50–2.50)	1.78–2.30
Post-ICT	2.30 (0.77)	2.50 (1.75–2.50)	1.98–2.62	2.07 (0.66)	2.00 (1.50–2.50)	1.79–2.34
p-value (pre-ICT vs post-ICT) *		0.58		*p*-value (control)*	0.33	
FSBT (s)						
Pre-ICT	37.87 (5.58)	40.00 (37.00–40.00)	36.40–39.33	38.57 (3.06)	40.00 (39.28–40.00)	37.32–39.81
Post-ICT	39.26 (2.18)	40.00 (40.00–40.00)	38.37–40.15	38.28 (3.44)	40.00 (38.13–40.00)	36.70–39.85
p-value (pre-ICT vs post-ICT) *		**0.04**		*p*-value (control)*	0.13	
TUG test (ms)						
Pre-ICT	901.91 (185.67)	848.00 (793.50–995.00)	826.03–977.79	894.39 (148.36)	911.00 (803.50–995.00)	833.76–955.03
Post-ICT	814.83 (163.92)	849.50 (670.00–905.00)	739.11–890.56	892.96 (149.87)	901.00 (797.00– 979.50)	831.71–954.21
p-value (pre-ICT vs. post-ICT) *		**0.005**		*p*-value (control)*	0.86	

ICT: intensive circuit class therapy; EDSS: Expanded Disability Status Scale; FSBT: Four-Stage Balance Test; TUG test: Timed Up and Go test.

*Student's *t*-test for dependent samples.



Control group	Median (25th–75th percentile)	ICT group: EDSS	FSBT	TUG test	MFIS	BID	MSWS-12	SF36 - E	SF36-RLEP	SF36-EWB
Median (25th–75th percent.)		0 (0–0)	0 (0– (-0.15)	- 121.00 (-205.25–(-19.00))	- 5.00 (-11.5–(-2.00))	- 2.00 (-5.00–0.50)	- 1.00 (-3.00–0)	5.00 (2.50– 17.50)	0 (0–16.50)	8.00 (0–16.00)
EDSS	0 (0–0)	p = 0.323*								
FSBT	0(2.5–0)		**p = 0.005 ***							
TUG test	- 12.00 (-28.50–37.50)			**p = 0.005***						
MFIS	-1.00 (-2.50–1.50)				**p = 0.001***					
BID	1.00 (-1.00–1.00)					**p = 0.002***				
MSWS -12	1.00 (0–1.00)						**p = 0.001***			
SF36 - E	0 (-0.33–5.00)							**p = 0.018***		
SF36-RLEP	0 (0–0)								**p = 0.027***	
SF36-EWB	0 (0–4.00)									**p = 0.034 ***

MFIS – Modified Fatigue Impact Scale; **ICT** – Intensive circuit class therapy; **BDI** – Beck Depression Inventory; **MSWS-12** – Twelve-Item Multiple Sclerosis Walking Scale; **SF36-E** – Energy/fatigue; **SF36-RLEP** – Role limitations due to emotional problems; **SF36-EWB** – Emotional well-being; **EDSS** – Expanded Disability Status Scale; **FSBT** – Four-Stage Balance Test; **TUG test** – Timed Up and Go test

* Mann-Whitney U test for independent samples

Fig. 2. Comparison of differences, arranged by the results of outcomes for individuals and tests. MFIS: Modified Fatigue Impact Scale; ICT: intensive circuit class therapy; BDI: Beck Depression Inventory; MSWS-12: Twelve-Item Multiple Sclerosis Walking Scale; SF36-E: Energy/fatigue; SF36-RLEP: Role limitations due to emotional problems; SF36-EWB: Emotional well-being; EDSS: Expanded Disability Status Scale; FSBT: Four-Stage Balance Test; TUG test: Timed Up and Go test.

*Mann–Whitney *U* test for independent samples.

may help to reduce the existing high demands on busy physiotherapists in conventional one-on-one exercise. This is the first study with long-term design, including an homogenous group of DMT-treated RRMS patients with mild-to-moderate disability and preserved ambulation (EDSS 1.0–4.0).

MS affects a wide range of sensory and motor pathways, leading to deteriorating perception, vestibular sense, and control of muscles, all of which may disturb balance and coordination. Balance disruption can lead to impaired walking ability and reduced mobility, the retention of which are ranked as among the most important factors in maintaining a good quality of life for individuals with MS (27). Balance and mobility limitations are significant concerns for individuals with MS. Over 90% of people with MS report problems with mobility (25) and over 50% of individuals with the disease report falling in a 6-month period (28). Several studies have demonstrated that poor balance and loss of mobility contribute to considerable patient burden, adversely affecting factors such as independence and quality of life (4). The ability to walk is compromised in MS, and more than 50% of the MS population experience inadvertent falls in the course of daily life (29). Even a mild disability arising out of MS may significantly affect adaptation of gait; hence patients walk at lower preferred speeds, with shorter stride lengths, longer dual support times, and altered lower limb kinematics (30). A range of balance and mobility impairments contribute to an increased risk of falls and to limitations of activity. Greater postural sway, impaired forward leaning, impaired visually-dependent sway and leg weakness have each been demonstrated as predictive of future falls in MS (31). As balance deficits and immobility are also among the most important problems for patients with MS, interventions that aim to improve their balance and gait impairments and reduce the consequences of the disease are needed. Studies evaluating the efficacy and clinical value of exercise-based interventions in improving balance and mobility in patients with MS, however, have returned inconclusive results. For example, a meta-analysis examining the effects of physiotherapy on balance in persons with MS found low evidence for positive outcomes (32). This may be due, in part, to the failure of most exercise interventions to acknowledge that balance control is complex and multifaceted. Further studies examining the effects of physiotherapy on balance are thus required. In the current study, significant improvements were noted in both the TUG test ($p=0.005$) and the FSBT test ($p=0.04$) in the ICT group after 12 weeks of therapy, while there was no significant change in either of these tests in the control group after the same period of follow-up. These results confirm the positive effects of ICT physiotherapy on balance, and suggest that ICT could also have positive impacts on

Table VI. Questionnaire outcomes

	ICT (*n*=24)			Control (*n*=24)		
	Mean (SD)	Median (25th–75th percentile)	95% CI	Mean (SD)	Median (25th–75th percentile)	95% CI
MFIS						
Pre-ICT	27.43 (15.76)	28.00 (16.50–38.50)	20.99–33.88	26.13 (17.65)	28.00 (9.50–41.00)	18.92–33.35
Post-ICT	21.48 (14.34)	20.00 (11.00–29.50)	15.62–27.34	25.74 (16.62)	27.00 (9.50–40.50)	18.95–32.53
p-value (pre-ICT vs post-ICT)*		**0.0014**		*p*-value (control)*	0.52	
BDI						
Pre-ICT	7.61 (6.15)	7.00 (2.50–11.00)	5.10–10.12	7.96 (6.90)	7.00 (2.00–9.50)	5.14–10.78
Post-ICT	4.74 (3.39)	6.00 (1.00–8.00)	3.35–6.12	8.30 (6.81)	7.00 (3.50–10.50)	5.52–11.09
p-value (pre-ICT vs post-ICT)*		**0.019**		*p*-value (control)*	0.31	
MSWS-12						
Pre-ICT	17.74 (6.90)	15.00 (13.50–20.00)	15.00–20.56	17.43 (5.72)	18.00 (12.00–20.00)	15.10–19.80
Post-ICT	16.17 (6.19)	13.00 (12.00–18.00)	13.64–18.70	17.91 (5.60)	19.00 (12.00–21.00)	15.62–20.20
p-value (pre-ICT vs post-ICT)*		**0.03**		*p*-value (control)*	0.06	
SF-36 – RLEP (%)						
Pre-ICT	76.87 (29.22)	100.00 (67.00–100.00)	64.93–88.81	75.35 (32.21)	100.00 (67.00–100.00)	62.18–88.51
Post-ICT	87.04 (19.37)	100.00 (67.00–100.00)	79.13–94.96	73.87 (33.64)	100.00 (50.00–100.00)	60.23–87.50
p-value (pre-ICT vs post-ICT)*		**0.049**		*p*-value (control)*	0.33	
SF-36 – E (%)						
Pre-ICT	51.30 (16.67)	50.00 (40.00–65.00)	44.49–58.12	52.17 (25.31)	45.00 (35.00–70.00)	41.83–62.52
Post-ICT	58.70 (17.00)	60.00 (55.00–70.00)	51.75–65.64	51.52 (23.42)	45.00 (35.00–70.00)	41.95–61.10
p-value (pre-ICT vs post-ICT)*		**0.036**		*p*-value (control)*	0.74	
SF-36 – EWB (%)						
Pre-ICT	75.13 (14.37)	80.00 (64.00–88.00)	69.26–81.00	72.52 (15.55)	72.00 (64.00–88.00)	66.17–78.87
Post-ICT	82.61 (10.06)	84.00 (76.00–90.00)	78.50–86.72	73.22 (14.29)	72.00 (66.00–88.00)	67.38– 79.06
p-value (pre-ICT vs post-ICT)*		**0.0018**		*p*-value (control)*	0.58	

MFIS: Modified Fatigue Impact Scale; ICT: intensive circuit class therapy; BDI: Beck Depression Inventory; MSWS-12: Twelve-Item Multiple Sclerosis Walking Scale; SF-36-E: Energy/fatigue; SF-36-RLEP: Role limitations due to emotional problems; SF-36-EWB: Emotional well-being.

*Student's *t*-test for dependent samples.

the risk of falls in patients with MS, and help shield them from traumatic injuries. Furthermore, significant improvement was also evident in MSWS-12 in the ICT group ($p=0.03$), while no significant difference was found in the control group in the interval between the initial examination and 12 weeks later.

The results of this study follow a positive trend similar to the already published data of Chisari et al. (33), in which a group of 17 patients with MS showed significant improvement in the TUG test and a positive trend in the SF-36 questionnaire. In another study published by Tramonti et al. (14, 15), a group of 15 patients with MS showed only an insignificant trend in TUG test, but a clear improvement in the MFIS and MSWS-12 questionnaires. However, both studies were more task-oriented and lacked a control group. The current results extend this knowledge by adding a control group and performing a broader range of tests. The current data are in agreement with the recently published study by Ozkul et al. (12).

The results of all the above-mentioned studies thus suggest that ICT could have positive impacts on gait even in RRMS patients with mild-to-moderate disability, and confirm that physiotherapy can be effective in ameliorating patients' gait problems, as has been demonstrated previously (34).

Fatigue is one of the most common and devastating symptoms of MS, with negative impacts extending from general functioning to overall quality of life (35). Both controls and exercising patients with MS in the current cohort already had mild-to-moderate pre-existing fatigue that limited their activities of daily life. Both the cause(s) and consequences of MS fatigue are considered multidimensional, and a multidisciplinary approach to successful symptom management is required. A number of published reviews have examined the effectiveness of certain types of fatigue management interventions for patients with MS. For example, reviews of pharmacological intervention trials (i.e. amantadine and modafinil) on fatigue in MS have noted that current evidence for their use is weak and inconclusive (36). In contrast, a review of exercise training (6) suggests that exercise-based interventions may be beneficial for MS fatigue management. Among others, physical therapy methods, such as endurance exercise programme, resistance exercise programme (37), vigorous cool room treadmill training (38), or balance specific exercises (39) proved effective to alleviate fatigue. The data presented herein demonstrated a positive effect for ICT in alleviating the fatigue, confirmed by improvements in both MFIS

($p = 0.0014$) and SF-36 (Energy/Fatigue) ($p = 0.036$) after the therapy in the ICT group, while no significant difference on either of these scales was found in the control group. These results thus provide further support for the positive effects of exercise training on fatigue in patients with MS, broadening the spectrum of training methods suitable for this purpose. Since fatigue has a significant negative impact on activities of daily life, and pharmacological intervention trials are inconclusive, physical therapy may prove to be the only effective treatment option for this exhausting MS symptom.

Depression is a further frequent comorbidity in patients with MS. According to existing reviews, the lifetime prevalence of major depression in patients with MS ranges from 20% to 50%, depending on the population sample and diagnostic criteria employed (40); the annual prevalence is estimated at 16% (41). These findings are in agreement with the data from this study, which indicate a prevalence of depression, judged by BDI questionnaire, at a level of 26% in the MS patient cohort at the beginning of this study. Such a figure is considerably higher than that occurring in the general population or among patients with general medical conditions other than MS (40). A comprehensive treatment plan for depression should include pharmacotherapy, psychotherapy, and cognitive behavioural therapy, each one alone or in combination with others. Screening for suicidal intent is incremental, in the light of the high cumulative lifetime risk of suicide (42). This study showed significant improvement in terms of answers to the questionnaires related to symptoms of depression, i.e. the BDI ($p = 0.019$) and the SF-36 questionnaire in those subscales related to mental health and mood disorders, RLEP ($p = 0.049$) and EWB ($p = 0.0018$) in tests performed after ICT training, in comparison with pre-ICT testing in the ICT group. No significant difference was found in the control group. These findings suggest that ICT could make an effective contribution to the treatment and/or prevention of major depression in patients with MS.

This study has a number of limitations. It includes a relatively low number of patients. The improvement in patients' gait ability and fatigue could be biased by the positive cardiovascular effects of ICT. Questionnaires about fatigue/energy and depression could feature significant overlap, since these symptoms are closely related; they could also be affected by the noted improvement in social functioning.

ICT also contributes the beneficial factor of social connection. Furthermore, it is usually designed for smaller groups of patients (often 6–10 patients) and thus reduces the already high demands on busy physiotherapists of conventional one-on-one exercise.

CONCLUSION

This study demonstrates that ICT is an effective therapy for patients with RRMS with mild-to-moderate disability in the alleviation of problems with gait and balance. Significant positive effects of ICTs were also recorded on fatigue and symptoms of depression.

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The authors have no conflicts of interest to declare.

Ethics approval

The research was approved by the local ethics committees (no. 01-051218). All subjects gave informed, written and signed consent.

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