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ORIGINAL ARTICLE

Exploring the feasibility of a mild and short 4-week combined upper limb and breathing exercise program as a possible home base program to decrease fatigue and improve quality of life in ambulatory and non-ambulatory multiple sclerosis individuals

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Abstract

Purpose To evaluate the feasibility of a combined upper limb and breathing exercise for a home-based program and to explore its effect on primary fatigue and quality of life in ambulatory and non-ambulatory individuals with multiple sclerosis (MS) in a short time.

Method Nineteen individuals with MS were assigned into semi-controlled pre-post feasibility study based on Expanded Disability Status Scale (EDSS) status and divided into two groups: exercise (five ambulatory, five non-ambulatory; EDSS 1.0–8.0) and related control with no exercise (four ambulatory, five non-ambulatory; EDSS 1.0–7.5). Exercise group performed combined upper limb and breathing exercise in a controlled group (2 days/week, 60 min/session) accompanied by independent home exercise (3 days/week, ≥ 20 min/session). Participants underwent measures of fatigue impact (Modified Fatigue Impact Scale (MFIS) and quality of life (RAND Medical outcomes study 36-item short-form health survey (SF-36)) before and after a 4-week period.

Results The MFIS (physical, psychosocial, total) showed statistically significant group-by-time interaction in ambulatory ($p = 0.033$, $d = 1.60$; $p = 0.039$, $d = 1.59$; $p = 0.033$, $d = 1.62$) and non-ambulatory individuals ($p = 0.009$, $d = 2.42$; $p = 0.018$, $d = 1.96$; $p = 0.0008$, $d = 3.92$). Physical functioning (SF-36) showed statistically significant group-by-time interaction in ambulatory ($p = 0.014$, $d = 2.14$) but no significance in non-ambulatory ($p = 0.368$, $d = 0.68$) individuals. Despite the absent statistical significance, there were large intervention effects on MFIS cognitive scores for ambulatory ($d = 1.28$) and non-ambulatory ($d = 1.47$), and on other SF-36 scores for ambulatory (general health: $d = 1.76$ and pain: $d = 1.02$) and non-ambulatory (physical limitation: $d = 1.03$ and emotional well-being: $d = 0.94$) individuals.

Conclusion Our 4-week program reduced some aspects of fatigue and improved some aspects of quality of life in a small group of ambulatory and non-ambulatory individuals with MS. Good feasibility and significant positive changes from baseline warrant further exploratory work.

Trial registration Name of the registry: The Impact of Exercise Training on Living Quality in Multiple Sclerosis. Registration: The study was registered at www.clinicaltrial.gov on July 14, 2017. First participant enrollment: August 28, 2017. URL: 602-01/17-01-147; Trial registration ID: NTC03222596.

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Keywords Multiple sclerosis · Ambulatory · Non-ambulatory · Quality of life · Fatigue · Exercise program

Abbreviations

CNS	Central nervous system
EDSS	Expanded Disability Status Scale
HE	Home exercise
MS	Multiple sclerosis
MSSC	MS Society Center
MFIS	Modified Fatigue Impact Scale
QOL	Quality of life
SF-36	Medical Outcomes Study 36-Item Short-Form Health Survey
UL	Upper limb

Introduction

Multiple sclerosis (MS) is a chronic and progressive neurodegenerative disease that involves unpredictable episodes of inflammatory demyelination and axonal transection in the central nervous system, which can ultimately result in functional limitations, disability and thus reduced quality of life (QOL) [1, 2]. Fatigue is the most common symptom displayed in patients with MS and a big contributor to disability, which largely determines the QOL in patients with MS [3].

Fatigue often results from respiratory dysfunction in patients with MS [4–7] and a fact is that respiratory muscle weakness increases as upper limbs (ULs) become increasingly involved or weakened. The first respiratory muscles to be affected are the abdominal muscles followed by the intercostal muscles, and the diaphragm. Thus, by the time the inspiratory function is seriously compromised, the patients are bedridden with all associated complications [4–8]. Combined exercises, which include respiratory and UL muscles could be an efficient rehabilitation strategy for slowing down this progression.

However, patients with MS with relatively little UL involvement are unlikely to have serious impairment of respiratory muscle function compared to patients with poor ambulation [4]. This is one of many reasons why clinical trials examine the effect of exercise in patients with MS often using a moderate or vigorous intensity exercise and cardiorespiratory training including the whole body or lower limbs, which low mobility people cannot handle [9, 10]. Not much has been explored or investigated about the low-intensity exercise effect, especially with only ULs included, which would be more appropriate for patients with low mobility. Many studies indicate that different types of UL rehabilitation strategies can improve UL function in MS [11], but they provide poor information about isolated UL exercise effect on fatigue and QOL [12], especially in individuals with Expanded Disability Status Scale [13] (EDSS) score > 6.5 [10]. Therefore, it is important to find an exercise program, which can be practical, not demanding, and easy to handle, and most of all productive for everyone with MS.

By improving the strength of the UL and respiratory muscles with a combined UL and breathing exercise program in patients with MS, it is likely that further progression of respiratory weakness will slow down, exercise capacity and overall physical functioning will also improve and fatigue will be reduced [7, 11, 14].

Since MS fatigue does not correlate with the degree of neurological impairment or disability in individuals with MS [15] we included ambulatory and non-ambulatory individuals in our study. Thus, the purpose of this study was to evaluate the feasibility of a mild combined UL and breathing exercise program as a possible home base program and to explore its effect on primary fatigue and quality of life in both ambulatory and non-ambulatory individuals with MS in a short time. Our hypothesis was that 4 weeks of a continuous UL exercise program with an accent on breathing can efficiently attenuate primary fatigue and improve the QOL in both ambulatory and non-ambulatory individuals with MS.

Methods

Study design

This study has a randomized semi-controlled parallel-group design and was performed in the MS Society Center (MSSC) and at home [16]. The MSSC is the official but familiar meeting place with enough space for performing exercises. The sample size was not determined based on power analysis given a pilot nature of a study [17]. It was designed to verify feasibility of a UL and breathing exercise and to explore possible effects on fatigue and the QOL in a group of ambulatory and non-ambulatory individuals with MS for the future larger trial. Baseline testing was performed during the 2 days by the independent researcher who was blinded to the allocation group of the patients in the MSSC.

All 19 participants, who met the criteria, were after clinical and neurological examinations and baseline assessment, randomly assigned into two groups based only on the EDSS score (Table 1) by a principal researcher. To ensure concealment of allocation, principal investigator had only EDSS score from each participant without any other information on the participant. The exercise group exercised under physiotherapist guidance and the control

Table 1 Characteristics of the subjects and medications

Variables	Exercise	Control
N	10	9
Age (year), mean ± SD	53.9 ± 10.7	48.2 ± 9.3
Sex (*N*), M/F	6/4	6/3
Type of MS (*N*)		
Relapsing-remitting	4	6
Primary progressive	2	0
Secondary progressive	4	3
EDSS median (range)	6.5 (1.0–8.0)	7.0 (1.0–7.5)
EDSS ambulatory median (range)	3.0 (1.0–6.0)	4.75 (1.0–6.5)
EDSS non-ambulatory median (range)	7.0 (7.0.-8.0)	7.0 (7.0–7.5)
EDSS ambulatory (1.0–6.5) (*N*)	5	4
EDSS non-ambulatory (7.0–8.0) (*N*)	5	5
SMMSE median (range)	30 (28–30)	30 (29–30)
Disease-modifying drugs (*N*)		
Interferon beta-1a	1	0
Fingolimod	1	1
Azathioprine	0	1
Glatiramer acetate	1	2
None	7	5

Noncategoric values are expressed as mean ± SD. Categoric values are expressed as median (range). *EDSS*, Expanded Disability Status Scale; *F*, female; *M*, male; *SMMSE*, Standardized Mini-Mental State Examination

group performed no exercise. The exercise group exercised 2 days/week, 60 min/session in the MSSC and performed independent home exercise (HE) 3 days/week for 4 weeks, at least 20 min/session.

The control group performed no exercise during the investigation but they were required to visit the MSSC 2 days/week (≤ 60 min) where they could freely socialize, having thereby approximately the same contact with the investigators as the exercise group. The control group was offered the exercise program at the end of the study, which everyone accepted.

The on-going physical therapy (without UL and breathing exercises 2/week for 45 min) was unchanged during the study for all patients (exercise and control group). At the end of the study (day after the last session), outcome measures were collected by the same independent researcher who assessed the baseline data.

Participants

The patients with diagnosed MS were randomly selected based on previous EDDS score (from 6 months ago) from the MSSC register. To establish the participants' interest in the research, the first contact was by phone. From 31 potential participants, 19 individuals with MS were recruited from the MSSC. Participant flow through enrolment is included in the Consolidated Standards of Reporting Trials (CONSORT) diagram (Fig. 1).

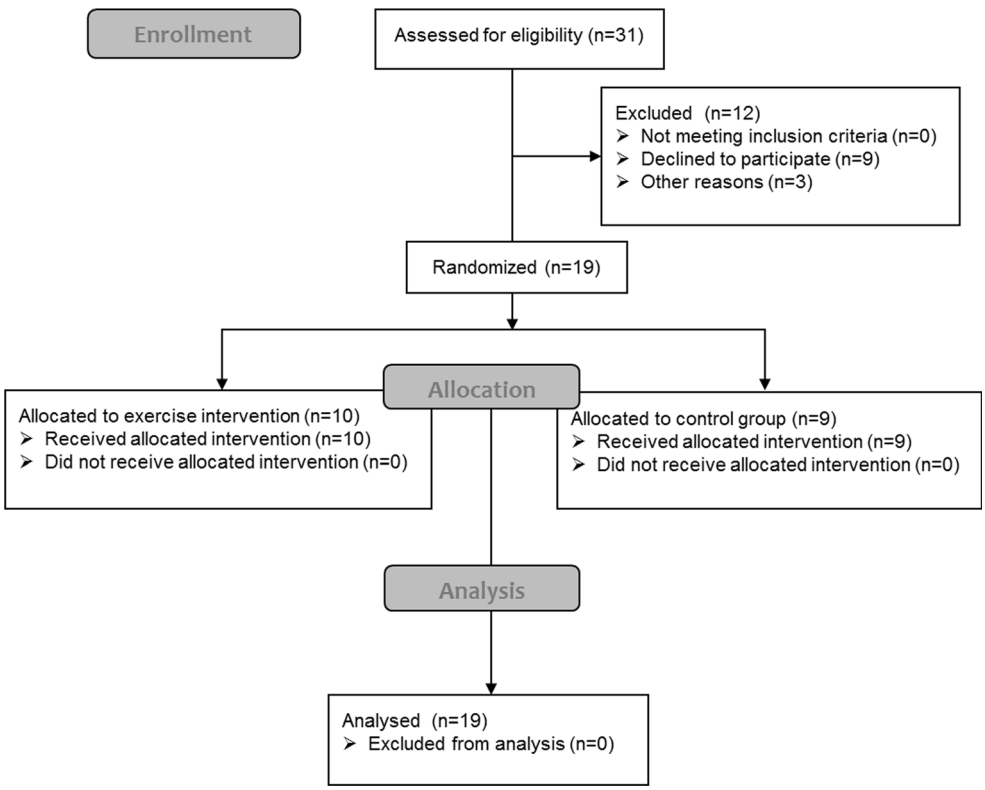

Fig. 1 Consolidated Standards of Reporting Trials (CONSORT) diagram

Before being included in the study, all 19 individuals were invited to the MSSC to meet the study inclusion and exclusion criteria checked by a two physicians (researchers). The physician (the principal researcher) assessed the participants' characteristics (sex, age, medications). Another physician (researcher blind to the intervention), who was trained to assess EDSS status, as well the type of MS based on standard diagnostic criteria (Table 1) [18], confirmed EDSS score.

The inclusion criteria were as follows: a diagnosis of MS with mild to severe disability (EDSS score between 0.0 [normal neurological exam] and 8.0 [essentially restricted to wheelchair, retains many self-care functions, generally has effective use of arms]), adults between the age of 18 and 70 years, patients with Standardized Mini-Mental State Examination [19] > 24 and with no contraindications for performing breathing and UL exercises.

The exclusion criteria were an exacerbation of MS or corticosteroid treatment within the past 4 weeks, the presence of concomitant neurological and musculoskeletal disorders affecting arms, acute or chronic lung pathologies, breathing difficulties or any other serious illness that might interfere with the intervention. Participants using MS disease-modifying drugs were included.

All subjects signed written informed consent and the study was approved by the local ethical committee (602-01/17-01-147) and registered in the ClinicalTrials.gov (www.clinicaltrial.gov). Subject characteristics and medications are presented in Table 1.

Outcome measures

Fatigue

The fatigue was measured using Modified Fatigue Impact Scale (MFIS). It is a reliable, valid measurement tool used to assess the impact of fatigue on physical, cognitive, and psychosocial functioning within the past 4 weeks [7, 20, 21]. It consists of 21 items and the scoring ranges from 0 to 82. A higher score reflects a greater fatigue impact.

Quality of life

Measures of health related QOL were obtained using Research ANd Development (RAND) short-form 36—Item Health Survey 1.0 (SF-36) [22]. It is a 36-item self-report, reliable and valid questionnaire used to assess the participants' perception of the QOL [7, 22, 23]. It consists of eight domains that measure the perception of QOL associated with physical functioning and physical limitations, social activities, physical pain, general and emotional health, emotional limitations, and energy/fatigue. The scoring ranges from 0 to 100. A higher score reflects a better QOL.

Exercise protocol

The physiotherapist first demonstrated and explained each exercise. The exercise program was performed with both visual feedback and continuous verbal orders from the physiotherapist. After each session, the physiotherapist gave the participants a reminder how to perform HE (at least 20 min/session: 5–10-min warm up, 5-min breathing, 10–45-min UL).

Adherence was monitored every week by registering the number of completed sessions at the MSSC and at home. The amount of physical activity performed with HE was monitored 2/week by asking the number of sessions per week and duration of each exercise during a session.

During the exercise the participants were sitting in the chair. The exercise program (the range of motions, resistance of elastic bands, exercise speed) was individually adapted to each patient. The participants were told to stop exercising if they felt tired, weak, pain, or any other discomfort. After each exercise, there was a 30–60-s pause. Each exercise began with 15 min of warm-up divided into two parts: diaphragmatic and thoracic breathing (5 min) and active mobility of the ULs including the shoulders and elbows (10 min).

For the breathing exercises, the basic principle was to inhale and exhale as completely as possible, but slowly to prevent hyperventilation and dizziness. The diaphragmatic or abdominal breathing (1.5 min) was performed for the strengthening of the abdominal muscles and the diaphragm, and the thoracic breathing (1.5 min) for strengthening the intercostal muscles (3×-20-s pause-3×).

After warming up, each UL exercise was divided into three parts: range movement (10 min), coordination (10 min), and strengthening exercises with minimal resistance (10 min).

The slow deep breathing through the nose followed every movement. The exercises were performed bilaterally, one arm after another (10× if tolerated), and then simultaneously (5×) with a 30–60-s pause in between. If the participants could not perform 10× each arm separately, they stopped at 5 and had a longer pause.

Exercises for coordination and arm strengthening started from the proximal to the distal joints. Range movement exercises included arm elevations, elbow flexion-extension, elbow flexion in combination with shoulder abduction and wrist flexion-extension.

Coordination exercises included open and closed eyes with elbow flexion with touching the ipsilateral shoulder/ear, or contralateral shoulder/ear.

Strengthening exercises were performed with dumbbells (0.5 kg) or elastic straps (Elastic bands, TheraBand; The Hygenic Corporation). Exercise with dumbbells included arm elevation, internal shoulder rotation, elbow flexion-extension, and wrist flexion-extension.

Exercise with elastic straps included arm elevation, diagonal combination of shoulder external rotation, and elbow flexion-extension.

At the end of the training session, the last 10 min was devoted to static stretching of the muscle groups that were used during exercising.

Data analysis

Data were analyzed using the software program Statistica, Version 13.3. Descriptive statistics examined the distributions and range of scores within the two groups confirming that the groups were comparable at the start of study (Table 1). This data were presented by mean and standard deviations (SD) (e.g., age), median and range (e.g., EDSS, SMMSE), and as total number (e.g., sex, MS type, medications). The outcome data (MFIS and SF-36) were analyzed separately for ambulatory and non-ambulatory subjects within and between intervention and control groups (Tables 2, 3, and 4). According to normality of data distribution (MFIS and SF-36), which was tested using Kolmogorov-Smirnov test, the results were presented as mean and SD and parametric tests were performed to analyze the data for ambulatory and non-ambulatory subgroups (exercise and control) [16].

To compare pre- and post-exercise data for outcome measures in ambulatory and non-ambulatory subgroups, Student's *t* test for dependent variables were used (Tables 2, 3, and 4) [7].

The analytic model that involved a two-way mixed-model, repeated-measures analyses of variance (ANOVA) on the outcome measures, with time (pre and post) included as a within-subjects factor, and group (exercise or control) included as a between-subject factor, provided the same interaction *p* values (group-by-time) as Student's *t* test for comparing between subgroups pre- to post-intervention changes (Tables 2, 3, and 4) [16]. A nominal significance level of 0.05 was used in all testing.

Given that the current study involved a small sample, reaching statistical significance in many measures using those analyses was unlikely. Also, since *p* values alone do not indicate the size of an effect, or non-statistically significant effects can have important clinical significance [24], we computed effect sizes for the changes in outcomes measures per subgroup as Cohen's *d* and they were interpreted as criteria: small (0.2), moderate (0.5), and large (0.8) [17, 25].

Results

Compliance

Overall compliance (i.e., percentage of exercise sessions attended over the 4-week intervention) was 98% (SD = 4.2%). All 10 participants completed at least 90% of sessions (i.e., 7 of 8 possible sessions guided by physiotherapist) and complied with the prescribed intensity and duration of each exercise session. Out of 10 participants, 6 of them completed all 12 HE 20 min/day, 3 completed 11 to 8 HE and one participant completed 7 to 0. From 10 participants, 7 of them performed HE for 30–45 min/session.

All 19 participants completed the assessments. No participant felt harm during the exercise training. Tables 2, 3, and 4 show the outcome measures at baseline and post-exercise program, pre- to post-intervention mean differences, and within and between group comparisons for ambulatory and non-ambulatory subjects. Table 2 shows MFIS variables, Tables 3 and 4 show SF-36 variables for ambulatory and non-ambulatory subjects.

Fatigue

There was a statistically significant group-by-time interaction on MFIS scores for the exercise ambulatory subjects: physical $F(1.8) = 6.61$, $p = 0.033$; psychosocial $F(1.8) = 6.00$, $p = 0.039$, and total $F(1.8) = 6.54$, $p = 0.033$ with overall large effect scores (physical $d = 1.60$; psychosocial $d = 1.59$, and total $d = 1.62$) (Table 2). Although, there was a non-statistically significant group-by-time interaction on MFIS cognitive component scores for ambulatory subjects $F(1.8) = 4.11$, $p = 0.077$), the effect size was found large ($d = 1.28$).

There was a statistically significant group-by-time interaction on MFIS scores for the exercise non-ambulatory subjects: physical $F(1.8) = 12.43$, $p = 0.009$; psychosocial $F(1.8) = 9.21$, $p = 0.018$, and total $F(1.8) = 30.87$, $p = 0.0008$ with overall large effect scores (physical $d = 2.42$; psychosocial $d = 1.96$ and total $d = 3.92$) (Table 2). Although there was a non-statistically significant group-by-time interaction on MFIS cognitive component scores for ambulatory subjects ($F(1.8) = 4.72$, $p = 0.066$), the effect size was found large ($d = 1.47$).

These variables for the control ambulatory and non-ambulatory subjects did not change.

QOL

There was a statistically significant group-by-time interaction on SF-36 physical functioning scores for the exercise ambulatory subjects ($F(1.8) = 11.52$, $p = 0.014$ with large effect score ($d = 2.14$). A statistically significant group-by-time interaction on SF-36 general health scores for the exercise non-ambulatory subjects was found ($F(1.8) = 6.15$, $p = 0.042$ with large effect score ($d = 1.76$) (Table 2).

All other group-by-time interactions on SF-36 measures were non-statistically significant but with a large effect score on pain variable ($d = 1.02$), and moderate effect scores on physical ($d = 0.71$) and emotional limitation ($d = 0.63$) (Table 3), emotional well-being ($d = 0.63$), energy/fatigue ($d = 0.69$) and social functioning ($d = 0.64$) variables in

Table 2 Fatigue measures (physical, cognitive, psychosocial and total) for ambulatory and non-ambulatory individuals

Group Questionnaire MFIS (0–82)	Exercise (*n*: ambulatory = 5; non-ambulatory = 5) Mean ± SD	Control (*n*: ambulatory = 5; non-ambulatory = 4) Mean ± SD	*p* values[b]	*d*
Physical ambulatory				
Pre-training	19.2 ± 5.7	12.2 ± 7.7		1.60
Post-training	14.8 ± 7.8	11.8 ± 7.0	.033†	
Change in MFIS	− 4.4 ± 3.4	− 0.4 ± 0.9		
p values[a]	.043*	.374		
Physical non-ambulatory				
Pre-training	24.8 ± 5.2	30.8 ± 3.8		2.42
Post-training	18.4 ± 3.2	30.0 ± 4.7	.009†	
Change in MFIS	− 6.4 ± 3.0	− 0.8 ± 1.3		
p values[a]	.008*	.318		
Cognitive ambulatory				
Pre-training	12.2 ± 9.4	10.0 ± 7.2		1.28
Post-training	9.6 ± 8.6	9.8 ± 6.3	.077	
Change in MFIS	− 2.6 ± 2.1	− 0.2 ± 1.6		
p values[a]	.048*	.798		
Cognitive non-ambulatory				
Pre-training	15.8 ± 4.6	15.0 ± 9.4		1.47
Post-training	11.00 ± 3.8	13.8 ± 8.5	.066	
Change in MFIS	− 4.8 ± 3.0	− 1.3 ± 1.5		
p values[a]	.021*	.194		
Psychosocial ambulatory				
Pre-training	2.4 ± 1.3	4.0 ± 3.0		1.59
Post-training	1.4 ± 0.9	4.2 ± 2.4	.039†	
Change in MFIS	− 1.0 ± 0.7	0.2 ± 0.8		
p values[a]	.034*	.621		
Psychosocial non-ambulatory				
Pre-training	4.2 ± 2.3	2.5 ± 2.0		1.96
Post-training	3.0 ± 2.2	2.8 ± 2.0	.018†	
Change in MFIS	− 1.2 ± 0.4	0.3 ± 1.0		
p values[a]	.003*	.637		
Total ambulatory				
Pre-training	33.8 ± 15.0	23.8 ± 15.2		1.62
Post-training	27.8 ± 18.3	23.6 ± 14.0	.033†	
Change in MFIS	− 6.0 ± 4.5	− 0.2 ± 2.3		
p values[a]	.041*	.854		
Total non-ambulatory				
Pre-training	44.8 ± 5.7	51.3 ± 6.1		3.92
Post-training	31.2 ± 5.4	51.3 ± 6.2	.0008†	
Change in MFIS	− 13.6 ± 4.7	0.0 ± 1.4		
p values[a]	.002*	1		

[a] Student's *t* test

[b] ANOVA

$p < .05$ is significant.*Significance between pre- and post-data within subgroup. † Significance between changes in each subgroup. *d* calculated as change in exercise condition minus change in control condition divided by pooled standard deviation of change

ambulatory subjects (Table 4). Further, for non-ambulatory subjects, large effect scores were also found on physical limitation ($d = 1.03$) (Table 3) and emotional well-being ($d = 0.94$) (Table 4), and moderate effect scores on physical functioning ($d = 0.68$), emotional limitation ($d = 0.56$) (Table 3) and energy/fatigue ($d = 0.52$) (Table 4).

Table 3 Quality of life measures (general health, physical functioning, physical limitation and emotional limitation) for ambulatory and non-ambulatory individuals

Group Questionnaire SF-36 (0–100)	Exercise (*n*: ambulatory = 5; non-ambulatory = 5) Mean ± SD	Control (*n*: ambulatory = 5; non-ambulatory = 4) Mean ± SD	*p* values[b]	*d*
General health ambulatory				
Pre-training	52.0 ± 19.2	63.0 ± 12.5		0.18
Post-training	47.0 ± 14.4	56.0 ± 22.0	.771	
Change in SF-36	− 5.0 ± 11.7	− 7.0 ± 9.7		
p values[a]	.396	.183		
General health non-ambulatory				
Pre-training	44.0 ± 13.0	26.3 ± 10.3		1.76
Post-training	52.0 ± 7.6	22.5 ± 8.7	.042[†]	
Change in SF-36	8.0 ± 9.1	− 3.8 ± 2.5		
p values[a]	.120	.057		
Physical functioning ambulatory				
Pre-training	57.0 ± 27.7	79.0 ± 29.2		2.14
Post-training	65.0 ± 30.2	76.0 ± 33.6	.014[†]	
Change in SF-36	8.0 ± 5.7	− 3.0 ± 4.5		
p values[a]	.034*	.208		
Physical functioning non-ambulatory				
Pre-training	8.0 ± 8.4	3.8 ± 4.8		0.68
Post-training	12.0 ± 10.4	3.8 ± 4.8	.368	
Change in SF-36	4.0 ± 8.2	0.0		
p values[a]	.337			
Physical limitation ambulatory				
Pre-training	30.0 ± 20.9	65.0 ± 48.7		0.71
Post-training	50.0 ± 25.0	70.0 ± 41.1	.289	
Change in SF-36	20.0 ± 27.4	5.0 ± 11.2		
p values[a]	.177	.373		
Physical limitation non-ambulatory				
Pre-training	30.0 ± 27.4	12.5 ± 14.4		1.03
Post-training	50.0 ± 35.4	12.5 ± 14.4	.153	
Change in SF-36	20.0 ± 27.4	0.0		
p values[a]	.177			
Emotional limitation ambulatory				
Pre-training	73.4 ± 43.4	53.2 ± 44.8		0.63
Post-training	80.0 ± 44.7	53.2 ± 44.8	.346	
Change in SF-36	6.6 ± 14.7	0.0		
p values[a]	.373			
Emotional limitation non-ambulatory				
Pre-training	86.7 ± 29.8	50.0 ± 43.1		0.56
Post-training	93.4 ± 14.8	66.5 ± 38.7	.417	
Change in SF-36	6.7 ± 15.1	16.5 ± 19.1		
p values[a]	.373	.181		

[a] Student's t-test

[b] ANOVA

$p < .05$ is significant.*Significance between pre- and post-data within subgroup. [†] Significance between changes in each subgroup. *d* calculated as change in exercise condition minus change in control condition divided by pooled standard deviation of change

Discussion

The aim of this study was to evaluate the feasibility and possible effects of a mild and short duration exercise program on primary fatigue and the QOL in ambulatory and non-ambulatory individuals with MS. To our knowledge, there are no other reports examining the effects of a 4-week combined UL and breathing exercise on primary fatigue and the QOL in subjects with MS with EDSS between 1.0 and 8.0.

In this study, beside group exercise, most of the participants completed all 12 HE, or exercised 30–45 min/session 2/week.

MS patients are characterized by reduced exercise tolerability and muscle weakness, often leading to decreased motivation and physical inactivity [3].

Most of the participants in our study subjectively stated they do not have enough motivation to exercise alone at home for whole 60 min, and that the lack of motivation is largely influenced by their increased everyday-present fatigue.

Table 4 Quality of life measures (emotional well-being, pain, energy/fatigue, and social functioning) for ambulatory and non-ambulatory individuals

Group Questionnaire SF-36 (0–100)	Exercise (*n*: ambulatory = 5; non-ambulatory = 5) Mean ± SD	Control (*n*: ambulatory = 5; non-ambulatory = 4) Mean ± SD	*p* values[b]	*d*
Emotional well-being ambulatory				
Pre-training	74.0 ± 27.3	70.4 ± 15.6		0.63
Post-training	78.4 ± 18.2	68.8 ± 16.6	.343	
Change in SF-36	4.4 ± 12.5	− 1.6 ± 4.5		
p values[a]	.475	.476		
Emotional well-being non-ambulatory				
Pre-training	68.8 ± 24.2	61.5 ± 14.5		0.94
Post-training	72.8 ± 19.1	58.0 ± 12.4	.199	
Change in SF-36	4.0 ± 7.5	− 3.5 ± 8.4		
p values[a]	.298	.465		
Pain ambulatory				
Pre-training	70.0 ± 27.4	88.0 ± 16.8		1.02
Post-training	80.0 ± 27.4	79.0 ± 28.8	.141	
Change in SF-36	10.0 ± 22.4	− 9.0 ± 13.4		
p values[a]	.373	.208		
Pain non-ambulatory				
Pre-training	63.5 ± 30.7	36.3 ± 47.5		0.02
Post-training	72.5 ± 28.5	45.6 ± 36.4	.966	
Change in SF-36	9.0 ± 5.5	9.4 ± 18.8		
p values[a]	.021*	.391		
Energy/fatigue ambulatory				
Pre-training	53.0 ± 33.7	68.0 ± 12.0		0.69
Post-training	55.0 ± 12.5	65.0 ± 11.7	.301	
Change in SF-36	2.0 ± 7.6	− 3.0 ± 6.7		
p values[a]	.587	.587		
Energy/fatigue non-ambulatory				
Pre-training	58.0 ± 22.5	23.6 ± 12.5		0.52
Post-training	66.0 ± 17.1	29.3 ± 17.4	.476	
Change in SF-36	8.0 ± 12.0	3.0 ± 6.0		
p values[a]	.211	.391		
Social functioning ambulatory				
Pre-training	77.5 ± 18.5	85.0 ± 10.4		0.64
Post-training	79.5 ± 29.7	78.0 ± 13.0	.338	
Change in SF-36	2.0 ± 16.9	− 7.0 ± 10.2		
p values[a]	.804	.200		
Social functioning non-ambulatory				
Pre-training	65.0 ± 29.8	37.5 ± 27.0		0.31
Post-training	67.5 ± 20.9	34.4 ± 29.8	.666	
Change in SF-36	2.5 ± 24.0	− 3.1 ± 6.3		
p values[a]	.827	.391		

[a] Student's *t* test

[b] ANOVA

$p < .05$ is significant.*Significance between pre- and post-data within subgroup. *d* calculated as change in exercise condition minus change in control condition divided by pooled standard deviation of change

In our study, muscle weakness partly influenced the feasibility of the exercise in some participants. However, as stated above, the repetition of individual exercises has been carried out to their limits or when they felt weakness or discomfort, especially during exercise with elastic straps, which were the hardest for them. The most important, they

did not felt pain. Therefore, 60 min of continuous exercising with upper limbs, including breathing and stretching, was successfully carried out.

Immobility or no exercise practice in MS individuals reduce lung volume and can lead to various disorders like postural hypotension, constipation, urine retention, osteoporosis, depression, and deconditioning [14]. During baseline examination, the participants stated to have conditions, which average population has, like hypertension (under treatment), diabetes, osteoporosis, and back pain. Furthermore, no significant pulmonary diseases, including chronic obstructive, were established. However, lung volume capacity was not exanimated, so we could not state this with 100% certainty. However, it is well known that exercise physiotherapy, which includes upper limbs, has a good impact on final pulmonary function, exercise capacity, and QOL [26]. Physical symptoms more common for multiple sclerosis, which were present among these participants beside muscle weakness, were mostly walking difficulties, paraesthesia and tremor in upper and lower limbs, spasms in lower limbs, bowel or bladder dysfunctions, and coordination or balance impairment. However, all these conditions, including the MS-nonspecific, had no significant impact on exercise feasibility.

In addition, besides other multiple factors [27–30], lack of exercise can also lead to primary fatigue [14]. Moreover, Motl and Gosney identified the length and amount of exercise as significant exercise effect moderators on the QOL of patients with MS [31]. As well, we noticed that continuous exercising was important to achieve better QOL. Individuals who exercised irregularly (no exercising for whole week) had lower improvements in QOL in general.

It is likely that UL and breathing exercises in this 4-week study contributed to the strengthening of the UL (positive preliminary data for handgrip strength not shown) and respiratory muscles (see limitations) and increase of the exercise capacity, and thus reduced primary fatigue and improved QOL [6, 7, 14]. The exercise program improved physical, psychosocial, and cognitive fatigue in ambulatory and non-ambulatory subjects (Table 2). However, it is not clear why the control group showed a slight reduction in cognitive fatigue. This suggests that besides exercise program, other factors also contributed to the reduction of cognitive fatigue [32].

We could say that the QOL was improved in general in the exercise group, but probably a low participant number was the limiting factor for showing the statistical significance (Tables 3 and 4).

The first example was a significant improvement of QOL perception in non-ambulatory subjects probably due to reduced pain, and the same, but not statistically significant, improvement in ambulatory subjects. However, a large intervention effect on SF-36 pain variable can be seen in ambulatory subjects. It is also possible that ambulatory subjects did not improve significantly in this measure because it was not as low as in non-ambulatory subjects. However, we assume that the exercise program helped to reduce pain and improve the perception of QOL since pain is one of the main factors, besides fatigue and others, having a negative impact on the QOL in all patients with MS [33–35]. Besides the exercise itself, which helped to decrease pain, probably deep breathing exercises contributed as a relaxation technique [14, 36].

The control group had a tendency of worsening in some QOL measures (general health, physical functioning, emotional well-being, pain, energy/fatigue, and social functioning), especially ambulatory subjects (physical functioning) over the 4-week period. It is not clear why, because the environmental factors were the same for both groups.

This suggests that previous individual physical activity or regular physical therapy did not have a notable influence on the exercise study effect. In addition, the participants subjectively stated in the questionnaire upon completion of the exercise, that this exercise program in the group motivated them a lot and helped them accomplish more during the day, in a physical manner, although the results were not consistent with that statement. Besides the reduction of fatigue, the impact of a motivating environment on that accomplishment cannot be rule out.

Furthermore, respiratory and UL muscle strengthening could have stimulated brain structures for better functioning [3, 37–39] and thus improved mood, memory, cognition, and motivation [39, 40]. In addition, to motivate MS individuals with low mobility to engage in physical activity, participants exercised in social supporting surrounding with other MS individuals (EDSS 0.0–8.0) in familiar, less stressful settings unlike hospital-based care or rehabilitation centers or laboratories, which probably contributed to the outcome [41].

This minimal equipment exercise program may be recommended to patients having an EDSS score between 0.0 and 8.0 as a home base program, but needs further larger trial to confirm this possibility.

Study limitations

Improvements in some outcome measures are not statistically significant, partially due to a low number of participants included in this investigation. Therefore, there is undoubtedly a need for repeating this investigation in a larger group of participants. Those improvements could be also a result of a group-based exercise that could have caused more motivation for exercise regarding social interaction [32].

Recruitment involved participants only from one country region as a recruitment site. In addition, in our study, there were involved more males than females. Due to nature of the disease, we could not make a total restriction of everyday physical activities nor regular physical therapy for the individuals with MS.

In the future investigation, it is necessary to study the effect of this exercise program only in a group of non-ambulatory individuals (EDSS 7.0–8.0) and to perform breathing resistance exercises, e.g., by using a positive expiratory pressure (PEP) system. Since the fatigue and QOL are significantly influenced by a psychological factors (e.g., anxiety and depression) [20, 30, 33, 42], it would be also appropriate to explore these aspects in the next exercise intervention.

Conclusions

Our 4-week combined UL and breathing exercise program with independent HE significantly reduced some aspects of fatigue and improved some aspects of QOL in a small group of ambulatory and non-ambulatory individuals with MS. Ambulatory and non-ambulatory individuals could successfully complete this exercise program without exacerbation of MS. Good feasibility and significant positive changes from baseline warrant further exploratory work.

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Compliance with ethical standards

All subjects signed written informed consent and the study was approved by the local ethical committee (602-01/17-01-147) and registered in the ClinicalTrials.gov (www.clinicaltrial.gov).

Conflict of interest The authors declare that they have no conflicts of interest.

Disclaimer The authors alone are responsible for the content and writing of the paper.

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