International Journal of ChemTech Research
CODEN (USA): IJCRGG, ISSN: 0974-4290, ISSN(Online):2455-9555
Vol.10 No.5, pp 443-450, 2017

Effect of Balance Training on Multiple Sclerosis Related Fatigue: A Randomized Controlled Trial

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Abstract : Fatigue is a multidimensional and complex widespread symptom among patients with multiple sclerosis (MS). Fatigue and impaired upright postural control (balance) are common complaints in patients with MS; influencing each other. This work was aiming to investigate the benefits of balance training program in reducing fatigue in patients with remitting-relapsing (RRMS).This randomized controlled trial included 30 patients with RRMS; 10 in the control group and 20 in the study group with matched general and clinical characteristics. All patients were treated for successive four weeks (12 therapeutic sessions). Both groups had been treated by aerobic exercises using stationary bicycle endurance training with intensity of 65 % to 70% of the age predicted maximum heart rate (MHR).While the study group had received a designed balance training program in addition. Outcome measures included the fatigue severity scale (FSS) and the relative power ratio between slow to fast waves of quantitative electroencephalogram (QEEG) activity using the equation ($\theta+\alpha/\beta$). This study was registered with http://www.pactr.org/, number (PACTR201611001853408).Patients in the study group showed a statistically significant improvement in the FSS (P=0.025, 95% CI = 31.84 to 43.65). The ($\theta+\alpha/\beta$) ratio had significantly improved in both groups; the study group (P=0.0001, 95% CI= 1.63 to 2.51) and the control group (P=0.036, 95% CI= 1.80 to 2.95), however, improvement was more marked in the study group (P=0.03).Balance training exercises are effective in facilitating the sensory-motor integration and consequently reducing fatigue perception in patients with MS.
Keywords : Balance training, Fatigue, quantitative electroencephalogram, Multiple Sclerosis.

Introduction

Multiple sclerosis (MS) is an immune-mediated, neurodegenerative disease that affects approximately 2.5 million adults world-wide. This disease manifests in a wide range of symptoms including muscle weakness, extreme fatigue, imbalance, impaired speech, double vision, cognitive dysfunction, and paralysis [1].

Fatigue is one of the most common and disabling symptoms of MS and often presents in the earliest phase of the disease and described as the worst symptom by 40–50 % of patients [2]. Fatigue is defined as "subjective lack of physical and mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities".Itis a multidimensional symptom affecting both physical and cognitive domains [3].

Fatigue is most likely multifactorial, including both primary and secondary causes. The primary fatigue mainly originated from a dysfunction of central nervous system neuronal circuits[4, 5].However, secondary fatigue may becaused by sleeping disturbances, anemia, depression, or the use of immunomodulating therapies [6, 7].

Patients with MS who reported greater levels of fatigue had extensive cortical activation in non-motor cortical areas and reduced cortical inhibition with lower activity in the motor planning and execution regions [8, 9]. Successful management of fatigue necessitates a multidisciplinary treatment including medication (e.g., Amantadine and Modafinil) and rehabilitation (e.g., exercise, energy or fatigue self-management education, and cognitive behavioral therapy) [10].

Lack of postural control with balance dysfunction is reported as one of the causes of fatigue in patients with MS [11]. It is reported that fatigue is significantly related to balance and is a considerable predictor of balance as a function of central sensory integration in persons with MS [12].

The main objective of this study was to investigate the benefits of balance training program in reducing fatigue in patients with MS.

Methodology

This randomized controlled trial was conducted between June 2015 and December 2016 at the outpatient clinic of the Faculty of Physical Therapy, Cairo University, Cairo, Egypt. This study was registered with http://www.pactr.org/, number (PACTR201611001853408).

Participants: 40 patients with RRMSfrom both sexes were recruited from Kasr Al-Ainy Multiple Sclerosis Unit (KAMSU) as well as outpatient clinic at the Faculty of Physical Therapy, Cairo University, Egypt. All information about the study was explained to participants with an informed consent obtained from all of them. Only 30 participants completed this study (figure 1).

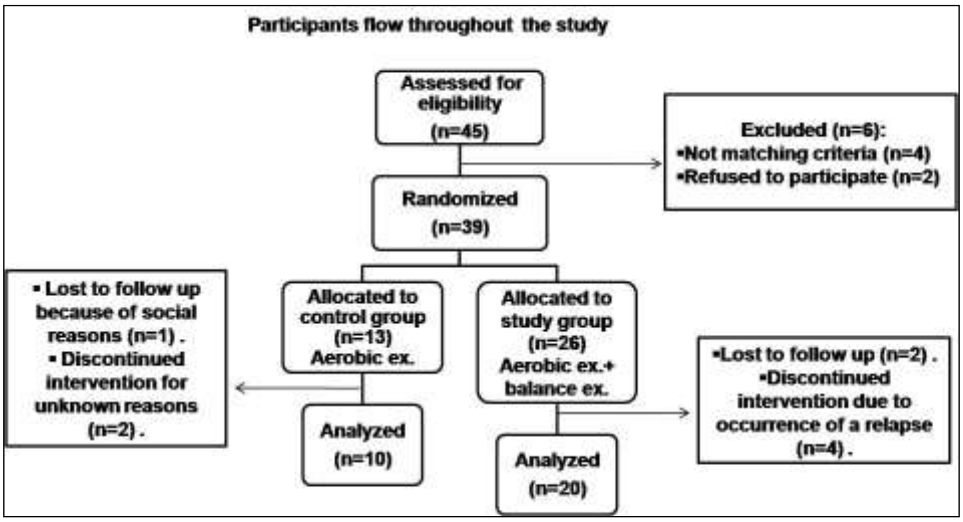

Figure (1) Participants flow chart throughout the study.

We had included right handed clinically defined RRMS patients, 20 to 50 years old, illness duration not more than 10 years, with no relapses over the past three months, ambulant with a score below four according to the Expanded Disability Severity Score (EDSS), a score below eight according to Hamilton Depression Rating Scale (HDRS 21), and with normal routine laboratory investigation. We had excluded patients who have any other neurological deficits or orthopedic abnormalities, secondary musculoskeletal complication such as contractures or deformities, peripheral vestibulopathy, hepatic, renal, hemopoeitic, thyroid and cardiovascular diseases, cognitive dysfunction, hearing deficits, epilepsy and EEG abnormalities.

Patient groups: patients included in the study were randomized by self- selecting a card corresponding to one of the two groups; control group (GI) and study group (GII). Subjects and examiner were blinded during randomization, except for the person who prepared the groups cards.

Patients in both groups were evaluated pre and post-treatment using the following battery of assessment:

1- The Fatigue Severity Scale (FSS): consists of nine questions that are responded to using a Likert scale ranging from 1 to 7, with lower scores meaning "disagreement" (greater disagreement with lower scores), and higher scores meaning "agreement". A score ≥ 36 is regarded as severe chronic fatigue, and a score < 36 indicates mild fatigue. Ratings are based on the experience of fatigue over the past seven days [13, 14].
2- Analysis of brain activity changes using the quantitative electroencephalogram (QEEG)

The EB-NEURO machine with Galileo NT software, Italy, was used for twenty minutes recording of artifact free digital EEG. The EEG records were carried out under the standard condition from a comfortable supine position with closed eyes. Full electrode capof 19 electrodes; from Electro-Cap International (ECI), of suitable size was used for the current study. The Ag/AgCl electrodes were applied according to the international 10/20 electrode placement system using a unipolar AR montage. The electrode gel maximizes skin contact and allows for a low-resistance recording through the skin. Impedance was kept below 5 Kilo Ohm (kilohm) to avoid polarization effects. A motor task (active right thumb opposition) was performed during EEG and video records.

Prior to QEEG assessment, participants were fully informed about all instructions, the nature of the assessment and the motor task was explained and tested with patients before recording. One person is responsible of explaining the test for all patients.

QEEG parameters and analysis:

The data were collected and analyzed during the period of repetitive motor task execution; three trials of 30 seconds thumb opposition of the right hand with 30 seconds rest in between. Analysis was performed for the data detected over C3 site which was located according to 10/20 system and represents the sensory-motor integration of the left hemisphere. The relative power ratio between the activity of slow (alpha and theta) to fast (beta) waves was calculated, as an outcome measure for fatigue, through the following equation $(\theta + \alpha)/\beta$. Decrement of this ratio is considered an indicator for fatigue improvement [8, 15, 16].

Treatment intervention

All patients were treated for 30 minutes three times weekly every other day for successive four weeks (12 therapeutic sessions). 10 patients were included in the control group and had been treated by aerobic exercises using stationary bicycle endurance training with intensity of 65% to 70% of the age predicted Maximum Heart Rate (MHR) [6, 17]. In the study group, 20 patients had received the same treatment of control group and a designed balance training program in addition. This training program is based on the sensory-motor integration strategies [18, 19] and was aiming to improve balance functions from upright standing posture and during walking. The training involved balance exercises from standing on firm and foam surfaces with open and closed eyes as follows; heel-toes raise, reaching activity in different directions, semi-squatting, tandem standing, stepping activities, standing on one leg and dual task activity; standing while counting backwards by 3s. Heel-toe walking; with open and closed eyes and walking with turns and changing directions were also performed.

Statistical analysis

All data were analyzed using SPSS version 18 software (SPSS Inc., Chicago, USA) and were normally distributed. Baseline descriptive statistics were compared using independent t-tests. The primary analysis employed a 2 (group) x 2 (time) multi measures analysis of variance (MANOVA) with post hoc comparisons to test for interactions between "time" and "group" with respect to fatigue. Statistical significance was set with an alpha value of $P < 0.05$. Data are presented as means ± standard deviation (mean ± SD) and 95% of confidence interval (95 %CI).

Results

Demographic and clinical characteristics of the subjects

Both groups were matched in their demographic and clinical characteristics as presented in **table (1)**.

Table (1): General demographic and clinical characteristics of the subjects.

General Characteristics	Control group (n=10)	Study group (n=20)	Comparison	
	Mean ± SD	**Mean ± SD**	**t-value**	***P*-value**
Age(yr)	35±8.718	36.55±9.987	0.4170	0.6799
Weight(Kg)	75.8±11.887	77.225±13.811	0.2782	0.7829
Height(cm)	164.1±8.386	164.25±7.946	0.04787	0.9622
Durationofillness(yr)	6.75±3.102	5.59±3.223	0.9404	0.3550
EDSS score	2.95±1.235	2.5±0.8111	1.201	0.2400
HDRS21score	3.5±2.273	4.15±2.059	0.7879	0.4374
Sex(M/F)	3/7	6/ 14		

Values were expressed as means ±SD, except for sex, which is expressed as nominal counts. SD: standard deviation, EDSS: Expanded Disability Severity Scale.HDRS21: Hamilton Depression Rating Scale-21, N=number, yr: years, kg: kilogram, cm: centimeter, M:Male,F:Female.

*Significant (P <0.05).

Results of the FSS score

As presented in table (2), post-treatment assessment of the study group showed a significant improvement in the scores of FFS as compared to the control group (P=0.025).

Table (2): Pre and post- treatment scores of FSS in both groups

FSS	Pre-treatment	Post-treatment	MD	95% CI	P-value
	Mean± SD	**Mean± SD**			
Control group (n=10)	41.8±13.28	35.3±10.88	6.5	31.84 - 43.65	0.54
Study group (n=20)	37.75±10.22	31.8±10.86	5.95	28.40 - 37.47	0.025*
MD	4.05	3.5			
P- value	0.363	0.413			

SD: standard deviation, MD: Mean difference, CI: confidence interval, *Significant (P <0.05).

Results of the QEEG: changes in the relative power of (θ+α/β) ratio at C3 point:

The results of both groups revealed post-treatment significant improvement of the cortical activation; in which the ratio was significantly reduced over C3 within the two groups but the improvement was more marked in the study group (P=0.03) **(table 3)**.

Table (3): Pre and post-treatment *(θ+α/β)*ratio.

(θ+α/β) ratio Over C3	Pre- treatment	Post-treatment	MD	95% CI	P-value
	Mean± SD	Mean± SD			
Control group (n=10)	2.60±1.06	2.07 ±0.97	0.53	1.80 - 2.95	0.036*
Study group (n=20)	2.8 ±0.67	1.34±0.08	1.46	1.63 - 2.51	0.0001*
MD	-0.2	0.73			
P-value	0.801	0.03*			

SD: standard deviation, MD: Mean difference, CI: confidence interval, *Significant (P <0.05).

Discussion

The present study provides an evidence for the effectiveness of balance training exercises in reducing fatigue in patients with RRMS. Fatigue was the main variable of interest in this work, in which the FSS score shows a significant improvement only in the study group (P=0.025). The results of this study can be supported by previous studies [18, 20, 21].A possible explanation for our results might be the relation between postural control and fatigue. Lack of postural control can reflect impairments of central sensory processing which contributes to MS-related fatigue as well. Therefore, postural control level and fatigue could potentially change each other [8].

Balance training works through enhancing neural adaptation at different sites of the central nervous system. Moreover, it induces adaptations in all the sensory systems assisting postural control; vestibular, visual, and somatosensory system, as well as in the motor systems controlling muscular output[22]. Consequently, it can stimulate neural plasticity in patients with proprioceptive, vestibular and even cerebellar disorders[23], change the central processing level and improve their postural control and fatigue as well[24]**.** In addition, balance training improves muscle weakness that may contribute to MS-related fatigue as well[25, 26].

Result of the control group of this study, is consistent with other reports that revealed a non significant difference in MS-related fatigue after aerobic training [27, 28, 29, 30]**.** These results can be correlated to the well known facts of fatigue subjectivity and multidimensionality among patients [27, 30]. In contrast, other studies had reported that endurance exercises can significantly reduce central fatigue [31, 32.] The contradictory results may be explained by different treatment protocol (five days weekly[31] compared to three times weekly in the present study) for longer program duration (eight weeks[32] compared to four in the present study)**.**

Our results also revealed a significant improvement of fatigue at cortical level. Different QEEG reports show that the (θ+α/β) ratio is higher in fatigued person compared to non-fatigued one[33]. Consequently, reduction of this ratio compared with the baseline evaluation is considered as an indicator of fatigue improvement. Results of the current work showed a significant reduction of the (θ+α/β) ratio in both groups over (C3) with statistically significant improvement between groups in favor to the study group (P=0.03).

Literature provides evidence that each type of motor training exercises; strength, endurance and task-specific training, is encoded through different forms of anatomic and neurophysiological changes across the motor cortex and spinal cord[18]**.**

Up to our knowledge, there are no studies measured the post-treatment effects of balance training on cortical activation in the correspondence of fatigue. Our results reported cortical changes at the sensory-motor cortex (C3) that can be correlated to the specific effect of each treatment intervention on neural plasticity in either group.

The different mechanisms by which the endurance exercises and balance training enhance the neuroplasticity, may explain the higher improvement detected at the left sensory-motor cortex (C3) in the study group compared to the control group. Endurance exercises mainly improve the cortical angiogenesis and provide a nutritive environment but do not induce a significant change on cortical circuitry [24, 34, 35]. However, balance training; which is based on sensory-motor integration strategies, is proved to be highly task-specific in which the CNS networks can be recruited more consciously for motor control [18, 36]; inducing neural plasticity of the spinal, corticospinal and cortical pathways[37, 38, 39]. Besides, the different sensory input derived to cortex during training, can improve the sensory integration and change the activity level of somatosensory processing. These changes consequently influence brain functions and help in reducing fatigue and improving postural control as well [9, 22, 40]. Together, these facts may explain why patients who had received balance and aerobic training show more significant results in their cortical activation compared to those who had only received aerobic training.

In conclusion, balance training exercises that is based on sensory-motor strategies, can be recommended as an essential component of multidimensional approach aiming to reduce fatigue and improve quality of life in patients with MS

Acknowledgments

The authors are very grateful to the patients with MS who participated in the study.

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