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Effect of high-tone external muscle stimulation on fatigue and functional outcomes in multiple sclerosis: A randomized controlled trial

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ABSTRACT

A major symptom experienced by subjects with multiple sclerosis is fatigue, which induces a decline in physical, cognitive, and functional capacity. Exercise and electrotherapy are cornerstones of rehabilitation that elicit acceptable effects on feelings of fatigue and on performing activities of daily living. A randomized controlled trial was conducted to investigate the effects of high-tone external muscle stimulation on fatigue and functional outcomes in multiple sclerosis patients. A total of 40 multiple sclerosis patients were allocated randomly to either: the study or control groups. The study group received high-tone external muscle stimulation, while the control group received a conventional selected exercise training program. Both groups received 3 sessions per week for one month. Both groups showed a significant improvement post-study compared with pre-study. There was a significant

reduction in Disability Status Scale (p=0.002), Fatigue Severity Scale scores (p=0.004), and total scores of Modified Fatigue Impact Scale (p=0.001) of the study group compared with that of the control group. High-tone external muscle stimulation showed an important improvement effect for both fatigue and functional outcomes in multiple sclerosis patients, being more effective than the conventional exercise training program; therefore, it should be considered a beneficial treatment method for patients with multiple sclerosis.

KEYWORDS

Multiple Sclerosis; Fatigue; Function; High-tone External Muscle Stimulation

1. INTRODUCTION

Demyelination and inflammation are hallmarks of the central nervous system (CNS) in multiple sclerosis (MS) leading to neurological manifestations, including fatigue and functional disability (Kubsik et al., 2014). Fatigue is considered one of the three most prevalent debilitating symptoms in MS, affecting 90 % of those patients (Judica et al., 2011; Nagaraj et al., 2013). In clinical practice assessment, an strategy to manage fatigue needs a multidisciplinary approach of medicine, behavior, exercise, and nutrition (Drerup et al., 2021; Oliva Ramírez et al., 2021).

An imbalance of homeostasis derived from interoceptive signals along ascending pathways to the insula and anterior cingulate cortex persuades physical, cognitions, behaviors, and felling of sickness (Covey et al., 2022). Furthermore, failure of circuits involving the thalamus, basal ganglia, and frontal cortex are contributing factors to the central fatigue (Leocani et al., 2008) while sleep disturbances, insomnia, pain, anxiety, urge incontinence, spasticity, physical inactivity, spasms, or depression are considered causes of secondary fatigue (Leocani et al., 2008; Beckerman et al., 2020). Perceived fatigability derived from the combination of physical and psychomotor performances are determined by functional capacity (Beckerman et al., 2020) (Conardsson et al., 2019).

Neuromuscular electrical stimulation (NMS) is used extensively as one of the rehabilitation modalities in neurology, musculoskeletal, and cardiopulmonary systems disorders (Heidland et al., 2013). High-tone external muscle stimulation (HTEMS) is a type of advanced NMS that has been shown to relieve pain, anxiety, and sleeplessness, and improve the overall quality of life (QOL) (Schaffler-Schaden et al., 2020). The hypotheses of HTEMS's are based on activating different tissues by delivering therapeutic electrical energy with multiple frequencies into whole-body cells via the skin

through cutaneous electrodes, leading to release of endogenous analgesics, and increase microcirculation by enhancing nitric oxide production (Kempf et al., 2018).

Oscillation of cells with electrical energy enhance endogenous analgesics, redistribute anti-inflammatory increase antioxidants, and increase the bioavailability of nitric oxide (Kempf et al., 2018; Heidland et al., 2013). At this point, the primary objective of this study was to investigate the clinical outcome of HTEMS on function and fatigue among MS patients.

2. METHODS

2.1. Participants

This study used a randomized, controlled, blinded, prospective, and a pre/post design. All the patients were divided randomly into two groups. The study group received HTEMS and stretching exercises, while the control group got a sham application of HTEMS and a selected exercise program. Both groups underwent 12 sessions, three times per week for one month.

The Institutional Ethics Committee of the Faculty of Physical Therapy, Cairo University, Egypt (No: P.T. REC/012/002866) and clinical trials.gov ID NCT04530669 gave their clearance to the study, as the study followed the consort guideline for non-pharmacological trials.

Forty MS patients participated, including relapsing-remitting (RRMS), secondary progressive (SPMS), and primary progressive (PPMS) multiple sclerosis. All patients received a standard disease-modifying therapy with disease stabilization for at least one year before conducting this study. The criteria of patients' selection were their ages, ranged from 18 to 50 years, and their body mass index (between 20 and 29 kg/m^2). The illness duration was equal to or fewer than 10 years. The exclusion criteria were cognitive impairment, co-existing neurological illnesses, and symptomatic orthopedic abnormalities.

The sample size was estimated using G*POWER statistical software to eliminate type II error (version 3.1.9.2; Franz Faul, Universitat Kiel, Germany (Faul et al., 2009)) [F tests, Mixed design, repeated measures, within-between interaction, $\alpha=0.05$, $\beta=0.2$, and effect size = 0.46]. We found that N=40 was the suitable size for this investigation. A computer-based randomization program was used to divide the patients equally either to study or control groups (Figure 1).

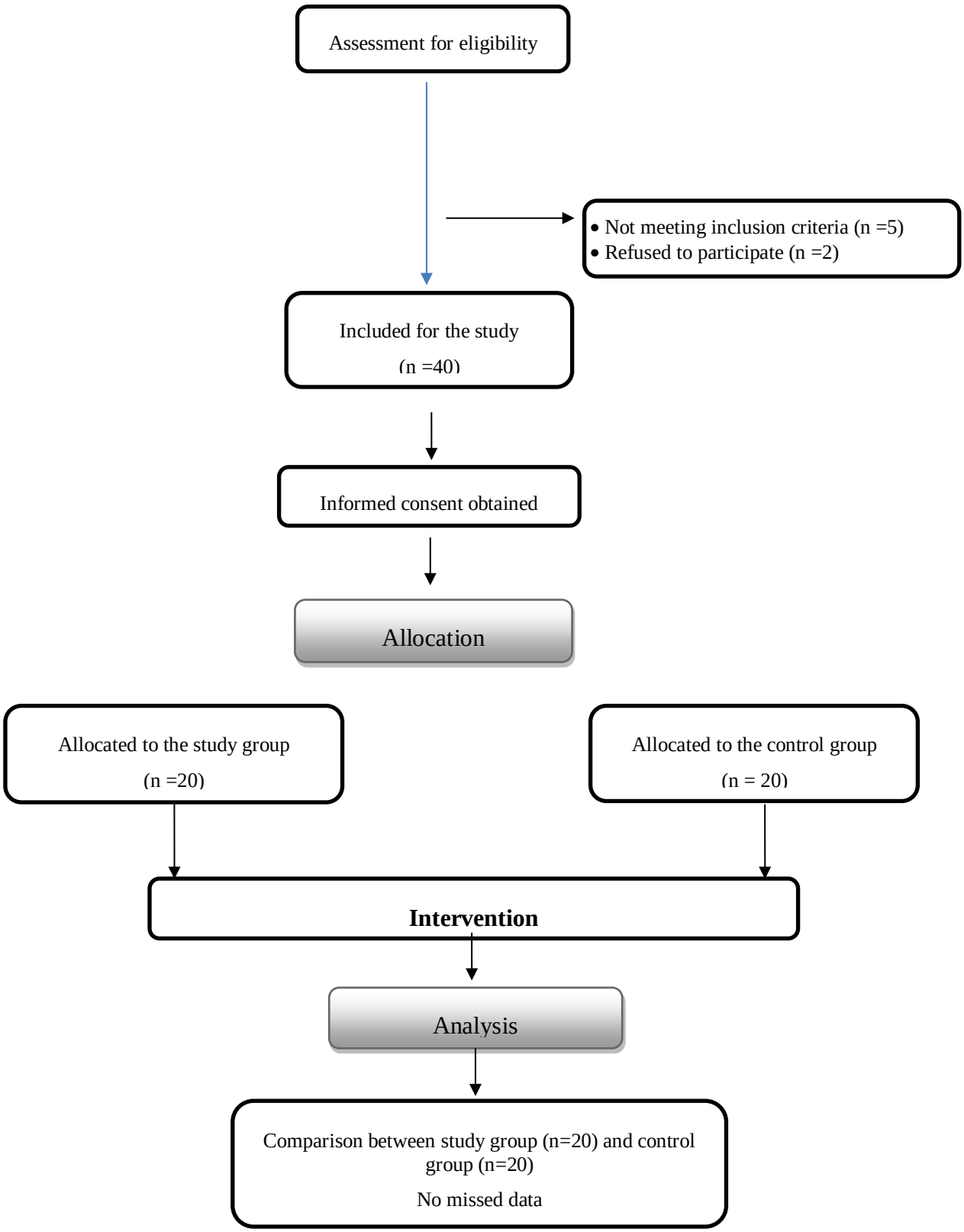

Figure 1. Flow chart showing the experimental design of the study

Before the study, all patients read and signed a written consent form, anonymity and confidentiality were guaranteed, and all methods were carried out by the applicable laws and institutional norms. After randomization, there were no reports of people dropping out of the study).

The study was blinded to the physical therapist who applied the intervention and was not involved in the measurements of the patients, and the assessor from the research team.

2.2. Outcome measures

Expanded Disability Status Scale (EDSS): The EDSS is a technique for assessing functional impairment and tracking changes in patients with MS. On a scale of 0–10, it was utilized to offer a detailed index of functional disability in MS patients (in unit steps of 0.5), as EDSS ratios of 0–3.5 indicate that the patient is in better functional condition and does not require assistance; ratios of 4.0–5.5 are based on walking distance; ratios of 6.0–9.5 indicate growing demands for assistance; and ratios of 10 indicate death, as the Disease severity was calculated by EDSS and categorized as mild MS (EDSS 0–3.5), moderate MS (EDSS 4–6.5) and severe MS (EDSS 7–9.5) (Karabudak et al., 2015).

The Fatigue Severity Scale (FSS): It's a nine-statement unidimensional questionnaire that assesses the degree and impact of fatigue on MS. Items are rated on a scale of 1 to 7, with 1 indicating complete disagreement and 7 indicating perfect agreement. Eight of the questions are on the physical effects of fatigue and how fatigue affects activities and responsibilities, while one is about the cognitive effects of fatigue. Low fatigue (FSS score <4), medium or borderline fatigue (FSS score ≥4 and <5), and high or severe fatigue (FSS score ≥5) were the three groups of FSS scores.

The Modified Fatigue Impact Scale (MFIS): It's part of the Multiple Sclerosis Quality-of-Life Inventory (MSQLI), and it measures how fatigue affects physical, cognitive, and psychosocial functioning. On a 5-point scale, the patients rated how often fatigue had impaired their functions over the previous four weeks (0 = never, 1 = seldom, 2 = occasionally, 3 = frequently, 4 = virtually constantly). A total MFIS score of (84) can be calculated, as well as the (9 items) subscale scores of (36) for physical, 10 items for cognitive scores of (40), and psychosocial tiredness including (2 items) with scores of (8) (Miskovic & Ehrlich-Jones, 2018)**.**

2.3. Interventions

a) **High-tone external muscle stimulation (HTEMS):** Electrical stimulation in the form of HTEMS is a medium frequency current with a frequency scanning from 4.096 to 32.768 Hertz. Simultaneous frequency changes with amplitude. The HTEMS device HiToP®touch gadget

(gboMedizintechnik, Rimbach, Germany). The manufacture did not provide any financial support for the study and had no role in the study design, data collection, analysis, interpretation, or writing of the report All patients in the study group received HTEMS in the form of the vitalization program. Five electrodes connected with flexible rubber pads arranged according to manufacture instructions to cover the whole – body as follows: two electrode pads on the soles of feet, two electrode pads on the outside of both forearms, and the rest on the back of the neck. Adjustment of intensity as follows, first, the intensity at the lower frequency of 4.096 Hertz was increased until the patient felt a pleasant tingle. Next step the intensity was then adjusted at a middle frequency of 16.384 Hertz till the patient felt a pleasant prickle sensation as well. Then, the frequency spectrum was automatically transferred in quartertone steps from 16.384 Hertz to 32.768 Hertz. When starting the program, the device conducts HTEMS through the skin to the whole body with different frequencies and intensities. The time lasted 60 minutes to ensure the whole – body was activated with HTEMS. The control group received a sham HTEMS application with the identical electrode placement as the study group, without the start of the program.

b) **The selected exercise training program:** Every session, both groups received the exercise training in the form of warming up in form of 8-10 repetitions of stretching exercise for the tight muscles according to every patient's assessment before the study to reduce stress on joints. For control group exercise training was conducted as follow ; cardiopulmonary enhancement by five minutes of gradual pulse raise exercise and resistive exercise training from 20-40 % of one- repetition maximum (Darling, 2021), for the trunk extensors, and abdomen crunch, as well as groups of lower and upper limbs, as a core stability program, The repetitions of exercise were 5-8 repetitions with a 60-second rest in between (Mehendale & Aruin, 2013)**.** Low-intensity endurance training 60 – 75% of target heart rate (THR) (Wellace et al., 2019) in form of walking on a treadmill, and cycling on a stationary cycle for 10 minutes. The session ended with a cool- five minutes of down exercise, including gradual pulse lowering exercise with breathing control, every exercise in the cooling down phase was repeated 8-10 times with a 60-second rest in between (Mehendale & Aruin, 2013)**.**

2.4. Statistical analysis

An unpaired t-test was employed to compare subject characteristics between groups. To compare the distribution of sex and type of MS between the two groups, the chi-squared test was used. To ensure that the data had a normal distribution, the Shapiro-Wilk test was utilized. Levene's test for

homogeneity of variances was used to determine group homogeneity. Analysis of covariance (ANCOVA) was conducted for comparison between groups at post treatment with base line assessment as a covariate. Paired t test was conducted for comparison of FSS and MIFS between pre and post treatment. The Mann–Whitney U test was conducted for comparison of median values of EDSS between groups and Wilcoxon signed ranks test was conducted for comparison between pre and post treatment. For all statistical tests, the significance level was set at $p < 0.05$, and the statistical program for social studies (SPSS) version 25 for Windows was utilized (IBM SPSS, Chicago, IL, USA).

3. RESULTS

Regarding the characteristics of the sample, Table 1 listed the study and control groups' characteristics. All the patients' characteristics did not show significant differences between groups ($p > 0.05$) at the beginning of the study.

Table 1. Baseline characteristics of patients

	Study group	Control group	MD	t- value	p-value
	Mean ± SD	Mean ± SD			
Age (years)	36.1 ± 8.95	34.1 ± 7.75	2	0.75	0.45
Weight (kg)	67.4 ± 12.02	68.25 ± 9.28	-0.85	-0.25	0.81
Height (cm)	161.65 ± 6.45	160.15 ± 5.41	1.5	0.79	0.43
BMI (kg/m²)	25.97 ± 3.84	26.63 ± 3.5	-0.66	-0.57	0.57
Duration of MS (years)	6.85 ± 2.66	7.75 ± 2.09	-0.9	-1.18	0.24
Duration of last attack (months)	7.65 ± 1.42	8.05 ± 1.46	-0.4	-0.87	0.38
Sex, n (%)					
Females	16 (80%)	14 (70%)		($\chi^2 = 0.53$)	0.46
Males	4 (20%)	6 (30%)			
Type of MS, n (%)					
PPMS	3 (15%)	4 (20%)			
RRMS	2 (10%)	4 (20%)		($\chi^2 = 1.14$)	0.56
SPMS	15 (75%)	12 (60%)			

Note: SD, standard deviation; χ^2, Chi-squared value; p-value, level of significance; RRMS, Relapsing-Remitting Multiple Sclerosis; SPMS, Secondary Progressive Multiple Sclerosis; PPMS, Primary Progressive Multiple Sclerosis.

With regard to the effect of treatment on FSS, MFIS and EDSS, there was a significant interaction of treatment and time as shown in Tables 2 and 3 ($F_{(6,33)} = 6.73$, $p = 0.001$, $\eta^2 = 0.55$). Also, there was a significant main effect of time ($F_{(6,33)} = 80.64$, $p = 0.001$, $\eta^2 = 0.93$). Furthermore, there was a significant main effect of treatment ($F_{(6,33)} = 3.21$, $p = 0.01$ $\eta^2 = 0.36$).

Table 2. Mean values of FSS and MIFS pre- and post-treatment of study and control groups

	Study group					Control group				
	Pre-treatment	Post-treatment				Pre-treatment	Post-treatment			
	Mean ±SD	Mean ±SD	MD (95% CI)	t-value	P value	Mean ±SD	Mean ±SD	MD (95% CI)	t	P
FSS	5.77 ± 1.03	3.34 ± 1.07	2.43 (1.91: 2.93)	7.21	0.001	5.39 ± 0.92	4.12 ± 0.77	1.27 (0.76: 1.77)	0.96	0.001
MIFS										
Physical	27.5 ± 3.79	16.25 ± 5.65	11.25 (9.16: 13.33)	7.93	0.001	28.2 ± 3.87	22.65 ± 4.06	5.55 (3.46: 7.63)	16.13	0.001
Psychologic	4.95 ± 1.87	2.55 ± 1.87	2.4 (1.78: 3.01)	5.64	0.001	5.15 ± 1.88	4.05 ± 1.79	1.1 (0.48: 1.71)	15.98	0.001
Cognitive	18.8 ± 7.79	8.95 ± 5.37	9.85 (7.58: 12.11	7.86	0.001	17.2 ± 8.57	13.45 ± 6.61	3.75 (1.48: 6.01)	3.86	0.001
Total	51.25 ± 9.66	27.75 ± 10.37	23.5 (19.83: 27.16)	9.76	0.001	50.55 ± 8.04	38 ± 7.76	12.55 (8.88: 16.21)	14.34	0.001

Note: FFS, Fatigue Severity Scale, MFIS, Modified Fatigue Impact Scale; SD, Standard deviation; MD, Mean difference; CI, Confidence interval; p-value, Level of significance

Regarding the comparison between study and control groups, in the pre-treatment there was no significant difference between groups ($p > 0.05$). In the post-treatment, the study group's group showed statistically significant improvement of all variables over control group ($p < 0.01$) (Tables 2 and 3).

Table 3. Median EDSS pre and post treatment of study and control groups

EDSS scale	Study group	Control group	U - value	p-value
	Median (IQR)	Median (IQR)		
Pre-treatment	6 (7-5)	6 (6.75-5)	188	0.73
Post-treatment	2.75 (3.5-1.62)	4 (4-3)	86	0.002
Z - value	-3.93	-3.96		
p-value	0.001	0.001		

Note: EDSS, Expanded Disability Status Scale; IQR, interquartile range; U- value, Mann-Whitney test value; Z- value: Wilcoxon signed ranks test value, p value: Probability value

The adjusted mean difference in FSS was -0.89, $p = 0.004$. There was also a significant decrease in physical (adjusted mean difference = -5.97, $p < 0.001$), psychological (adjusted mean difference = -1.42, $p < 0.01$), cognitive (adjusted mean difference = -5.43, $p < 0.001$), and total scores of MFIS (adjusted mean difference = -10.68, $p < 0.001$) of the study group compared with that of control group post-treatment (Table 4).

Table 4. Mean values of FSS and MIFS and adjusted group difference post-treatment between study and control groups

	Study group	Control group			
	Mean ± SD	Mean ± SD	Adjusted Group Difference (95% CI)	F value	P value
FSS	3.34 ± 1.07	4.12 ± 0.77	-0.89 (-1.48: -0.3)	9.42	0.004
MIFS					
Physical	16.25 ± 5.65	22.65 ± 4.06	-5.97 (-8.81: -3.14)	18.21	0.001
Psychologic	2.55 ± 1.87	4.05 ± 1.79	-1.42 (-2.59: -0.25)	6.13	0.01
Cognitive	8.95 ± 5.37	13.45 ± 6.61	-5.43 (-7.82: -3.04)	21.15	0.001
Total	27.75 ± 10.37	38 ± 7.76	-10.68 (-15.45: -5.91)	20.54	0.001

Note: FSS, Fatigue Severity Scale; MFIS, Modified Fatigue Impact Scale; SD, Standard deviation; CI, Confidence interval; p-value, Level of significance

4. DISCUSSION

To the best of our knowledge, this is the first randomized controlled trial (RCT) study to investigate the clinical outcome of HTEMS application on fatigue and function levels in MS. The results of the current study showed that HTEMS increases physical function and decreases fatigue among MS patients, more than the conventional exercise training program, and without any adverse effects.

The exact mechanisms of this improvement by HTEMS are uncovered completely, however, the main objective of HTEMS is to introduce the bioelectric current with different frequencies into the body cells which leads to enhancing cells metabolism, replenishing body energy, and producing cell structure oscillation to their normal frequency, hence improving cell activities and increase the energetic potential of the cells (Dudek, 2002), leading to the redistribution of endogenous anti-inflammatory process (Morris & Berk, 2015). A previous study approved that the HTEMS increased reactive oxygen species (ROS) production (Dong et al., 2021), enhancing the release of endogenous analgesics, and decreasing pain sensation by inhibiting sympathetic afferent activity (Kempf et al., 2018). Recently Enoka et al (Enoka et al., 2021) reported that both voluntary muscle contraction and electrical stimulation are able to reduce the level of fatigue. Another explanation of improvement in the current study is that the HTEMS could improve the axonal regeneration (Ransom et al., 2020), as MS has been classified as an immune demyelinating disease elicited by endogenous myelin-associated antigens such as myelin oligodendrocyte glycoprotein, proteolipoprotein, and myelin basic protein (Lopez et al., 2021).

Liu et al. (2021) found that the application of HTEMS can significantly decrease depression-related symptoms of fatigue and sleep disruption .

The selected planned exercise training program for MS patients leads to significant improvements in cardiorespiratory fitness, muscle strength, flexibility, stability, cognition, and quality of life (QoL) (Motl & Sandroff, 2015), which is supported by (Mehendale & Aruin, 2013) who proposed that conventional exercise treatment can improve MS fatigue (Andreasen et al., 2011), as well as the core stability and balance training decrease the risk of fall hence improve MS functional state (Mahmoud et al., 2022). A possible mechanism of exercise to reduce fatigue is improving neuroprotection, neuroplasticity, and deregulation of the hypothalamus-pituitary-adrenal (HPA) axis (Kargarfard et al., 2012).

5. CONCLUSIONS

High-tone external muscle stimulation showed a significant improvement effect for both fatigue and functional outcomes in multiple sclerosis patients, being more effective than the conventional exercise training program; therefore, it should be considered a beneficial treatment method for patients with multiple sclerosis.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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