Self-Acupressure for Multiple Sclerosis-Related Depression and Fatigue: A Feasibility Randomized Controlled Trial

Hossein Rahimi[1] iD , Nasim Mehrpooya[2] iD, SeyyedAbolfazl Vagharseyyedin[1] iD,
Hamidreza BahramiTaghanaki[3] iD

1. Dept.of Nursing,School of Nursing and Midwifery, Birjand University of Medical Sciences, Birjand, Iran
2. Dept.of Nursing,School of Nursing and Midwifery,Neyshaboor University of Medical Sciences, Neyshaboor, Iran
3. Dept.of Complementary and Chinese Medicine, Persian and Complementary Medicine School, Mashhad University of Medical Science, Mashhad, Iran

Article Info

Corresponding Information:
Hossein Rahimi,
Dept. of Nursing, School of Nursing and Midwifery, Birjand University of Medical Sciences, Birjand, Iran

E-Mail:
Hosseinrahimi92@yahoo.com

ABSTRACT

Background & Objective: Depression and fatigue are common in patients with multiple sclerosis (MS). These complications exacerbate the symptoms of MS. This study aimed to determine the effect of self-acupressure on depression and fatigue in MS patients.

Materials & Methods: In this randomized clinical trial (RCT), 96 participants from the MS Association of Mashhad, Iran completed the demographic form, the Depression, Anxiety Stress Scales (DASS-42), and the Fatigue Severity Scale (FSS). Then, they were randomly assigned to intervention and sham groups. Participants in the intervention group pressed the Shenmen and Yin Tang acupoints, and the sham group pressed 2.5 cm below the Shenmen and 3 cm above the Yin Tang acupoints for 15 minutes every day for one month. The participants completed the DASS-42 and FSS one hour after the final intervention in each group. Also, the chi-square, independent t-test, and paired t-test were used in the study.

Results: The statistical analysis showed that the mean fatigue and depression scores were not significantly different between the two groups at the baseline ($P>0.05$). However, the mean scores of fatigue and depression significantly reduced in the intervention group compared to sham group one hour after the last intervention ($P<0.05$).

Conclusion: Self-acupressure is a simple and inexpensive intervention that may reduce depression and fatigue among MS patients.

Keywords: Acupressure, Depression, Fatigue, Multiple sclerosis.

Introduction

Multiple sclerosis (MS) is a chronic and common neurodegenerative disease of the central nervous system (CNS). In 2019, the number of MS patients worldwide was estimated to be more than 2.5 million (1). According to the Iranian MS Association, there are about 40,000 MS patients in Iran (2).

In MS patients, inflammation, damage, and scars are seen in the myelin. Myelin damage leads to balance, swallowing, visual, and defecation disorders and muscle spasms. Also, MS can be associated with psychological disorders; but these conditions have received less attention (3).

Depression is a common disorder in MS patients. Marrie *et al.* (2015) estimated the prevalence of depression among these patients to be 979 cases per 100,000 people. Depression reduces the quality of life (QOL), impairs general health, and increases the severity of fatigue (4).

Fatigue is another common symptom reported in 68% of MS patients. It decreases physical and mental energy, leading to a disruption of daily activities (5). Fatigue has many causes that originate directly from the nature of the disease or complications such as depression, anxiety, and sleep disorders. Moreover, it has some adverse effects on daily activities and social relationships (6). Therefore, the treatment of these complications seems necessary.

Medications are the most well-known method for managing depression and fatigue among patients with MS. In general, psychiatric drugs have beneficial effects in treating psychological disorders. However, most MS patients refuse to take them due to their

serious side effects. In addition, medications impose a very high cost on both patients and the healthcare system **(7)**. Hence, most patients prefer to choose and use available and inexpensive treatments with fewer side effects. One of these methods is complementary and alternative medicine (CAM). Acupressure is a CAM that does not require any special tools compared to other treatments. This method was defined as a treatment by pressing acupoints using a finger or non-invasive tool to achieve therapeutic effects **(8)**.

In traditional Chinese medicine philosophy, it is believed that illnesses are caused by an imbalance of vital energy (Chi). According to this philosophy, health is the result of balance in the Chi. The Chi circulates through 12 principal meridians between the organs of the body. There are 361 points on these meridians **(9)**, each of which are associated with specific parts of the body. The therapist uses these critical points on the skin's surface to stimulate and induce the body's natural self-healing abilities **(10).**

Previous studies **(11-13)** have shown the positive effect of acupressure on depression in the general population, as well as among hemodialysis patients and the elderly with chronic knee pain. However, there have been limited studies examining the effect of acupressure on depression in MS patients. Furthermore, there are several studies with conflicting results. For example, Lan *et al.* (2015) showed that acupressure did not significantly reduce depression among patients with hepatocellular carcinoma (HCC) **(14)**. Also, the effects of acupressure on fatigue are not consistent. Lan *et al.* (2015) and Bastani *et al.* (2015) reported the positive effects of acupressure on reducing fatigue in patients with HCC and women with MS, respectively **(14, 15)**. However, the results of a study by Kluger *et al.* (2016) showed that acupuncture intervention did not affect reducing fatigue in Parkinson's patients **(16)**.

As stated, the findings contradict the effect of acupressure on depression and fatigue in patients. On the other hand, more acupressure interventions using different acupoints will gather as much evidence as possible about the CAM method. This study, therefore, was conducted to determine the effect of self-acupressure on depression and fatigue in MS patients.

Materials and Methods

Type of Study

This study is a randomized clinical trial (RCT) conducted in 2019. The trial was registered at the Iranian Clinical Trial Registry (IRCT20190515043601N5).

Sample of the Study

The research environment was the MS Association in Mashhad, Iran. Participants were selected using a convenience sampling method. The inclusion criteria were patients between 20 to 45 years old; having

remitting-relapsing MS; having a minimum six-month history of MS diagnosis; obtaining a score between 0 and 5.5 on the Expanded Disability Status Scale (EDSS); lack of any history of psychotic disorders, addiction to drugs, stimulants, and smoking; a lack of regular use of sedatives; a lack of skin lesions in acupressure or sham points; and not being pregnant. In order to determine the degree of disability of the participants, the EDSS (1983) was used **(17)**. This tool examines the condition of the pyramidal, cerebellar, sensory, brainstem, intestines and bladder, visual function, and cerebral function. A neurologist performed clinical examinations of patients and determined their scores on this scale. The minimum score on this scale is 0, and the maximum obtainable score is 10. A score of 0 means a typical performance, and 10 indicates death due to MS. Scores of 1 to 4.5 indicate patients who can walk without the use of assistive devices **(17)**. In the present study, the reliability of the EDSS was calculated using a Cronbach's alpha of 0.87. Exclusion criteria included the lack of willingness to continue participating in the research and exacerbation of MS symptoms during the intervention.

The sample size was determined according to the pilot study (mean different=2.62, pooled standard deviation=2.83). The sample size for each group was 48. With a possible 10% drop in samples, 53 people were considered for each group.

During the data collection from November 2019 to April 2020, 117 participants were evaluated to enter the study. Out of these participants, 11 could not participate either because they were unwilling to take part in the research or because they did not meet the inclusion criteria. In the next step, all participants completed demographic information forms (including age, gender, education, employment status, level of education, and duration of MS), the Depression, Anxiety Stress Scales (DASS-42), and the Fatigue Severity Scale (FSS). This was a double-blind study. The data collector and data analyzers were blinded to the data.

Primary outcomes

The primary outcomes in the present study included depression and fatigue. To measure participants' depression, the DASS-42 was used. This tool, which has been invented by Lovibond and Lovibond (1995), has both short and long forms. Its main form has 42 items, each examining the psychological structures of stress, anxiety, and depression. Depression subscale includes 14 items. The item's response format is on a 4-point Likert-type scale ranging from "never=0" to "always=3". Higher scores imply increased depression. Studies have shown that the validity for depression is 0.71 **(18)**. In the present study, the reliability of the depression subscale was measured by calculating Cronbach's alpha to be 0.75.

Meanwhile, the FSS was used to measure fatigue severity. This tool has nine items scored from 7 (completely agree) to 1 (completely disagree). The total score is calculated by dividing the sum of the

scores by 9. The overall rating is between 1 and 7, where a higher score indicates more fatigue. Krupp *et al.* (2000) found the validity of the fatigue severity criterion correlated with a Cronbach's alpha of 0.91 [19]. In the present study, the Cronbach's alpha for this scale was calculated at 0.89.

Randomization

Participants were assigned to intervention or sham groups using the blocking method, based on which the researcher prepared 106 opaque envelopes. The blocks were 4 in size and 1: 1 in ratio. Finally, an envelope was given to each patient based on which the patients were assigned to each group.

Intervention

The intervention was performed in two stages. In the first stage, the acupressure educator (ZR) was trained under the supervision of a Chinese medicine specialist. The researcher had to obtain a certificate and approval from a complementary medicine specialist to enter the clinic and perform the intervention.

The second stage consisted of three training sessions of 30 to 40 minutes for the participants of intervention group. The number of participants in each session was 8 to 10. In the first session, the goals were to acquaint the researcher and the participants, discuss the psychological and physical complications of MS, and explain the designed intervention.

In the second session, the educator taught the locations of acupoints (the left and right Shenmen, and the Yin Tang) to the intervention group participants. The Yin Tang acupoint is located at the midway between the medial/inner ends of the two eyebrows. The Shenmen acupoints are located at the ulnar, the end of the transverse crease of the wrist, and in the small depression between the ulna and pisiform bones [20]. Also, during this session, the educator explained the method and amount of pressure on the acupoints. He asked the participants to press right on the Shenmen first, and then left on the Shenmen and, finally, on the Yin Tang acupoints. The pressure was applied using the pulp of the thumb. one of the researchers (ZR) asked the participants to press each acupoint for 30 seconds and then gradually increase the pressure to feel the warmth and tingling of the targeted areas. At this stage, the participants were asked to hold the weight for 4 minutes and then release the hand pressure for 30 seconds. Each acupoint was pressed individually; then, after the end of the intervention at each location, the same routine was performed on another acupoint. By ensuring the correct method of the intervention, the participants were able to perform self-acupressure. The intervention was conducted every day between 9:00 a.m. and 10:00 a.m. for 15 minutes (5 minutes on each Shenmen, and 5 minutes on the Yin Tang acupoints). In the third session, while ensuring the proper acupressure training for each of the participants, a compact disc (CD) containing the acupressure video

was presented to the participants, which was approved by a Chinese medicine specialist.

Participants in the sham group were taught to use the pulp of the thumb to press 2.5 cm below the Shenmen point (to the forearm) and 3 cm above the Yin Tang acupoint. The length and frequency of the intervention were the same in both groups.

For one month, the researcher reminded the patients to intervene every day from 8 to 9 in the morning using the Auto SMS Reminder mobile application. It is noteworthy that every day after performing the intervention, the participants in each group recorded the acupressure activities in the checklist. At the end of day 30, DASS-42 and FSS were re-completed by participants from both groups (Figure 1).

Ethical Considerations

Ethical approval (IR.BUMS.REC.1398.218) was obtained from the ethics committee of Birjand University of Medical Sciences, Iran. Participants at each stage of the study could refuse to continue participating in the study. Participants were assured of the confidentiality of the collected data.

Data Analysis

Data analysis was performed with the SPSS software (version 16.0) using descriptive statistical tests, i.e., frequency and percentage, to describe the demographic characteristics. Also, the chi-square test was employed to compare the distribution of demographic variables. In the inferential section, the Kolmogorov-Smirnov test was applied to test the normal distribution of the data. Finally, the mean depression and fatigue scores between the groups were compared using the independent t-test, and the paired t-test was used for intra-group comparison. A significance level of $P<0.05$ was expected.

Results

In the present study, 53 participants in the sham group and 53 participants in the intervention group were investigated. In the sham group, nine people were excluded from the study because they were unwilling to continue participating in the research, and two others were excluded due to death. In the intervention group, nine people were excluded from the study because they were unwilling to continue the intervention. Finally, the data was analyzed in 44 MS patients in the sham group and 42 patients in the intervention group.

There was no significant statistical difference between the two groups in terms of demographic variables and EDSS scores before the intervention ($P>0.05$; Table 1).
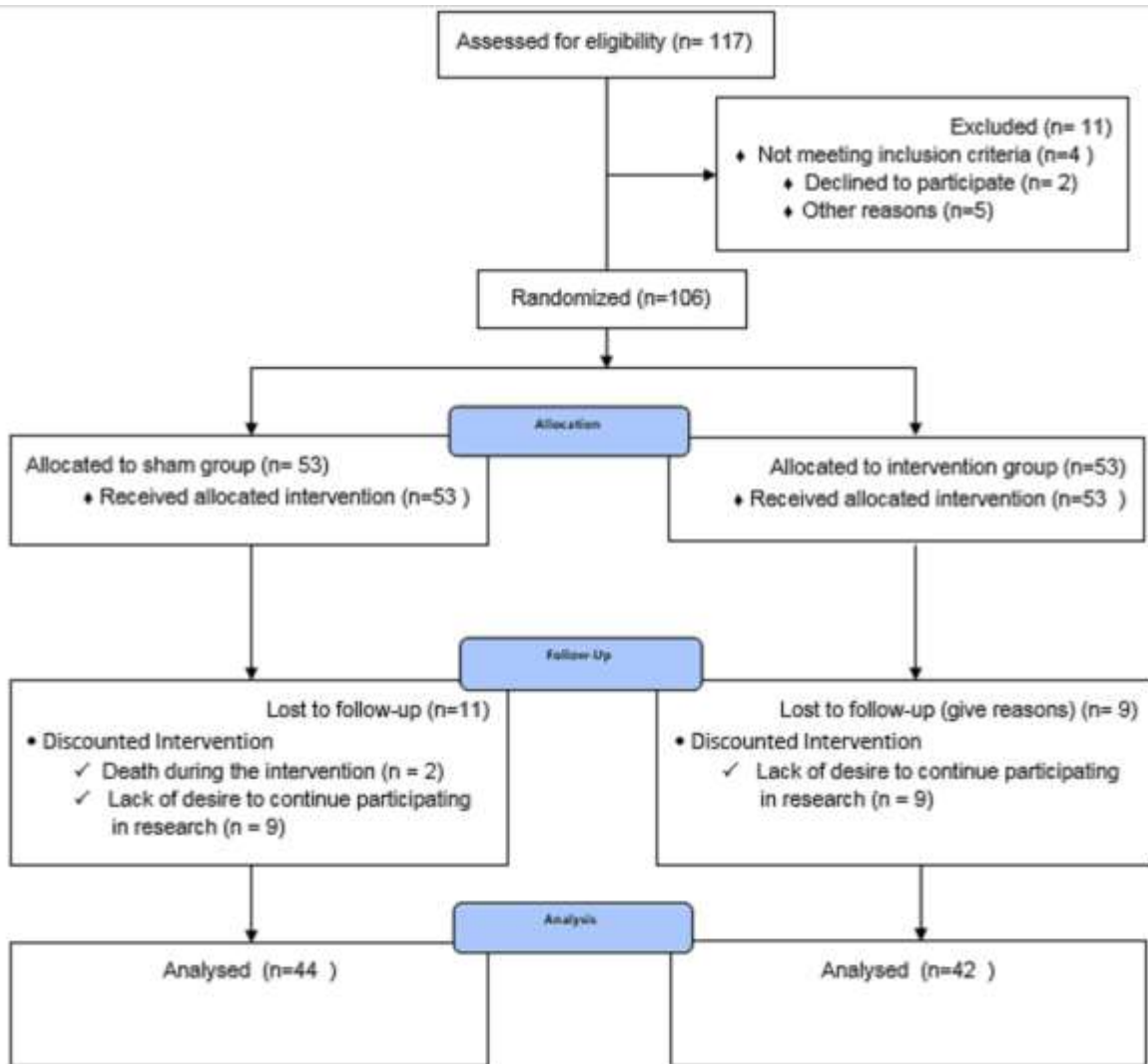
Figure 1

Table 1. Comparison of the demographic characteristics in the two groups

		Groups		Results
		Intervention	Sham	
Sex	Male	11 (25%)	12 (28.5%)	X2=0.15 P=0.79
	Female	33 (75%)	30 (71.4%)	
Age	25-20	8 (18.2%)	9 (21.4%)	X2=4.39 P=0.22
	30-26	10 (22.7%)	9 (21.4%)	
	35-31	10(22.7%)	10(23.8%)	
	45-36	16(36.4%)	14(33.3%)	
Education level	High school	5(11.4%)	5(11.9%)	X2=1.13 P=0.77
	Diploma and postgraduate	15(34.1%)	13(3.9%)	
	Bachelor	15(34.1%)	15(35.7%)	
	Master's degree and more	9(20.5%)	9(24.4%)	

		Groups		Results
		Intervention	Sham	
Marital status	Single	17(38.6%)	19(45.2%)	X2=0.57 P=0.48
	Married	27(61.4%)	23(54.7%)	
Job	civil servant	12(27.27%)	10(23.80%)	X2=0.51 P=0.46
	self-employment	14(31.81%)	9(21.42%)	
	Unemployed	18(40.92%)	23(54.78%)	
Duration of illness	6 to 12 month	8(18.18%)	10(26.19%)	X2=0.17 P=0.86
	13 to 19 month	19(43.18)	17(40.47%)	
	20 to 26 month	6(13.63%)	9(21.42%)	
	More than 27 month	11(25.00%)	6(11.92%)	
EDSS scores	0.5 to 1.5	7(15.90%)	9(21.42%)	X2=0.25 P=0.69
	1.6 to 2.6	12(27.27%)	15(35.71%)	
	2.7 to 3.7	16(36.36%)	14(33.33%)	
	3.8 to 4.5	9(20.47%)	4(9.54%)	

The mean scores of pre-intervention depression in the intervention and sham groups were 11.48±3.10 and 11.45±3.57, respectively, which were not statistically different (P=0.98). Paired t-tests showed that the mean scores of pre-intervention depression in the intervention group decreased from 11.48±3.10 to 9.66±2.50 in the post-intervention phase, which was statistically significant (P<0.001). In the sham group, the mean depression score after the intervention was 11.36±3.58. The independent t-test showed that after the intervention, there was a statistically significant difference between the mean scores of depression in the two groups (P=0.02; Table 2). The results of the independent t-test also showed that the mean changes in the score of depression in the intervention group were significantly lower than in the sham group (P<0.001; Table 3).

Table 2. Comparison of mean scores of depression and fatigue before and after intervention within and between groups

		Groups		P value [a]	
		Intervention	Sham		
		Mean ± SD	Mean ± SD		
Depression	Before	11.48±3.10	11.45±3.57	t=0.03	P =0.98
	After	9.66±2.50	11.36±3.58	t=2.34	P =0.02
P value[b]		0.001< P 5.50=t	0.08= P 1.78=t		
Fatigue	Before	4.26±1.61	4.02±1.62	t=0.62	P =0.53
	After	3.85±1.48	4.01±1.59	t=0.45	P =0.66
		t=3.46 P =0.001	t=0.54 P =0.59		

[a] Independent samples test, [b] paired sample t-test

Table 3. Comparison of mean changes in depression and fatigue scores in two groups

	Groups		P value [a]
	Intervention	Sham	
Depression	-1.82±2.19	0.09±0.29	t=5.17, P<0.001
Fatigue	-0.40±0.77	-0.01±0.14	T=3.7, P =0.002

[a] Independent samples t-test

The mean pre-intervention fatigue scores in the intervention and sham groups were 4.26±1.61 and 4.02±1.62, respectively, which were not statistically significant (*P*=0.33). The results of the t-test showed that the mean pre-intervention fatigue scores in the intervention group had decreased from 4.26±1.61 to 3.85±1.48 in the post-intervention phase, which was statistically significant (*P*=0.001). The mean post-intervention fatigue score in the sham group was 4.01±1.59. The t-test showed that in the post-intervention phase, there was no statistically significant difference for the mean fatigue scores between the two groups (*P*=0.66; Table 2). The results of the independent t-test also showed that the mean changes in the score of fatigue in the intervention group were significantly lower than in the sham group (*P*=0.002; Table 3).

Discussion

Depression and fatigue are common in MS patients (5, 21). This study aimed to determine the effect of acupressure on depression and fatigue in MS patients.

Our results indicated that acupressure on the Shenmen and Yin Tang acupoints is an effective intervention to reduce depression and fatigue among MS patients. The studies conducted by Cho *et al.* (2004) and Tsay *et al.* (2004) on hemodialysis patients, Wu *et al.* (2007) on patients with chronic obstructive pulmonary disease (COPD), and Tse *et al.* (2010) on elderly patients with chronic knee pain are consistent with the findings of the present study (13, 22-24). In explaining the mentioned results, several possible mechanisms can be noted. First, the arrangement of the direct effect of acupressure on hormones affecting depression is discussed. In depressed patients, cortisol increases and serotonin decreases. Acupressure reduces the secretion of cortisol by inducing effects on the hypothalamic-pituitary-adrenocortical axis (25). Researchers believe that the proper stimulation of acupoints increases the activity of serotonergic neurons. Increased serotonin production eventually improves symptoms of depression (26). Another mechanism is pain control. Most MS patients suffer from neuropathic pain. Studies have shown that neuropathic pain leads to depression (27). According to gate control theory, following the stimulation of the acupoints, impulses occur more than four times faster than painful impulses. Therefore, painful impulses will be blocked, and the patient's pain tolerance threshold will increase (28).

Yet another mechanism that can explain acupressure's anti-depressant effects is the secretion of opiate-like neurotransmitters following the implementation of acupressure on Shenmen and Yin Tang acupoints. Acupressure by secreting endorphins modulates the physical and psychological response to pain (29). Another mechanism that can be mentioned is related to the secretion of enkephalins. The stimulation of GV29 and HT7 points causes the secretion of enkephalins. Enkephalins are effective in improving mood and behavior and have anti-depressant effects (30). The last mechanism for the effect of acupressure on depression in MS patients is parasympathetic activity following acupressure. By activating the parasympathetic nervous system, acupressure leads to a sense of calm and improves the process of thinking and problem solving (31).

However, Lan *et al.* (2015) showed that acupressure did not affect reducing depression in patients with HCC (14). One of the reasons for the difference between the results of the mentioned studies and the results of the present study could be related to the difference between the acupoints used. In the study by Lan *et al.*, Fengchi, Baihui, Shenting, Yangbai, Jingming, Yin Tang, Cuanzh, and Taipan acupoints were used. In addition, the acupressure was performed twice a day for five days. The duration of each acupoint massage was limited to 4 minutes. Another reason could be related to the scales used to measure depression. In the present study, the DASS-42 was used. However, in the study carried out by Lan *et al.,* the Visual Analogue Scale (VAS) was used.

The results of present study showed that acupressure on Shenmen and Yin Tang acupoints reduces fatigue in MS patients. In this regard, Vagharseyyedin *et al.* (2019) showed that acupressure could significantly reduce fatigue in patients with migraines (32). Other studies have shown a positive effect of acupressure on the fatigue of women with MS, patients with HCC, and hemodialysis patients (3, 14, 33). In explaining the above results, it can be said that acupressure-based interventions reduce the secretion of inflammatory mediators such as cytokines (34). Pro-inflammatory cytokines such as IL8, IL6, and TNF-α are associated with fatigue, so an increase in these factors in the CNS and cerebrospinal fluid leads to higher levels of fatigue in MS patients (34). Also, acupressure heightens microcirculatory activity in tissues. Increasing microcirculation reduces fatigue by improving the excretion of fatigue-causing molecules from tissues rich in metabolites that cause fatigue (35).

One of the limitations of the present study is its relatively small sample size. The selection of research samples from only one center (MS Association of Mashhad) was another limitation. The existence of the age limit in the inclusion criteria is the last limitation of the present research.

It is suggested that in future studies, researchers investigate the effect of other acupoints on the fatigue and depression of MS patients. We also recommend comparing the impact of other CAM methods such as aromatherapy with acupressure on fatigue and depression in MS patients. Future studies can compare the effects of acupressure on different psychological problems of MS patients.

Ethical considerations

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