Amantadine and the place of acupuncture in the treatment of fatigue in patients with multiple sclerosis: an observational study

Mohsen Foroughipour,1 Hamid Reza Bahrami Taghanaki,2 Morteza Saeidi,1 Mojtaba Khazaei,3 Payam Sasannezhad,4 Ali Shoeibi4

ABSTRACT

Background Fatigue is a common symptom in patients with multiple sclerosis (MS). It has significant negative effects on the quality of life of patients with the condition. There are few therapeutic modalities for fatigue, which are also usually not sufficiently effective. The aim of this study was to evaluate the efficacy of acupuncture on this common symptom of patients with MS.

Methods In this before-and-after clinical trial, 40 patients with definite diagnoses of MS, according to the ‘McDonald’ criteria, were studied. Patients who had Expanded Disability Status Scale (EDSS) scores greater than 4, or who had another disease that could be potentially responsible for their fatigue, were excluded from the study. In all, 20 patients with fatigue refractory to amantadine underwent 12 sessions of acupuncture. Fatigue was scored according to the Fatigue Severity Scale (FSS).

Results A total of 15 (37.5%) patients with MS with fatigue responded to amantadine. The mean FSS score reduction after 2 months of treatment was 8±4, which was statistically significant (p<0.001). Of the 20 patients who were resistant to amantadine, 5 (25%) responded to acupuncture combined with amantadine treatment. The FSS scores of the 20 patients who were refractory were significantly reduced after this treatment (mean: 13±6, p<0.001).

Conclusions Acupuncture appears to be associated with benefits for a proportion of patients with fatigue who are resistant to conventional drugs such as amantadine, and this finding justifies further research.

Multiple sclerosis (MS) is a well recognised neurological disorder, especially among young people between 15 and 45 years old.1 2 Fatigue is one of the most common symptoms in patients with MS and is defined as ‘the sense of loss of energy’.3 Fatigue is observed in 70% to 90% of such patients4 5 and is one of the most disturbing symptoms of the disease.6 It has unfavourable effects on various life activities of patients including recreation, daily routines and self-care, and can even lead to losing job opportunities. It can also worsen other symptoms of the disease such as sleep abnormalities, anxiety and mood disturbances.7 Although the exact aetiology is still unknown, it seems that fatigue in patients with MS is multifactorial, and different abnormalities including nerve conduction block, autoimmune disorders, endocrine problems and involvement of muscle may contribute to fatigue.8–10 The main therapeutic modalities suggested internationally for fatigue in patients with MS consist of: (1) drugs such as: amantadine, pemolin, potassium channel inhibitors and antidepressants11 12 (2) rehabilitation and exercise therapy13 (3) complementary therapies including yoga and acupuncture14 and (4) behaviour and cognitive therapies.14 Among these, medication, namely amantadine and antidepressants, is the most common treatment used in Iran. The current worldwide literature only appears to provide evidence for drugs, especially amantadine, in the treatment of MS fatigue.15 16

Acupuncture has been widely used in other clinical contexts than fatigue as a safe treatment with few side effects and very little risk of toxicity.17–21 Although acupuncture has been used for the treatment of fatigue in various disorders such as systemic lupus erythematosus, chronic
fatigue syndrome,22 23 and cancer and its treatments (radiation or chemotherapy).24–29 to the best of our knowledge, there are only a few case reports concerning the efficacy of acupuncture in MS fatigue.14 30 31 and this is believed to be the first clinical trial addressing this issue. The aim of this study was to determine the effects of acupuncture in the treatment of fatigue in patients with MS whose symptoms are resistant to conventional drug therapies.

METHODS
For 12 months from August 2010, all patients who attended the MS Clinic of Ghaem Hospital of Mashhad University of Medical Sciences, Iran, and were diagnosed as having a definite case of MS according to the ‘McDonald’ criteria32 were assessed for fatigue. Fatigue was scored according to the Fatigue Severity Scale (FSS).33 The FSS is a questionnaire comprising nine questions, each corresponding to a scale between 1 and 7. The summary score provides a total ranging from 9–63. An FSS score greater than 30 was defined as significant and an indication for treatment based on previous literature.33 34 Consequently, 40 patients entered into the study.

The included patients received amantadine (100 mg twice a day) for 2 months. A total of 15 patients responded well to amantadine and had FSS score less than 30 after a 2-month treatment period. Out of 25 patients who were resistant to amantadine (FSS score >30 after 2 months of amantadine treatment), 20 were selected randomly (using random draw method out of a box) for acupuncture treatment; only 20 could be treated because of limited resources. Treatment with amantadine alone was continued for the other five patients who were drug resistant. The selected group continued amantadine in combination with acupuncture for ethic grounds: even though the patients whose FSS scores were greater than 30 were defined as refractory in this study, we did not want to deprive them from any potential effects of treatment with amantadine after 2 months since the 2-month period is merely a supposed effect-measuring time.

Inclusion criteria were: having definite diagnosis of MS (any clinical type), fatigue as a major symptom (FSS score greater than 30) and an Expanded Disability Status Scale (EDSS) (range 0–10) score less than 4 (that is, below the level of ‘significant’ disability). Exclusion criteria for study were: having another simultaneous disease such as infection, thyroid disorders, etc., with fatigue as their potential symptom; using drugs, other than amantadine, with anti-fatigue properties such as modafinil, ritalin, pemolin, and so on; and a history of acupuncture treatment in the previous 6 months.

A total of 12 sessions of acupuncture were conducted every other day (Saturdays, Mondays and Wednesdays for 4 weeks) by one of the authors (HRBT, specialist in complementary and alternative medicine with considerable experience in acupuncture) and FSS scores were recorded at the end of the last session of acupuncture. Each session of acupuncture lasted about 30 min using a 1.5 cun (40 mm×0.25 mm) stainless steel acupuncture needles (Hanyi, Beijing) according to Traditional Chinese Medicine (TCM) acupuncture based on literature sources.34 Needles were inserted bilaterally into acupuncture points SP6, SP9, ST36, GB34, KI3, KI6; BL60, BL62, LI4 and LI11. For each point, the needle was first inserted with a guide tube, then advanced deeper to the appropriate tissue level for each point. De qi was not obtained and no manual or electrical stimulation were used. At the end of each session and before the beginning of the next session all patients were evaluated for side effects such as local or systemic infection, organ injuries, haemorrhage and local bruising, fainting or syncope, etc.

The ethics committee of the Mashhad University of Medical Sciences approved this study and all patients signed informed consent forms. For patients who were minors, a responsible adult signed the informed consent form. Categorical data are presented as n (%), and non-categorical data are presented as mean±SD. All statistical assessments were evaluated at the 0.05 level of significant difference. Statistical analyses were performed using SPSS V.11.5 statistics software (SPSS Inc, Chicago, Illinois, USA)

RESULTS
A total of 31 women (77.5%) and 9 men (22.5%) with MS and significant fatigue (FSS score greater than 30) were included in this study. The mean age of patients was 34.17±9.52 years (maximum: 55 years and minimum: 12 years). Amantadine was prescribed for all patients. The group mean FSS scores were 48±8.6 and 40±12.6 before and after 2 months of amantadine treatment respectively, the reduction of 8±4 being statistically significant (p<0.001). In all, 37.5% of patients (15 cases) responded to treatment but 25 (62.5%) still had an FSS score >30. Among these non-responders, 20 patients were selected randomly for acupuncture treatment, mean age 33.85±10.85 years and 75% (15 cases) were women. A total of 5 (25%) of the patients who received 12 sessions of acupuncture responded showing an FSS score less than 30 at the end of 12th session. Figure 1 summarises the design and results of this study.

For the group receiving acupuncture (20 cases), the mean fatigue scores was 49.1±8.9 and 35.1±9.9 before and after acupuncture treatment respectively, with a mean reduction of 13±6 which is statistically significant (p<0.001). In regards to the responders (5 out of 20), the mean reduction of FSS score after acupuncture stood at 20.6±7.2, which is obviously significant in light of the general reduction pattern observed. No significant side effects were observed in patients who underwent acupuncture.
**DISCUSSION**

In the present study, 15 (37.5%) patients with MS with fatigue responded to amantadine. This is in concordance with other studies that showed an efficacy of 30% to 40% for amantadine in the treatment of fatigue. The mean reduction of FSS score after amantadine treatment was 8±4, which is statistically significant and consistent with previous research.

Although anxiety, insomnia, nightmare and levodopa reticularis have been reported as the main side effects of amantadine treatment in patients with MS, such effects were not observed in the current patient cohort. In this study, acupuncture was associated with some effect in the treatment of refractory fatigue in 25% of patients. The mean reduction in FSS score of patients undergoing acupuncture (20 cases) was 13±6 (p<0.001). To the best of our knowledge there are a few case reports regarding efficacy of acupuncture in the treatment of fatigue in patients with MS, such effects were not observed in the current patient cohort.

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The main limitations of this study are as follows: (1) the responders were not followed up to determine the duration of the effect of acupuncture; (2) it was not possible to compare the effects of ‘acupuncture plus amantadine’ and ‘amantadine alone’ in separate groups due to the small sample size, or to form a third ‘placebo’ group since deprivation of medicine from the patients would be regarded as unethical; and (3) the possibility of placebo effect of additional time/attention rather than effect of acupuncture treatment itself cannot be excluded in this study. In light of the above limitations, further study with appropriate sample size is seriously recommended.

Based on the findings of this study, acupuncture appears to be associated with benefits for a proportion of patients with fatigue who are resistant to the conventional drugs such as amantadine, and justifies further research.

**Summary points**

- Amantadine reduces fatigue in about 35% patients with MS.
- Acupuncture benefited a quarter of non-responders.

**Contributors**

MF: contributions to conception and design, acquisition of data, drafting the article and revising it critically for important intellectual content, final approval of the version to be published. HRBT: contributions to conception and design, acquisition of data, drafting the article and revising it critically for important intellectual content, final approval of the version to be published. PS: contributions to conception and design, acquisition of data, drafting the article and revising it critically for important intellectual content, final approval of the version to be published. MK: contributions to conception and design, acquisition and analysis of data, drafting the article and revising it critically for important intellectual content, final approval of the version to be published. AS: guarantor of the work and reporting the work, contributions to conception and design, acquisition of data, drafting the article and revising it critically for important intellectual content, final approval of the version to be published.
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