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RESEARCH ARTICLE

# Therapeutic Effect of Co-Administration of Amantadine and Aspirin on Fatigue in Patients with Multiple Sclerosis: A Randomized Placebo-Controlled Double-Blind Study

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**ABSTRACT**

Fatigue is recognized as one of the most disabling and frequent symptoms of multiple sclerosis (MS). Amantadine appears to have some proven ability to alleviate the fatigue in MS. The aim of this study was to assess the efficacy of co-administration of amantadine and aspirin for the treatment of fatigue in multiple sclerosis. Forty-five ambulatory patients aged 20–50 years with a diagnosis of MS, a stable disability level ≤6 on the Kurtzke extended disability status scale (EDSS), and a mean score ≥4 on the fatigue severity scale (FSS) were eligible for the 6 weeks, randomized placebo-controlled double-blind study. Patients were randomly assigned to receive either amantadine hydrochloride (100-mg) and aspirin (500 mg) or amantadine hydrochloride (100 mg) and matching placebo twice daily throughout 6 weeks. Efficacy was evaluated by self rating scales, using the FSS. Data analysis was performed by T test, chi-square test, Wilcoxon and ANOVA tests. Mean FSS for the amantadine+aspirin group was 3.56±0.5 and mean FSS for amantadine + placebo group was 4.16±0.5 at day 30. Mean FSS for the amantadine + aspirin group was 3.36 ± 0.5 and mean FSS for amantadine + placebo group was 3.96 ± 0.5 at day 42. Amantadine and aspirin treated patients showed a significantly greater reduction in fatigue, as measured by the FSS, than those patients were treated with amantadine and placebo ($p$<0.001). Our findings demonstrate that co-administration of amantadine and aspirin was significantly better than amantadine and placebo in treating fatigue in MS patients.

**Keywords:** *Multiple sclerosis, Amantadine, Aspirin, Fatigue*

Fatigue is one of the most common neurologic disabling symptoms of multiple sclerosis (MS) and one that is often difficult to manage [1-4]. Fatigue has been defined as a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual or desired activities and affects 75%-90% of patients with MS, with as many as 46%-66% experiencing fatigue on a daily basis, and 50- 60% of patients consider fatigue their most serious symptom [5-6]. Fatigue can affect quality of life, depression, anxiety, motor function and sleep patterns and it is closely associated with perceived general and mental health, but does not correlate with patient age or score on the Expanded Disability Status Scale (EDSS) [5-10]. Despite its severity and frequency, little is known about the underlying cause. Several pharmacological and non-pharmacological treatment approaches have been tested for MS-related fatigue, with disappointing results [6,7,11]. Double-blind controlled studies of amantadine hydrochloride modafanil, 4-Aminopyridine, carnitine and pemoline have reported that these drugs have modest efficacy in reducing the fatigue of MS patients [5,7,11-14], but these studies all had significant limitations such as sample size,disase subtype ,inclusion and exclusion criteria . Amantadine is an antiviral agent, with dopaminergic properties, which produce statistically significant improvements in MS patients' reports of fatigue in some studies [6,15]. Also, Aspirin showed to reduce MS-related fatigue [16]. However, these agents have never been administered together

**Table 1.** Disease characteristics in two groups of patients

| Variables | Amantadine and Aspirin N (%) (n=21) | Amantadine and Placebo N (%) (n=24) | *p* value |
|---|---|---|---|
| Gender | | | 0.155 |
| Male | 5 (23.8) | 2 (8.3) | |
| Female | 16 (76.2) | 22 (91.7) | |
| MS type | | | 0.590 |
| Secondary progressive | 4 (19) | 5 (20.8) | |
| Relapsing Remitting | 17 (81) | 19 (79.2) | |
| EDSS Score | | | 0.262 |
| < 2 | 7 (33.3) | 6 (25) | |
| 2-5 | 4 (19.1) | 10 (41.7) | |
| > 5 | 10 (47.6) | 8 (33.3) | |

compared in a double-blind treatment study. Our aim in this study was to assess the efficacy of the combination therapy of aspirin and amantadine on fatigue in MS patients.

## MATERIAL AND METHODS

This was a randomized placebo-controlled double-blind study (Iranian Randomized Clinical Trial number was 201112208430N3). Patients with MS were enrolled in this study at Shafa Hospital in Kerman, Iran. Ethical approval for this study was obtained from the Health Research Ethics Board of Kerman University of Medical Sciences. Patients were enrolled after having given written informed consent. Eligibility for enrollment was determined at the screening visit 1 week before the baseline visit. We screened men and women aged between 20 and 50 years and had an EDSS score of 6.0 or less. To assure that only patients with fatigue participated, only those patients with a baseline Fatigue Severity Scale (FSS) score of 4.0 or more were entered. The FSS (a one-dimensional scale) is probably the most widely used fatigue rating scale. It consists of 9 items, scores ranging from 1 (complete disagreement) to 7 (complete agreement) with higher scores indicating more severe fatigue. Mean FSS scores 4–5 are thought to indicate "borderline fatigue" and mean FSS scores ≥4 "fatigue" [5]. Fatigue had to have persisted as a problem for more than 2 months and subjects should have FSS score of 4.0 or more in the screening visit. Patients with current or recent (within 2 months) use of medications that might influence fatigue (benzodiazepines, imipramine, azathioprine, or cyclophosphamide) or the following medications were excluded: stimulants, sedative-hypnotics, major tranquilizers, β-blockers, immunosuppressants, non steroidal anti inflammatory drugs, steroids and IFN-β. Other exclusion criteria were: pregnancy, congestive heart failure, renal or hepatic impairment, epilepsy, diabetes mellitus, active gastric or duodenal ulcer, psychiatric disorder, alcohol or drug abuse, major depression, asthma, narcolepsy, other pathology possibly contributing to fatigue such as anaemia or hypothyroidism and unwillingness to discontinue amantadine or aspirin treatment. Patients were randomly assigned to receive either amantadine hydrochloride (in 100-mg tablets) and aspirin (500 mg) or amantadine hydrochloride (100 mg) and matching placebo twice daily throughout 6 weeks. The administration of the drug and placebo was managed by a physician who was unaware of the research protocol, except for maintaining a record of the research medication that the patient was currently receiving (bottle A or bottle B). The patients were also blinded to the study medication with preprinted medication code labels. Patients were questioned regarding side effects when they returned for testing and medication after each treatment period. Data on demographics, disease course and disease characteristics were obtained at baseline FSS scores were assessed at day 0, day 30 and at the end of the treatment (day 42).T test and chi-square test were used to compare group means when necessary assumptions were met. The primary analysis of differences in FSS was performed using non-parametric Wilcoxon test for dependent variables. Treatment effects between groups were analyzed for days 0, 30 and 42 (immediately before, during, and immediately after treatment) with a repeated-measures ANOVA procedure and planned post-hoc contrasts. In addition, the correlation between EDSS and FSS at the beginning of the study was calculated by Pearson correlation test. Data analysis was performed by SPSS 16.0. The level of significance was set at 0.05. Data are given as means ± SD unless otherwise indicated.

## RESULTS

All Forty-five patients (38 women and 7 men) completed the study (mean age 33.1 ± 7.4 years; mean disease duration 50.9 ± 36.8 months). Thirty-six patients had relapsing remitting (RR) MS and 9 had secondary progressive (SP) MS. As shown in Tables 1 and 2, two treatment groups were similar regarding age, gender distribution, duration of MS, type of MS; EDSS score, or mean FSS. At the commencement of the study, there was no significant linear correlation between EDSS and FSS in MS patients ($r$ = -0.224, $p$ = 0.140).

**Table 2.** Patient demographic variable and disease characteristics in two treatment groups

| Variables | Amantadine and Aspirin (n=21) | Amantadine and Placebo (n=24) | *p* value |
|---|---|---|---|
| Age (year) | 32.05 ± 8.06 | 34.04 ± 6.9 | 0.379 |
| Disease Duration (month) | 43.1 ± 26.2 | 57.8 ± 43.5 | 0.173 |
| Duration of Fatigue (week) | 32.95 ± 19.9 | 33.5 ± 21.06 | 0.929 |
| Last attack (week) | 13.6 ± 12.7 | 13.3 ± 17.2 | 0.950 |

The data are expressed as mean ± standard deviations.

**Table 3.** Mean scores for the amantadine + aspirin and amantadine + placebo groups on the Fatigue Severity Scale (FSS) throughout study visits

| Variables | Amantadine and Aspirin (n=21) | Amantadine and Placebo (n=24) | *p* value |
|---|---|---|---|
| FSS | | | |
| Day 0 | 5.266 ± 0.5 | 5.36 ± 0.48 | 0.81 |
| Day 30 | 3.56 ± 0.5 | 4.16 ± 0.5 | <0.001* |
| Day 42 | 3.36 ± 0.5 | 3.96 ± 0.5 | <0.001* |
| *p* value | <0.001 | <0.001 | |

*Significant. The data are expressed as mean ± standard deviations.

Prior to initiation of treatment, fatigue as measured by the FSS significantly declined in both groups between the initial and the second study visit, 1 month later (F = 8.8, $p = 0.000$).

During the treatment course, patients experienced significant reduction in fatigue as measured by the FSS (F = 10.1, $p = 0.000$) which was also, dependent of treatment group assignment. The improvements in fatigue were greater in the treatment group than in the placebo group in both follow up visits. Therefore, clinical improvement in these measures can be attributed to synergic effects of aspirin (Table 3, Fig 1). Side effects leading to study withdrawal occurred in none of the patients.

## DISCUSSION

This is the first study to directly compare amantadine, with aspirin and amantadine combination therapy on MS–related fatigue. Our study demonstrated a significant decrease on the Fatigue Severity Scale in the MS group receiving amantadine and aspirin opposed to the amantadine and placebo group after 6 weeks of treatment (Fig 1). This finding did not correlate with gender, MS subtype, disease duration and EDSS Score (Tables 2 and 3). At present, some pharmacological and non-pharmacological treatments are available for MS-related fatigue [6,17,18]. Effectiveness of both pharmacological and psychosocial/psychological interventions was modest at best and often absent [19]. The first-line agents consist of amantadine and modafinil [11,19,20]. Amantadine was superior to placebo on a previously validated self-report MS fatigue measure and the patients' verbal reports [21, 23]. Four short term studies indicated that fatigue was reduced with amantadine treatment in 20%-40% of patients with MS who had mild to moderate disability [5,24]. Based on the results as reported in a meta-analysis performed by Branas et al, there is an overall tendency to positive results with amantadine in all trials [7]. On the other hand, the results of some studies favored aspirin for Modified Fatigue Impact Scale scores and treatment preference [16,25]. Wingerchuk in a double-blind crossover study (30 patients) showed that fatigue was reduced with aspirin [16]. Also, Wingerchuk *et al.* in another study on 3 women with luteal phase–associated MS pseudoexacerbations showed asprin would relieve MS-related fatigue [25].

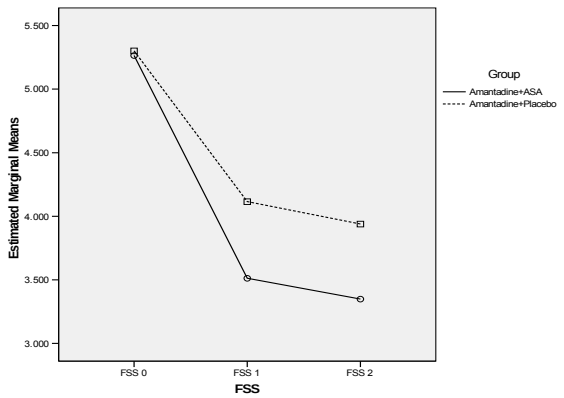


**Fig 1.** Mean FSS changes in two treatment groups throughout the study period.

The mechanisms underlying fatigue in MS are still poorly understood [15,22,26]. From a pathophysiological point of view, fatigue in MS is multifactorial, involving dysregulation of the immune system, alterations in the nervous system related to disease progression, neuroendocrine and neurotransmitter modifications, and other issues comprising physical deconditioning, sleep disturbances, depression and medication side effects [22,27-29]. Also,

there is now strong evidence to suggest that fatigue results from reduced voluntary activation of muscles by means of central mechanisms. Given that axonal demyelination is a pathological hallmark of MS, activity-dependent conduction block [ADCB] has been proposed as a mechanism underlying fatigue in MS. This ADCB results from axonal membrane hyperpolarization, mediated by the $Na^+/K^+$ electrogenic pump, with conduction failure precipitated in demyelinated axons with a reduced safety factor of impulse transmission. In addition, $Na^+/K^+$ pump dysfunction, as reported in MS, may induce a depolarizing conduction block associated with inactivation of $Na^+$ channels. These processes may induce secondary effects including axonal degeneration triggered by raised levels of intracellular $Ca^{2+}$ through reverse operation of the $Na^+$-$Ca^{2+}$ exchanger. Restoration of normal conduction in demyelinated axons with selective channel blockers improves fatigue and may yet prove useful as a neuroprotective strategy, in preventing secondary axonal degeneration and consequent functional impairment [30]. Additional factors may be physiological. It has been reported that an increase in proinflammatory cytokines may be a possible contributor to primary fatigue in MS [31] .In addition, treatment with natalizumab and IFN-β may produce secondary fatigue in MS in conjunction with an initial adverse effect of flu-like symptoms [26,31,32]. Also, it was suggested that fatigue could be caused by peripheral or central inflammation or venous insufficiency [21,28,33-36]. Proposed pathological mechanisms of fatigue in MS include neuronal factors such as dysfunction of premotor, limbic, basal ganglia or hypothalamic areas; disruption of the neuroendrocrine axis leading to low arousal, alteration in serotoninergic pathways, changes in neurotransmitter levels, and altered CNS functioning caused by a disruption of the immune response [20]. Imaging studies using positron emission tomography suggest that fatigue in MS is related to hypometabolism of specific brain areas, including the frontal and subcortical circuits [37].

The mechanism for amantadine's fatigue treatment effect is not known [18,38,39]. In one fatigue treatment study [40] that used amantadine, responders had higher levels of β-endorphin and β-lipotropin and lower levels of lactate than nonresponders. These changes may have been due to direct effects of the drug or to concomitant metabolic changes associated with lowered fatigue. Also, the mechanism of asprin on fatigue in patients with *MS* is not clear. Maybe, its efficacy is related to its anti-inflammatory property [16]. We saw a significant fatigue improvement in patients who received aspirin in addition to amantadine comparing those who used amantadine alone on FSS. It seems that this finding is secondary to different properties of each drug and co-administration of these drugs shows this nice finding. In this study, patients only were enrolled with secondary progressive and relapsing Remitting MS, but studies have failed to demonstrate an association between MS-related fatigue and the level of disability, clinical disease subtype, or gender, although recent data show an association between MS-related fatigue and depression [36,37]. Assessment of the safety profile of co-administration of amantadine and aspirin in patients with MS was of primary consideration in the design of this study, and the results of the trial showed that treatment with amantadine and aspirin was well tolerated. The small number of patients included and short duration of study are the limitations of this survey. The results of this trial, which does not have the problems of interpretation indicated for crossover trials, shows the same direction and therefore provide some reassurance of the validity of the pattern of findings.

In conclusion, this study provides preliminary results indicating that co-administration of amantadine and aspirin may be a well tolerated and effective treatment for fatigue in patients with MS. Nevertheless; more studies on a larger scale with longer duration are needed to confirm this finding.

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