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The effectiveness of amantadine and dalfampridine in improving fatigue in patients with multiple sclerosis: A randomized, double-blind, clinical trial

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Yasaman Sadeqi[1], Seyed Mohammad Baghbanian[2], Aliyeh Bazi[3], Monireh Ghazaeian[1,4], Sahar Fallah[5]

[1] Department of Clinical Pharmacy, School of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran
[2] Department of Neurology, School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran
[3] Department of Clinical Pharmacy, School of Pharmacy, Zabol University of Medical Sciences, Zabol, Iran
[4] Pharmaceutical Research Center, Mazandaran University of Medical Sciences, Sari, Iran
[5] Department of Biostatistic, Ibne Sina Medical and Educational Center, Mazandaran University of Medical Sciences, Sari, Iran

Keywords
Fatigue; Amantadine; Dalfampridine; Multiple Sclerosis; Effectiveness

Abstract

Background: Fatigue is a common complication associated with multiple sclerosis (MS). The aim of this study was to evaluate the impact of dalfampridine and amantadine on fatigue in patients with MS.

Methods: This was a randomized, double-blind, clinical trial on patients with MS. The recruited patients were adults (≥ 18 years old) diagnosed with MS; their Expanded Disability Status Scale (EDSS) was between 0.0 and 5.5, and their fatigue was confirmed by the Modified Fatigue Impact Scale (MFIS). They were randomly assigned to the amantadine (100 mg twice daily) and dalfampridine (10 mg twice daily) for eight weeks. The primary outcome was the improvement of fatigue score, and the secondary outcome was assessment of quality of life by the Short-Form Health Survey (SF-36) and any reported side effects.

Results: A total of 69 patients were recruited, and 54 of them were analyzed. The mean MFIS significantly improved in both groups after one and two months compared to baseline: amantadine: first month: 40.63 ± 14.35 (P = 0.040), second month: 36.56 ± 17.12 (P = 0.010); dalfampridine: first month: 38.29 ± 15.23 (P = 0.001), second month: 34.26 ± 18.30 (P = 0.001). However, the amount of changes from baseline was not significantly different (amantadine, P = 0.090; dalfampridine, P = 0.130).

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Corresponding Author: Monireh Ghazaeian
Email: ghazaeianm@gmail.com

The amount of changes in quality of life showed no significant improvement (P = 0.210).

Conclusion: The results showed that dalfampridine was not different with amantadine in improving fatigue in patients with MS; besides, it showed an acceptable safety profile. Therefore, it can be considered as a possible beneficial therapeutic agent in MS fatigue.

Introduction

One of the most common and debilitating symptoms in patients with multiple sclerosis (MS) is fatigue,[1] affecting between 53% and 90% of cases.[1,2] Fatigue is defined as lack of physical or mental energy or both.[3]

Fatigue has many negative effects on the lives of patients with MS. The patient frequently needs to rest and sleep, even though his/her feeling of fatigue does not improve subsequently. The person is not able to participate in activities that require long-term physical activity. These patients usually have minimal physical activity for fear of worsening fatigue and heat, which in turn intensifies their weakness, fatigue, and other health-related issues.[4] There are two types of fatigue in patients with MS: primary and secondary. Secondary fatigue in these people can worsen by heat, depression, sleep disorders, bacterial or viral infections, thyroid disorders, anemia, and some medications such as antidepressants, hypnotics, sedatives, and antispasmodics.[4,5]

Amantadine is widely used as a first-line treatment for fatigue in patients with MS.[6-8] Amantadine acts on various receptors such as cholinergic, dopamine, and N-methyl-D-aspartate (NMDA) glutamate, but the mechanism by which it affects patients' fatigue is still unknown. Side effects reported with this drug are mild and include nausea and dizziness, which do not require treatment.[9]

Dalfampridine is used in the symptomatic treatment of walking impairment in patients with MS.[10] A recent study showed that this medicine could also reduce fatigue in patients with MS.[11]

Despite the high prevalence of fatigue in patients with MS and its potential impact on the quality of daily life as well as factors affecting the severity of this symptom in different patients, so far limited studies have been done on available treatment options to improve patients' symptoms. Furthermore, due to limited evidence, no therapeutic agent such as amantadine has been approved for treating MS fatigue. In many cases, the results of studies are not consistent with each other. The aim of the present investigator-initiated, randomized, double-blind, mono-center trial was to compare the effectiveness of amantadine and dalfampridine in improving fatigue in patients with MS.

Materials and Methods

Study design: This randomized, double-blind clinical trial was performed on two treatment groups (Amantadin, Amin Company vs. Dalfampridine, Cinnagen Company) in MS patients with fatigue. This study was conducted in the Multiple Sclerosis Clinic of Ibne Sina Teaching Hospital, Sari, Iran. It was approved by the Ethics Committee of Mazandaran University of Medical Sciences, Sari (IR.MAZUMS.REC.1399.325) and was performed under the ethical standards of the Declaration of Helsinki. All participants provided their written informed consent before enrolment. The study was also registered in the Iranian Registry of Clinical Trials (IRCT20190804044429N2).

Patients were randomized to one of the treatment groups and received amantadine (100 mg/day orally in the first two weeks and then 100 mg twice daily) or dalfampridine (10 mg/day for the first two weeks and then 10 mg twice daily). The duration of treatment for both groups was eight weeks. All patients were evaluated at baseline and after one and two months of treatment. All side effects experienced by the patients were recorded during the study period.

Inclusion and exclusion criteria: Patients were included if they met the following criteria: adults (≥ 18 years old), diagnosis with MS according to the McDonald criteria 2017,[12] the Expanded Disability Status Scale (EDSS) score between 0.0 and 5.5, and clinical evidence of fatigue established by the Modified Fatigue Impact Scale (MFIS) score over 33.

On the other hand, the exclusion criteria included severe depression, hypothyroidism, severe anemia [hemoglobin (Hb) < 9 g/dl], breastfeeding or pregnancy, history of cerebral or cardiovascular ischemic disease, uncontrolled blood pressure, narcolepsy, history of seizure, taking drugs that could have an impact on fatigue including antipsychotic agents, monoamine oxidase inhibitors, benzodiazepines, tricyclic antidepressant drugs, anticonvulsants, beta-blockers, and barbiturates, MS relapse treated with corticosteroids in the last 30 days, and finally hypersensitivity reaction to dalfampridine, amantadine, or other study components.

Sample size, randomization, and blinding: Following the study of Khazaei et al.[13] regarding fatigue score, we estimated the sample size at 22 patients in each group by considering a power of 80% and a significance level (α) of 0.05. Assuming an attrition rate of 10% through the study period, we selected a sample size of 27 for each group. The patients were randomized based on simple computerized randomization to receive amantadine or dalfampridine. The principal neurologist, researchers, statistician, and patients were blinded to treatment assignments.

Outcome measurement: The primary outcome was evaluated at baseline as well as after one and two months of treatment using a self-administered measure of fatigue, namely the 21-item MFIS (score range: 0-84, with lower scores indicating less fatigue). This instrument was used to evaluate the primary outcome of the present study, i.e., improvement in fatigue caused by MS.[14] The secondary outcome was the assessment of the health-related quality of life, which was measured by the self-administered 36-item version of the short-form health survey (SF-36) questionnaire. SF-36 evaluates the two health dimensions (physical and mental) using two composite scores: the physical composite score (PCS) and the mental composite score (MCS).[15] Besides, we monitored recruited patients weekly and recorded patient-reported side effects. All scales were validated regarding validity and reliability of Persian versions.[16,17]

Data were statistically analyzed in SPSS software (version 22, IBM Corporation, Armonk, NY, USA). Quantile-quantile (Q-Q) plot method and Kolmogorov-Smirnov test were used to investigate the normal distribution of data. The mean and standard deviation (SD) were used to describe quantitative data, and number and percentage were used for qualitative data. T-test and chi-square tests or, if appropriate, non-parametric tests were used to compare the mean scores between the two groups. Paired t-test was used to compare the intragroup effects, and the generalized estimating equations (GEE) method was used to compare the intergroup effects. Notably, P-values less than 0.05 were considered statistically significant.

Results

Between June 12, 2020 and February 25, 2021, a total of 69 patients were examined and 54 of them completed the study protocol and were analyzed (Figure 1). No differences were observed between the two groups regarding demographics and clinical characteristics. Baseline characteristics of patients are presented in table 1.

The fatigue score was evaluated using the MFIS instrument, which showed no significant differences between the two groups during the study intervals (P = 0.860, P = 0.270, P = 0.280 (Table 2). In contrast, while the amount of changes from baseline differed significantly within each group at study intervals (Table 2), these changes were not significantly different between the two groups of the study (P = 0.090, P = 0.130) (Table 3).

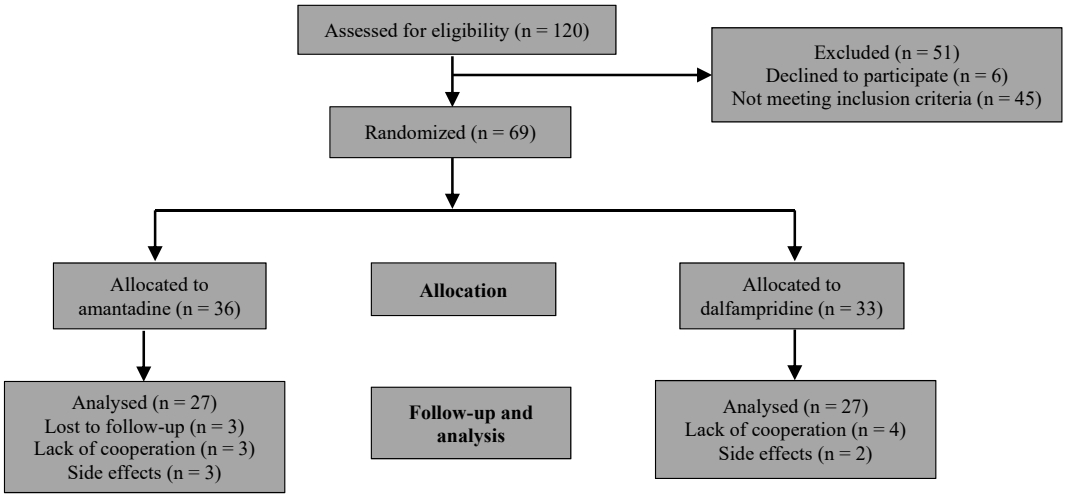

Figure 1. Flowchart of study design and patient assignments

Table 1. Baseline characteristics

Variable	All patients	Amantadine (n = 27)	Dalfampridine (n = 27)	P
Age (year) (Mean)	-	35.37	32.93	0.240
EDSS (Mean)	-	1.77	1.14	0.100
Sex [n (%)]				
Men	9 (16.7)	3 (11.1)	6 (22.2)	0.270
Women	45 (83.3)	24 (88.9)	21 (77.8)	
MS type [n (%)]				
CIS	6 (11.1)	3 (11.1)	3 (11.1)	NA
PPMS	1 (1.9)	0 (0)	1 (3.7)	
PRMS	1 (1.9)	1 (3.7)	0 (0)	
RRMS	43 (79.6)	20 (74.1)	23 (85.2)	
SPMS	3 (5.6)	3 (11.1)	0 (0)	
DMDs [n (%)]				
Dimethyl fumarate	8 (14.8)	5 (18.5)	3 (11.1)	NA
Fingolimod	12 (22.3)	3 (11.1)	9 (33.3)	
Glatiramer acetate	4 (7.4)	1 (3.7)	3 (11.1)	
Interferon beta 1-a	6 (11.1)	2 (7.4)	4 (14.8)	
Interferon beta 1-b	6 (11.1)	3 (11.1)	3 (11.1)	
Ocrelizumab	1 (1.9)	0 (0)	1 (3.7)	
Rituximab	13 (24.1)	9 (33.3)	4 (14.8)	
Teriflunomide	4 (7.4)	4 (14.8)	0 (0)	

EDSS: Expanded Disability Status Scale; MS: Multiple sclerosis; CIS: Clinically isolated syndrome; RRMS: Relapsing-remitting multiple sclerosis; SPMS: Secondary-progressive multiple sclerosis; PPMS: Primary-progressive multiple sclerosis; PRMS: Progressive-relapsing multiple sclerosis; DMDs: Disease modifying drugs; NA: Not available

Concerning quality of life, the results showed no significant difference in the mean score of SF-36. In both groups, the results improved by increasing the score of SF-36 in the second month versus the first month, but not statistically significant (P = 0.600 for amantadine group, P = 0.590 for dalfampridine group) (Table 2). Most reported side effects were mild. However, two patients in the dalfampridine group and three patients in the amantadine group were excluded from the study due to the side effects. In the dalfampridine and amantadine group, the most frequent side effects were dizziness and dyspepsia, respectively (Table 4).

Discussion

The results of our study showed that fatigue score improved in both study groups, and dalfampridine revealed beneficial effects similar to amantadine; therefore, it can be considered as one therapeutic agent for MS patients with fatigue.

Several mechanisms are believed to have a role in the pathogenesis of MS-related fatigue; they include secretion of proinflammatory cytokines, endocrine disturbances, axonal damage, and changed patterns of cerebral activation.[18] Amantadine has been used for many years as the first line of pharmacological treatment for MS-related fatigue, but the reports about its effectiveness are contradictory. In the study of Nourbakhsh et al., 136 patients were assigned to receive amantadine (maximum 100 mg twice daily), modafinil (maximum 100 mg twice daily), methylphenidate (maximum 10 mg twice daily), or placebo at six-week intervals.

Table 2. The study outcomes evaluation between two groups

Variables	Amantadine	Dalfampridine	P*	P**	P***
MFIS					
Baseline	46.74 ± 7.57	47.22 ± 11.71	0.860	-	-
First month	40.63 ± 14.35	38.29 ± 15.23	0.270	0.040	0.001
Second month	36.56 ± 17.12	34.26 ± 18.30	0.280	0.010	0.001
Quality of life (SF-36)					
Baseline	41.04 ± 15.11	42.29 ± 16.48	-	-	-
Second month	42.22 ± 17.72	44.44 ± 13.47	0.210	0.600	0.510

Values are shown by mean ± standard deviation (SD)
*Between groups; **Within amantadine group; ***Within dalfampridine group
MFIS: Modified Fatigue Impact Scale; SF-36: 36-item Short-Form Health Survey

Table 3. The analysis of amount of Modified Fatigue Impact Scale (MFIS) changes from baseline between two groups

Time	Amantadine	Dalfampridine	P
First month	-5.07 ± 2.35	-10.67 ± 2.23	0.090
Second month	-7.52 ± 2.67	-12.96 ± 2.36	0.130

Values are shown by mean ± standard deviation (SD)

The results of the study showed that none of the medications was superior to placebo in improving MFIS; besides, unlike the placebo group, most of the patients in the intervention groups reported adverse events.[19] Although our study findings showed that both amantadine and dalfampridine improved MFIS, we did not make a comparison with a placebo group in this regard, which might affect the interpretation of the results.

Table 4. Reported side effects during the period of the study

Side effects	Dalfampridine	Amantadine
Headache	3	0
Nausea	3	1
Flushing	0	1
Urinary retention	0	1
Pruritus	1	1
Dizziness	5	0
Sedation	0	1
Insomnia	1	0
Dyspepsia	3	2
Palpitation	1	0
Irritability	1	0
Muscle spasm	0	2
Weakness	2	1
Chilling	1	0

Ledinek et al. evaluated the effects of modafinil, acetyl-L-carnitine, amantadine, and placebo on 60 MS patients with fatigue.[8] The patients were assigned to receive 200 mg modafinil, 2 g acetyl-L-carnitine, 200 mg amantadine, or placebo for four weeks. MS-related fatigue was assessed by MFIS and the findings demonstrated that, compared to placebo, one month of treatment with amantadine significantly improved the mean fatigue score (mean differences: 17.3, P = 0.001) and quality of life as measured via the SF-36 (mean differences: 5.8, P = 0.039). Although similar to our study, the mean difference of fatigue score from baseline in the amantadine group was lower after one month of treatment, the quality of life in our study did not significantly improve. Single-blind design, disregarding contributing factors such as depression, and short follow-up were the major limitations of the study of Ledinek et al. that should be considered when interpreting the results.

There is some evidence that treatment with dalfampridine is effective for MS-related fatigue,[11,19,20] yet several studies have concluded that dalfampridine-extended release (ER) does not improve MS-related fatigue.[21-23]

In the cohort study by Mitsikostas et al., 92 of 102 recruited patients with MS who received prolonged-release fampridine (PR-FAM) were studied. As primary outcomes, cognition, depression, fatigue, and quality of life were assessed in these patients. The results showed that six months of treatment by PR-FAM could improve the mean score of all primary outcomes from baseline.[20]

In a recent study by Rocca et al., the efficacy of dalfampridine, amantadine, and placebo on MS-related fatigue was evaluated by 3-Tesla resting state functional connectivity (RSFC) magnetic resonance imaging (MRI). MFIS and RSFC were evaluated at baseline and after four weeks of treatment in 45 patients. In the dalfampridine group, RSFC changes correlated with the concomitant decline in the MFIS score, but fatigue improvement was not related to the administered treatment.[24] Short follow-up and small sample size were the major limitations of this study.

Consistent with previous studies,[8,20,24] the most commonly reported adverse effects in our study were dyspepsia and dizziness, which did not require treatment.

Our study has some limitations, including the small sample size and short follow-up. Moreover, as a contributing factor of fatigue severity, sleep disorders were not assessed in the present study.

Conclusion

Dalfampridine and amantadine have similar effects on fatigue in patients with MS. The mean differences of fatigue scores (according to MFIS) improved in the two study groups, but no significant benefit was noted in terms of quality of life. Both study groups tolerated the interventions well without showing any alarming sign.

Conflict of Interests

The authors declare no conflict of interest in this study.

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