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Short-term impact of fampridine on motor and cognitive functions, mood and quality of life among multiple sclerosis patients

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ABSTRACT

Objective: Previous studies have predominantly investigated the effect of fampridine on lower extremities motor functions while data on its impact on other symptoms of multiple sclerosis (MS) are scarce. The aim of our study was to assess the impact of fampridine on walking, arm/hand function, fatigue, cognitive function, mood and quality of life among responders.

Methods: Our prospective non-randomized study included 30 patients with different types of MS, aged 35–70, EDSS value 3.5–6.5. They were treated with 10 mg of fampridine twice daily. The examinations were performed before the treatment, after 14 days, when responders were defined by T25FW (Timed 25-Foot Walk) and 2-min walk test (2MWT) was performed, and after 28 days of treatment, when only the responders were examined. Standardized protocols and questionnaires were used to evaluate the impact of fampridine on walking speed (T25FW, 2MWT), arm/hand function (9-HPT – Nine-Hole Peg Test), cognitive function (PASAT – Paced Auditory Serial Addition Test), total MSFC score (Multiple Sclerosis Functional Composite), fatigue (MFIS – Modified Fatigue Impact Scale), mood (BDI – Beck Depression Inventory) and quality of life (EQ-5D index, EQ-VAS – Euro Quality of Life – 5 Dimension questionnaire and visual analogue scale) in responders.

Results: Response rate was 56.7%. Average improvement of T25FW and 2MWT after 14 days of treatment in responders was 3.6 s (34.5%) and 37.4 m (42.3%), respectively. This improvement persisted after 28 days of treatment. In non-responders there was no significant improvement of T25FW after 14 days ($p = 0.689$), but there was improvement of 2MWT for 13.4 m (14.3%) ($p = 0.000$). After 28 days of treatment significant improvement among responders occurred in total MSFC score ($p = 0.001$), 9-HPT ($p = 0.002$), BDI ($p = 0.005$), MFIS total score ($p = 0.003$), physical ($p = 0.001$), cognitive ($p = 0.008$) MFIS subscales, and EQ-5D index ($p = 0.012$). There were implied trends towards improvement in EQ-VAS and psychosocial MFIS subscale, yet not significant ($p = 0.057$ and $p = 0.127$, respectively). There was no statistically significant improvement of PASAT ($p = 0.432$).

Conclusions: The results of our study highlight the potential of fampridine for improving not only walking speed but also arm/hand function, physical and cognitive fatigue, mood and quality of life. There was no objective improvement of cognitive function. Further placebo-controlled studies will be needed for precise definition of fampridine's action beyond its impact on walking.

1. Introduction

Fampridine is the first drug licensed to improve walking ability in adult patients with all types of multiple sclerosis (MS) [1,2]. Fampridine, which is a prolonged-release form of 4-aminopyridine, is a fat soluble molecule that has the ability to cross the blood-brain barrier and acts as an inhibitor of voltage-gated potassium (Kv) channels [1]. Demyelination of the axons, characteristic of MS, leads to Kv channels exposure and consequent leakage of potassium ions from the nerve cells. That causes the resting membrane potential to move towards a more negative value and it is therefore more difficult to reach the threshold for firing and conduction of action potentials [3]. By binding to exposed Kv channels in demyelinated axons, fampridine inhibits the efflux of potassium ions, thereby improving the conduction of action potentials, synaptic and neuromuscular transmission. Fampridine may also have an

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immunomodulatory effect via blockade of Kv channels in immune cells involved in the pathogenesis of MS [4].

Fampridine leads to clinical improvement only in certain patients with MS. According to different studies the percentage of so-called responsive patients (responders) ranges from 30% to 74% [5–8]. Responsiveness to fampridine is determined after 14 days of treatment based on 20% [9] or 25% [2] improvement of walking speed at Timed 25 Foot Walk test (T25FW). Previous studies showed significant improvement in walking speed, lower extremity muscle strength and patients' perspectives on their ambulatory disability among responders [5,6]. On the other hand, data on the effects of fampridine on other various symptoms of MS are lacking or are discordant. Some suggest that the drug may also improve fatigue, arm/hand function, mood, cognitive function and quality of life [7,8,10–18].

The aim of our study was to assess the impact of fampridine on arm/hand function, fatigue, cognitive function, depression and quality of life among responders in addition to study its impact on walking ability.

2. Materials and methods

A prospective non-randomized study was conducted from 2013 to 2014 in the Centre for Multiple Sclerosis at the Department of Neurology, University Clinical Centre Ljubljana, Slovenia as a named patient programme. The patients with clinically definite MS, who fulfilled the entry criteria (EDSS of 3.5–6.5 and clinically significant impairment of ambulation) were invited to participate in the study. All the patients signed a written informed consent to participate in the study which was approved by Republic of Slovenia National Medical Ethics Committee and was performed in accordance with the Declaration of Helsinki. Thirty-two patients entered the study. Two people withdrew from the study prematurely due to acute illness and they were not included in the data analysis. The final research group therefore included thirty patients (15 women) with an average age of 48.3 ± 10.3 years and median EDSS value of 6 (5.0–6.5). Eleven patients (36.7%) had primary progressive (PPMS), eighteen (60.0%) secondary progressive (SPMS) and one (3.3%) relapsing-remitting (RRMS) type of MS.

Examinations were performed prior to treatment, after 14 and 28 days of treatment with fampridine (10 mg every 12 h). At the initial clinical visit the patients were acquainted with the drug administration and its possible side effects. They then filled in three questionnaires: The EQ-5D health-related quality of life questionnaire (Euro Quality of Life – 5 Dimension), Beck Depression Inventory (BDI) and Modified Fatigue Impact Scale (MFIS). Patients' arm/hand function was then tested with 9-HPT (Nine-Hole Peg Test), cognitive function was assessed by PASAT (Paced Auditory Serial Addition Test) and walking speed was tested by T25FW (Timed 25-Foot Walk) and 2-min walk-test (2MWT). 9-HPT, PASAT and T25FW are a part of MSFC protocol (Multiple Sclerosis Functional Composite). At the second visit, after 14 days of treatment, responders were defined based on 25% or greater improvement of T25FW. In addition, 2MWT was performed in all the patients. Fampiridine was introduced as a regular therapy to responders and they were invited to attend the third visit. Fampridine treatment was discontinued in the group of non-responders and their participation in the study was completed. During the third visit, after 28 days of treatment, responders underwent the same tests as performed at the initial visit. All tests in each patient were performed in the same order at the same time of day using the same walking aids. During the study the subjects could receive all regular MS therapy, including immunomodulatory and symptomatic therapy, whereas introduction of new drugs was not allowed.

2.1. MSFC

All tests of the MSFC protocol were performed according to the recommendations of the National Multiple Sclerosis Association Society from 2001 [19]. We used PASAT-3 test, sample A on MSFC protocol to assess cognitive function. We analyzed the results of each test separately, using the average time value of two consequent T25FW trials, average time value of four consequent 9-HPT trials (two by dominant and two by non-dominant hand) and the absolute value of PASAT result. According to the protocol, the time limit per trial for 9-HPT is 300 s. If the patient was not able to complete a test trial within this limit, we attributed the time of 300 s for this trial.

We also calculated the total MSFC score as described in the MSFC protocol, using the following formula [19]:

$$\text{MSFC Score} = \frac{\{(\text{Average}(1/9 - \text{HPT}) - 0.0439/)0.0101 + \{-(\text{Average } 25 - \text{Foot Walk} - 9.5353)/11.4058\} + (\text{PASAT} - 3 - 45.0311)/12.0771\}}{3.0}$$

2.2. 2-Min Walk Test (2MWT)

The 2MWT was performed as described elsewhere [20].

2.3. MFIS

The standard 21-item version of the MFIS scale, divided into three subscales: cognitive (MFIScog), physical (MFISphy) and psychosocial (MFISps), was carried out as described by National Multiple Sclerosis Society in 1997 [21]. We statistically analyzed the results of each subscale separately and also the total sum of all subscales together.

2.4. BDI

A modified Slovenian version of the latest BDI, which meets the criteria of depression according to fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM IV) was used. In this version, the question about libido/sex life was omitted resulting in a total sum of 60 instead of 63 points. The questionnaire was used to ascertain whether short-term fampridine treatment has any impact on mood disorders in patients with MS. We did not use BDI to determine the gravity of depression.

2.5. The EQ-5D health-related quality of life questionnaire

The Slovenian translation of the EQ-5 D questionnaire, which consists of a questionnaire and a visual analogue scale (EQ-VAS), was used [22]. The health states acquired from the questionnaire were converted to EQ-5D index value using The EQ-5D health states value set for Slovenia [23]. We statistically analyzed the impact of fampridine on EQ-5D index and EQ-VAS separately.

2.6. Statistical analysis

Data were analyzed by SPSS program for Windows®, version 20.0. The normality of distribution was checked using q–q plots, histograms and Shapiro–Wilk test. In the cases of normal distribution, *t*-test for dependent samples was used, otherwise Wilcoxon-signed rank test was performed (only for the comparison of 9-HPT test and EQ-5D index). All the data is presented as mean ± standard deviation. Significance was assumed for $p < 0.05$ in all tests.