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Research article

Assessment of motor function in patients with multiple sclerosis treated with Fampridine using motor-evoked potentials

Dan Trofin [1], Ilie Onu [1,2,†], Calin Corciova [1], Cristiana Onita [1], Daniela Marilena Trofin [3], Bogdan Ignat [4,†], Kristo Xhardo [5], Carmina Liana Musat [6,7,*], Mihaela-Alina Cristuta [8,*], Andrei Ciobica [9], Daniel-Andrei Iordan [10,11]

1. Department of Biomedical Sciences, Faculty of Medical Bioengineering, University of Medicine and Pharmacy "Grigore T. Popa" Iasi, 700454 Iasi, Romania
2. Department of Physiotherapy, Elipetro Med Clinic, 610119 Piatra Neamt, Romania
3. Clinical Recovery Hospital Iasi, 700661 Iasi, Romania
4. Department of Neurology, "Grigore T. Popa" University of Medicine and Pharmacy, Iași, Romania
5. Faculty of Physical Education and Sports, National University of Physical Education and Sports, 060057 Bucharest, Romania
6. Department of Morphological and Functional Sciences, Faculty of Medicine and Pharmacy, "Dunarea de Jos" University, 800008 Galati, Romania
7. "Sf. Apostol Andrei" Clinical Emergency County Hospital, 800578 Galați
8. Department of Physical and Occupational Therapy, "Vasile Alecsandri" University of Bacau, 600115 Bacau, 25 Romania;
9. Department of normal and pathological physiology, "Grigore T. Popa" University of Medicine and Pharmacy, 700115 Iași, Romania
10. Department of Individual Sports and Kinetotherapy, Faculty of Physical Education and Sport, "Dunarea de Jos" University of Galati, 800008 Galati, Romania
11. Center of Physical Therapy and Rehabilitation, "Dunărea de Jos" University of Galati, 800008 Galati

* Correspondence: carmina.musat@ugal.ro; cristuta.alina@ub.ro
† This author contributed equally to this work with the first author.

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Abstract: 1) Background: the purpose of the study is to consider the utility of Transcranial Magnetic Stimulation (TMS) in patients with Multiple Sclerosis (MS) and walking impairment, treated with Fampridine, as correlated with the 25-Foot-Walk test (T25-FW). Clinical benefits are usually seen within 2-4 weeks of starting treatment, and if not, discontinuation is required. (2) Methods: fifteen MS patients with gait impairments, classified between 3-5 and 7 on the EDSS (Expanded Disability Status Scale), were enrolled in the study and investigated by T25-FW and TMS. Assessments were performed before Fampridine 10 mg twice daily, at 5 and 12 days thereafter, and at 1 and 3 months later. The mean age was 42.8 years and the mean disease duration was 12.06 years. (3) Results: The evaluated patients recorded a 2.1-second improvement in gait measured on T25-FW after the first 12 days in 9 patients, which correlated with a 2-millisecond improvement in central motor conduction time (CMCT). In the other 6 patients, there was no visible clinical improvement. The CMCT, decreased by 0.5 ms and motor conduction velocity by 1 millisecond in 4 of these 6 patients. Fampridine administration was continued in the 4 cases. At the end of the 3-month period, their walking speed measured as on the T25-FW also improved by 2 sec. (4) Conclusions: the amelioration of TMS parameters anticipated the improvement of speed on the T25-FW. In spite of the early false negative clinical response, electrophysiological findings could predict a future clinical improvement if treatment is continued.

Keywords: Transcranial Magnetic Stimulation, multiple sclerosis, walking speed, Fampridine.

1. Introduction

Multiple sclerosis (MS) is a chronic neurological disease based on the pathophysiological phenomena of demyelination among the Central Nervous System (CNS), which leads to an accumulation of both physical and cognitive disabilities. MS is characterized by significant gait impairment, which is the main clinical feature. This burdensome feature is quantified using the Expanded Disability Status Scale (EDSS).

Neurodegeneration and development of symptoms in MS are based on ion channel dysfunctions [1]. There are several studies of Na+ and K+ channels that promote ion channel modulation as a promising therapeutic strategy in MS. Therefore, it is known today about the pathological Na+ channel blockade during the acute inflammatory attack, as well as the contribution of increased Na+ channel expression to the cascade of events leading to neurodegeneration, thus the pharmacological approach of this phenomenon in clinical trials. Nonetheless, the demyelination process is based on the physiopathology of the K (+) channels, and modulation of the fast K (+) conductance, in other words, the changes in axonal excitability that shift towards normal values, translate into symptoms amelioration [2].

Fampridine in the dose of ten milligrams twice daily may improve gait speed and endurance, as compared to baclofen, however, the positive results seem to relate to less than half of patients [3]. Fampridine ameliorates conduction in demyelinated axons by enhancing synaptic transmission as a voltage-dependent potassium channel blocker. Its result of improvement of walking speed seems independent of improvement of disability [4].

The walking speed and endurance can be quantified using walking test measurements, such as the 25-foot walk test (T25FW), which is considered to be an objective and reliable evaluation tool fulfilling both efficacy and tolerability criteria [5-7].

In the vast majority of cases, Fampridine's efficacy has been assessed by the use of the T25FW [8]. The most utilized therapeutic indication is the improvement of a walking disability associated with an EDSS ranked between 4 and 7 [9].

Fampridine seems to be usually well tolerated providing clinical benefit on different impaired gait patterns according to the T25W: para paretic, hemiparetic, or ataxic [7, 10].

The clinical benefit also influenced the EDSS of these patients by significantly decreasing its value. Nevertheless, even in such prospective studies cases that reveal the positive influence of Fampridine in the clinical response, one must also rely on possible mild-moderate adverse events that can occur in up to half of the respondents, as well as accepting the fact that a gait pattern predictive for the clinical efficacy couldn't be identified so far [10]. Assessment of nerve excitability may however, in some cases, contribute to identifying patients most likely to respond to Fampridine [11].

Brambilla L. et al suggest by a multi-instrumental approach based on clinical evaluation scales correlated with neurophysiological methods (Motor Evoked Potential) and Diffusion Tensor Imaging before and after 14 days of treatment, that the modified neurophysiological and neuroradiological parameters correlate with the clinical and subjective improvement of the motor results, thus proposing electrophysiology and neuroimaging as useful tools for assessment of effectiveness and follow-up of MS patients with walking difficulties [12].

2. Material And Methods

2.1 Background

Our pilot study was performed in the Department of Physiotherapy Elipetro Med Clinic from Piatra Neamt and the Neurology Clinic from The Rehabilitation Hospital in Iași, during December 2021 and February 2023. The included patients had Relapse Remitting Multiple Sclerosis (RRMS) and Secondary Progressive Multiple Sclerosis (SPMS), according to the MacDonalds criteria of 2010. The following criteria were considered for the inclusion in the study: EDSS, the presence of walking impairment as a result of disease evolution as opposed to acute impairment as a result of a relapse, as well

as the absence of contraindications for performing Transcranial Magnetic Stimulation (TMS), especially any history of epileptic discharges.

The study protocol was approved by the Elipetro Med Clinic Committee with no. 45/06 December 2021. All patients were properly informed, agreed with their participation in the study, and signed a consent form. The included patients were tested clinically and with electrophysiological methods, as well as being well monitored for any possible adverse events during the treatment.

2.2 The Electrophysiological Study

We investigated 15 patients with MS and walking impairment, with EDSS between 3.5 and 7, averaging 4.6. 13 patients had RRMS, while the other 2, had SPRR. The age was between 30 and 55 years old, with an average age of 42.8 years. Eight patients were female, representing 53.33%, and 7 male patients, 46.67%. None of the female participants were pregnant during the study. Five of the 15 patients had paraparesis motor deficits, 4 patients had motor deficits on the right side of the body, 3 patients on the left side of the body and 3 patients had tetraparesis deficits. The duration of the illness inside the lot was between 5 and 23 years, with an average of 12.06 years.

The purpose of the study was to investigate a possible correlation between clinical (T25-FW) and paraclinical (TMS) parameters, related to the improvement of walking, after administration of Fampridine. The hypothesis is that early electrophysiological findings can act as predictors of the future clinical increase of speed in patients who do experience clinical improvements. On the other hand, for patients with no evidence of improvement of walking on the T25-FW after 2 weeks of treatment, but amelioration of the Motor Evoked Potential (MEP) latencies at TMS, further administration of Fampridine might be predicting a possible future clinical amelioration.

TMS was performed using the Magstim Rapid® device. We used the butterfly-shaped coil and the round-shaped coil. The butterfly-shaped coil generates a magnetic field of up to 1.2 Tesla, whereas the round-shaped coil generates a specific cone-shaped magnetic field, thus leading to diffuse stimulation. This is a good reason to use this round-shaped coil in current clinical practice for a more appropriate stimulation of the cervical and lumbar areas of the spine. MEP was obtained by placing surface electrodes on the abductor digit minimi muscle in the upper limb and on the tibialis anterior muscle in the lower limb. For follow-up of the evolution of electrophysiological parameters after Fampridine administration, we measured the motor conduction latency and the Central Motor Conduction Time (CMCT), prior to the drug administration, 5 and 12 days after, as well as 1 and 3 months after continuous administration of Fampridine 10 mg twice daily.

For the central stimulation, we used the butterfly-shaped coil, stimulating the right and left cerebral hemispheres, and collecting data from the abductor digit minimi muscle. For the lower limbs, the stimulation was similar, but collecting info from the tibialis anterior muscle. For the stimulation of the cervical and lumbar regions, we used the round-shaped coil, stimulating at C7 and L5 levels, and collecting data from the same two muscles.

2.3 The Clinical Evaluation

We measured the patients' walking speed using the T25-FW scale, at the mentioned interval of time according to Fampridine's first administration. The distance the patients had to walk was 7.62 m (25 feet). The rhythm was constant for the whole length; the patients went back through the same distance, with the time necessary measured as well. The two-timed values obtained were averaged. The walk was performed in a straight line. The patients were asked not to lean against the wall, however, in case of important motor deficits, they were allowed to use a cane. The clinical evaluation was performed by the neurologist and physiotherapists of the multidisciplinary team.

2.4 Quality of life

At the end of all the time periods described according to the Fampridine intake, the patients completed a satisfaction questionnaire regarding the quality of life (QoL). They

were asked to appreciate on a scale from 0 to 5 how they relate to the drug in terms of expectations and everyday activities (Table 1).

Table 1. The QoL evaluation scale the patients related to

Satisfaction degree
0 = bad
1 = stationary
2 = slightly better
3 = good
4 = very good
5 = exceptionally

2.5 Analysis of data

The statistical analysis was performed using SPSS, through the appliance of the Friedman test for paired samples. Considering the small lot, non-parametric tests were used, because of unequally-distributed data. The effect of the administration of the drug was measured in both clinical and electrophysiological reports at the mentioned time intervals.

3. Results

At the 12-day endpoint analysis, based on the electrophysiological evaluation, the group was divided into responders and non-responders. Nine patients presented early amelioration of the MEP and CMCT latencies, whereas the other 6 showed no significant improvement.

The following analysis, repeated measures ANOVA, was conducted only on the group of responders (n=9).

3.1 Quality of life

Regarding the quality of life, a significant main effect of time was observed (Fig. 1), Wilks' Lambda = 0.033, F (3, 6) =58, $p < 0.001$.

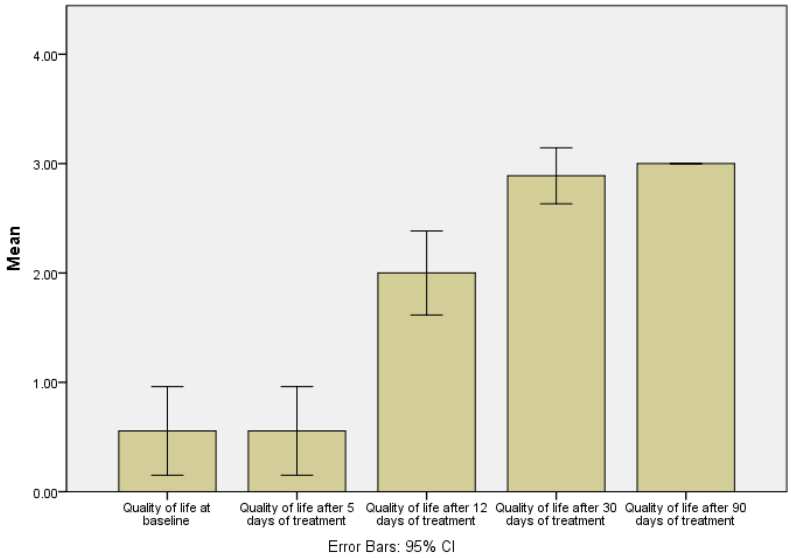

Fig. 1 The effect of fampridine on the level of quality of life

When we examined the pairwise comparisons for statistic differences within groups per daily quality of life, we observed significant differences between quality of life at baseline and quality of life on day 12 ($p < 0.001$), between quality of life at baseline and

quality of life on day 30 ($p < 0.001$), between quality of life at baseline and quality of life on day 90 ($p < 0.001$). Also, significant differences were observed between quality of life on day 5 and quality of life on day 12 ($p < 0.001$), between quality of life on day 5 and quality of life on day 30 ($p < 0.001$), between quality of life at day 5 and quality of life on day 90 ($p < 0.001$). Furthermore, significant differences were observed between quality of life on day 12 and quality of life on day 30 ($p < 0.001$) and between quality of life on day 12 and quality of life on day 90 ($p = 0.003$). The only non-significant differences observed were between quality of life baseline and quality of life at day 5 ($p = 1$) and between quality of life at day 30 and quality of life at day 90 ($p = 1$).

3.2 Timed-25-Foot-Walk test

Analyzing the Timed-25-Foot-Walk test results, a significant main effect of time was observed (Fig. 2), Wilks' Lambda = 0.011, $F(4, 5) = 112.621$, $p < 0.001$.

When examining the pairwise comparisons for statistic differences within groups related to the Timed-25-Foot-Walk test, we observed significant differences between the time obtained by the patients at baseline and the time obtained on day 12 ($p < 0.001$), between time obtained at baseline and time obtained on day 30 ($p < 0.001$), between time obtained at baseline and time obtained on day 90 ($p < 0.001$). Also, significant differences were observed between the time obtained by the patients on the 25-foot Walk test on day 5 and the time obtained on day 12 ($p < 0.001$), between time obtained on day 5 and time obtained on day 30 ($p < 0.001$), between time obtained at day 5 and time obtained on day 90 ($p < 0.001$). Significant differences were also observed between the time obtained by the patients on the 25-foot Walk test on day 12 and the time obtained on day 30 ($p < 0.001$) and between the time obtained on day 12 and time obtained on day 90 ($p = 0.003$). In addition, significant differences were also observed between the time obtained by the patients on the 25 Foot Walk test on day 30 and the time obtained on day 90 ($p<0.001$). The only non-significant differences observed were between the Timed-25-Foot-Walk test at baseline and the Timed-25-Foot-Walk test at day 5 ($p = 0.132$).

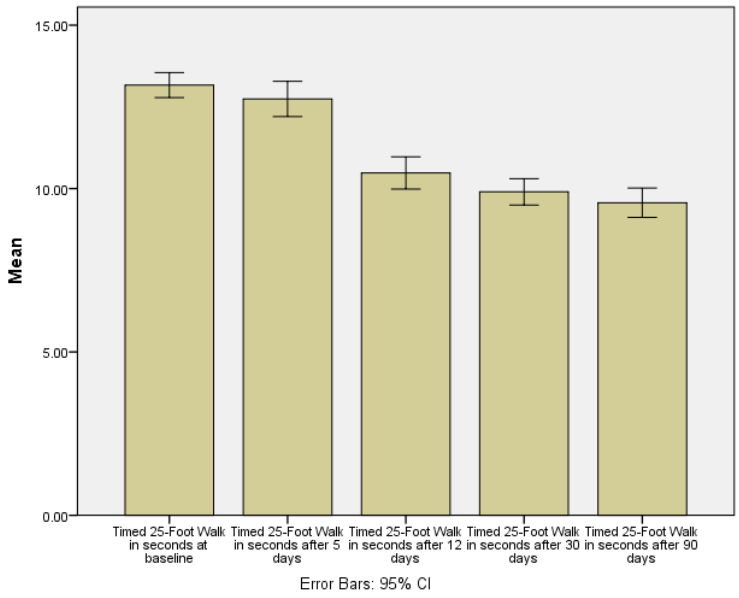

Fig. 2 The effect of fampridine on the time obtained by the patients on the 25 Foot Walk test

3.3 The Central Motor Conduction Time (CMCT) from the right hemisphere

Regarding the Central Motor Conduction Time (CMCT) from the right hemisphere, a non-significant main effect of time was observed (Fig 3), Wilks' Lambda = 0.202, F [4, 5] =4.931, p = 0.055.

However, when we examined the pairwise comparisons, to see if there was a statistical difference within groups dealing with the Central Motor Conduction Time (CMCT) from the right hemisphere, we observed significant differences between the CMCT at baseline and CMCT on day 5 (p = 0.035), between CMCT at baseline and CMCT on day 12 (p = 0.029), between CMCT at baseline and CMCT on day 90 (p = 0.03). Also, significant differences were observed between CMCT on day 30 and CMCT on day 90 (p = 0.005). Non-significant differences were observed between any other possible pair of time points where the CMCT was measured.

Fig. 3 The effect of fampridine on the time obtained by the patients on the Central Motor Conduction Time (CMCT) from the right hemisphere

3.4 The Central Motor Conduction Time (CMCT) from the left hemisphere

Analysis of CMCT from the left hemisphere revealed a significant main effect of time (Fig. 4), Wilks' Lambda = 0.130, F (4, 5) =8.387, p < 0.019.

During these next pairwise comparisons, we observed significant differences between the CMCT at baseline and CMCT on day 12 (p = 0.009), between CMCT at baseline and CMCT on day 90 (p = 0.037), between CMCT at day 5 and CMCT on day 12 (p = 0.031). Also, significant differences were observed between CMCT on day 30 and CMCT on day 90 (p = 0.004). Non-significant differences were observed between any other possible pair of time points where the CMCT was measured.

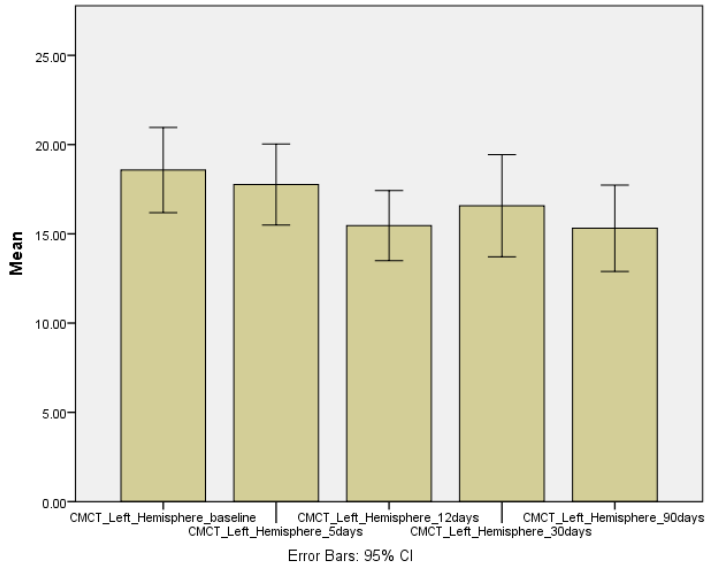

Fig. 4 The effect of fampridine on the time obtained by the patients on the Central Motor Conduction Time (CMCT) from the left hemisphere

3.5 The Central Motor Conduction Time (CMCT)

A significant main effect of time was observed, Wilks' Lambda = 0.106, F [4, 5] =10.556, p < 0.012. During pairwise comparisons, investigating statistical differences within groups, significant differences between the CMCT at baseline and CMCT were visible on day 5 (p =0.006), between CMCT at baseline and CMCT on day 12 (p = 0.014), between CMCT at baseline and CMCT on day 90 (p = 0.029). Also, significant differences were observed between CMCT at day 5 and CMCT at day 12 (p=0.040) and between CMCT at day 30 and CMCT on day 90 (p = 0.004). Non-significant differences were observed between any other possible pair of time points where the CMCT was measured. (Fig. 5)

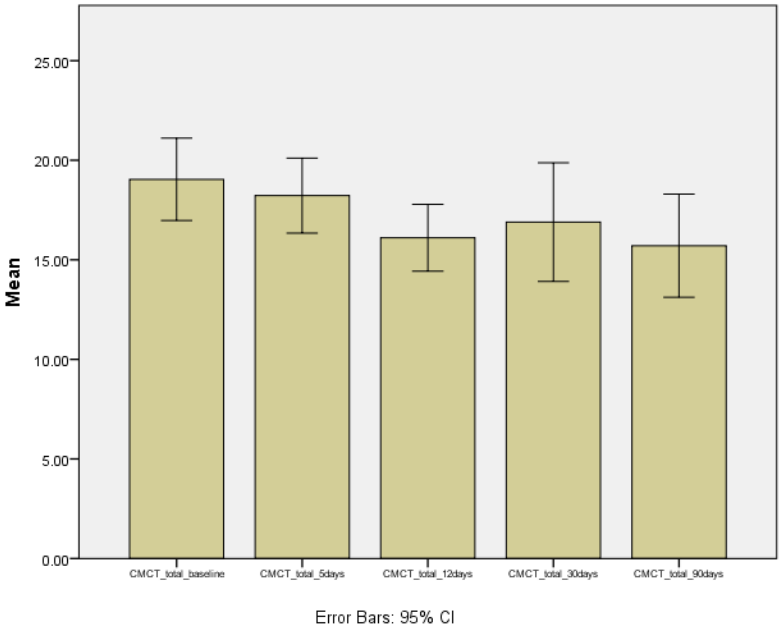

Fig. 5 The effect of fampridine on the time obtained by the patients on the Central Motor Conduction Time (CMCT)

3.6 The Central Motor Conduction Time (CMCT) from the right and left hemispheres in the lower limbs

CMCT from the left hemisphere in the lower limbs showed a significant main effect of time (Fig. 6), Wilks' Lambda = 0.159, F (4, 5) =6.612, p = 0.031.

Significant differences between the CMCT at baseline and CMCT were visible on day 12 (p = 0.044) by the use of pairwise comparisons. Also, significant differences were observed between CMCT on day 30 and CMCT on day 90 (p = 0.011). Non-significant differences regarding the CMCT in the lower limbs from the left hemisphere were observed between any other possible pair of time points where the CMCT was measured.

Regarding the Central Motor Conduction Time (CMCT) from the right hemisphere in the lower limbs a significant main effect of time was observed, Wilks' Lambda = 0.162, F [4, 5]=6.458, p = 0.033.

When we examined the pairwise comparisons for statistical differences within groups related to the CMCT from the left hemisphere in the lower limbs, we observed significant differences only between CMCT at day 30 and CMCT on day 90 (p = 0.002).

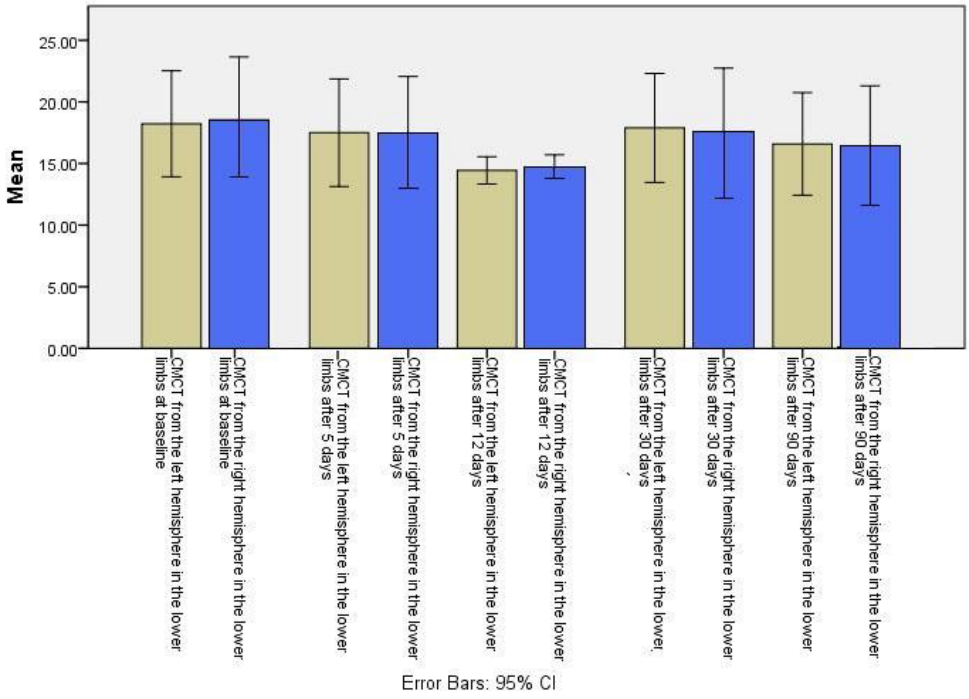

Fig. 6 The effect of fampridine on the time obtained by the patients on the Central Motor Conduction Time (CMCT) from the left and right hemispheres in the lower limbs

3.7 The Central Motor Conduction Time (CMCT) from the right and left hemispheres in the upper limbs

Analysis of CMCT from the left hemisphere in the upper limbs revealed a significant main effect of time, Wilks' Lambda = 0.148, F (4, 5) =7.221, p = 0.026.

When we examined the pairwise comparisons for the statistical difference within groups related to the CMCT from the left hemisphere in the upper limbs, we observed a statistically significant improvement between every time point in which this test was assessed (Fig. 7). Specifically, we found significant differences between CMCT at baseline and CMCT on day 5 (p = 0.039), CMCT at baseline and CMCT on day 12 (p = 0.003), CMCT at baseline and CMCT on day 30 (p = 0.001), CMCT at baseline and CMCT on day 90 (p < 0.001). Also, significant differences were observed between CMCT at day 5 and CMCT on day 12 (p =0.001), CMCT on day 5 and CMCT on day 12 (p < 0.001), CMCT on day 5 and CMCT on day 90 (p < 0.001). Furthermore, significant differences were observed between CMCT at day 12 and CMCT on day 30 (p = 0.005), CMCT on day 12 and CMCT on day 90 (p =0.001), CMCT on day 30 and CMCT on day 90 (p = 0.002).

Regarding the Central Motor Conduction Time (CMCT) from the right hemisphere in the upper limbs, a significant main effect of time was observed, Wilks' Lambda = 0.074, F [4, 5]=15.595, p = 0.005.

Analyzing in the same manner the CMCT from the right hemisphere in the upper limbs, we observed a statistically significant improvement between every time point in which this test was assessed. Specifically, we found significant differences between CMCT at baseline and CMCT on day 5 (p = 0.001), CMCT at baseline and CMCT on day 12 (p < 0.001), CMCT at baseline and CMCT on day 30 (p < 0.001), CMCT at baseline and CMCT on day 90 (p < 0.001). Also, significant differences were observed between CMCT at day 5 and CMCT on day 12 (p < 0.001), CMCT on day 5 and CMCT on day 12 (p < 0.001), CMCT on day 5 and CMCT on day 90 (p < 0.001). Furthermore, significant differences were observed between CMCT at day 12 and CMCT on day 30 (p < 0.001), CMCT on day 12 and CMCT on day 90 (p < 0.001), CMCT on day 30 and CMCT on day 90 (p = 0.034).

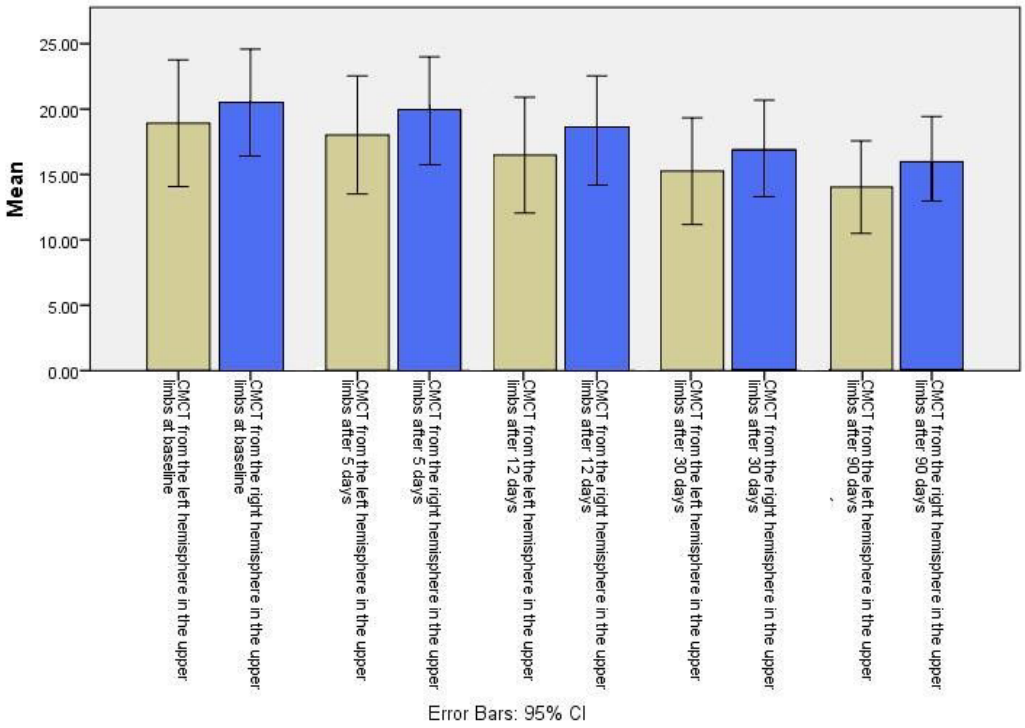

Fig. 7 The effect of fampridine on the time obtained by the patients on the Central Motor Conduction Time (CMCT) from the left and right hemispheres in the upper limbs

4. Discussion

According to our results, fampridine treatment significantly improves the quality of life from baseline to 90 days' time point ($p<0.001$). Furthermore, our study agrees that a 12-day period after beginning the treatment is necessary to observe any significant improvement. There was no difference regarding the quality of life between baseline and day 5 ($p=1$), however, a significant positive difference was observed between the quality of life at baseline and quality of life after 12 days ($p<0.001$), and also between quality of life after 5 days and quality of life after 12 days ($p<0.001$). The statistically significant improvement continues after 30 days ($p<0.001$), but it stops after this time point, the difference between day 30 and day 90 is statistically non-significant ($p=1$). To summarize, in our sample, statistically, fampridine treatment significantly improves the quality of life of the patients, after 12 days, yet this positive effect is diminishing and becomes non-significant after 30 days. In addition, our Wilks' Lambda analysis shows that there was a significant main effect of time on the quality of life ($p < 0.001$).

Somehow similar to the results obtained for the quality of life, the results for the 25-foot walk test also showed improvement from baseline to the 90-day time point ($p<0.001$). In addition, a minimum of 12 days after the beginning of the fampridine treatment is required to observe statistically significant improvements. No significant differences were found between baseline and day 5 ($p=0.132$), but a significant difference was observed between day 5 and day 12 ($p<0.001$), and also between baseline and day 12 ($p<0.001$). In contrast to the results from the quality of life, the improvement in the 25-foot walk test continued through the whole 90-day follow-up of the study. In addition, our Wilks' Lambda analysis shows that there was a significant main effect of time on the result of the 25-foot walk test ($p < 0.001$).

The results regarding the central motor conduction time (CMCT) also showed a significant main effect of time on the results obtained by the participants on this test ($p <0.001$). In addition, a significant improvement was also observed between baseline and after 90 days of treatment ($p=0.029$). Furthermore, improvements were also observed

between baseline and day 5 (p=0.006), suggesting that it takes fampridine less time to have a positive effect on the CMCT compared to the 25-foot walk test and the quality of life. The observed improvements continued through day 12 of the treatment (p=0.014). However, the positive effect of fampridine on the CMCT until the end of the 90 days of treatment (day 30-day 90, p=0.005).

The study has its limitations, as its weakness is especially related to the statistical significance while dealing with a small sample size. As a pilot study initially designed for at

least 28 participants, it had an important dropout rate, as 13 of the initial patients stopped medication due to personal reasons within the first 5 to 12 days. It is to be mentioned that it was not related to side effects. Even in our small remaining lot, the decision to continue the treatment beyond the first 2 weeks in patients without any important clinical amelioration shows interesting perspectives of both positively impacting the quality of life as well as the use of TMS for monitoring the therapeutic response, facts we considered worth sharing.

Gait impairment continues to be one of the major problems in MS, involving high healthcare costs worldwide for both therapy attempts as well as scientific research.

Fampridine, as a symptom-controlling therapeutic agent for gait improvement among these patients has been showing positive effects throughout the last years, especially by association with physical therapy [13]. In this context, we propose TMS as a useful tool not only for investigation of the relapse in MS but also for follow-up of specific symptomatic treatments, such as Fampridine. It can be used for measurements of the motor evoked potential's amplitude (MEP), the central motor conduction time (CMCT), and the motor threshold. A decrease in CMCT and an increase in the MEP amplitude can predict an improvement in speed, as correlated with the clinical evaluation of the T25-FW.

Fampridine is known to improve ambulation and endurance, but also, by the same mechanism of enhancing action potential formation in demyelinated axons by blocking potassium channels, it appears to improve cognitive fatigue as well [14, 15]. Fampridine

also seems to improve muscle strength and the rate of force development as measured not only by T25FW, but also by isokinetic dynamometry, Nine Hole Peg Test, and other muscle strength or manual functions monitoring tests [16, 17]. In other cases, there is mention of significant amelioration of the T25FW, whereas motor and cognitive fatigue seem to persist after 9 to 12 months [18].

The QoL in MS patients can not only be affected by walking difficulties alone but also by related fatigue, which affects more than 80% of the patients. It leads to early retirement and is considered the most burdensome clinical aspect of the disease by up to one out of four patients [6, 19]. Fampridine, in this case, joins exercise therapy, therapeutic interventions on cognitive behavior, or symptomatic treatments for secondary sleep disorders against MS-related fatigue, as up to this moment, it seems to be the only therapeutic agent with promising results for the treatment of both motor functions and motor fatigue [20]. Due to its high tolerability profile, Fampridine is even likely to lead to a favorable outcome in pregnancy [21].

It is not only the positive effect of Fampridine in improving walking that deserves to be mentioned but also the improvement of the psychological status [22-25]. Either in double-blind placebo-controlled studies or prospective monocentric open-label trials, Fampridine has been proven to have an effect upon patient self-reported psychological impact of MS, as well as a precognitive effect on verbal fluencies even in non-respondent to gait benefit patients, respectively [26]. Therefore, by improving not only the physical-related issues in MS but also cognitive fatigue and mood, Fampridine positively impacts QoL [24, 25]. Thus, it significantly improves after Fampridine administration [27-29]. Such already-known facts contributed to our idea of including a very simple QoL quiz for our patients.

The general state improved within our 4 patients determined Fampridine continuation, finally leading to acceptable results.

In spite of the significant reduction in the T25FW, adverse events may occur during treatment with Fampridine [30, 31]. These may include dizziness, insomnia, falls, nausea, and headaches. Ineffectiveness or inappropriate dosing counts as well, as well as anaphylactic reactions and seizures in rare cases. Adverse events might also include urinary tract infections (UTI), but there are studies that found similar results concerning the risk for UTI within dalfampridine patients and placebo groups [31, 32]. Two of our patients experienced dizziness at the beginning of the study as the only adverse event, however, with amelioration within the first week.

Arguments for generally continuing the therapy are, for all that, enough. Especially because even in case of discontinuity of treatment, followed by a return to therapy, in spite of the decreased walking speed over time, there is still evidence of an improvement as compared to non-responders [33].

Arababadi et al in 2014 demonstrated that Interleukin 4 (IL-4) has an important role in MS pathogenesis because IL-4 is a T-helper cell cytokine (2TH) that is involved in regulating immune responses [34]. IL-4 can exert either pro- or anti-inflammatory effects in specific neuronal populations [35]. Vani et al. in 2022 demonstrated that IL-4 and IL-10, have a protective role against MS, which could be a promising new treatment for MS in the future [36]. Strijbis et al demonstrated in 2020 that Fampridine is not only limited to the treatment of MS symptoms but also has an important neuroprotective effect [37] due to the control of demyelination and axonal degeneration along with inflammation [38].

5. Conclusions

There are patients with no visible clinical improvement of speed on the T25-FW after 2 weeks on Fampridine. This might be related to the type of disease. Our study provides evidence that this situation could require a separate analysis of the results.

Mild electrophysiological modifications could be predictors for future clinical improvement if the therapy is continued, as correlated with QoL assessment.

In our study, the concept of false negative clinical response to Fampridine emerges, suggesting TMS as a useful tool for predicting even mild clinical benefits. We can therefore conclude that, at least for research purposes at this moment, early electrophysiological findings using TMS could be useful as a predictive tool for future clinical amelioration.

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