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Randomized comparison of Functional Electric Stimulation in Posturally Corrected Position and Motor Program Activating Therapy: treating foot drop in people with Multiple Sclerosis

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ABSTRACT

BACKGROUND: Functional Electric Stimulation (FES) is recommended for foot drop in multiple sclerosis, although little is known about its therapeutic effect.

AIM: To evaluate a therapeutic effect immediately and two months after program termination (persistent and delayed effect) of a new approach using FES in combination with correcting the patients' postural system. More specifically, we evaluate the effects of this approach on the patients' clinical functions and compared it with individual physiotherapy.

DESIGN: Parallel randomised blind trial

SETTING: 2-month long treatments, Functional Electric Stimulation in Posturally Corrected Position (Group 1) and neuroproprioceptive facilitation and inhibition physiotherapy called Motor Program Activating Therapy (Group 2).

POPULATION: 44 subjects with Multiple Sclerosis

METHODS: Primary outcomes: gait (the 2-Minute Walk Test; Timed 25-Foot Walk test; Multiple Sclerosis Walking Scale-12) and balance (by e.g. Berg Balance Scale, BBS; The Activities-Specific Balance Confidence Scale, ABC; Timed Up and Go Test, TUG). Secondary outcomes: mobility, cognition, fatigue and subjects' perceptions (e. g. Multiple Sclerosis Impact Scale, MSIS; Euroqol-5 dimensions-5 levels, EQ-5D-5L).

RESULTS: Group 1 showed immediate therapeutic effect in BBS (p = 0.008), ABC (p=0.04) and EQ-5D-5L (self-care, p=0.019, mobility p=0,005). The improvement in EQ-5D-5L persisted and in TUGcognitive we documented a delayed effect (p=0.005). Group 2 showed an immediate improvement in BBS (p = 0.025), MSIS (p=0.043) and several aspects of daily life (the effect on

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health today was significantly higher than in Group 1, significant difference between groups p=0.038).

CONCLUSIONS: FES in the Posturally Corrected Position has an immediate therapeutic effect on balance and patients' perceptions comparable to Motor Program Activating Therapy, and higher persistent and even delayed therapeutic effect.

CLINICAL REHABILITATION IMPACT: The study results point to the importance of correcting the patients' posture when applying FES, the possibility to treat foot drop by individual physiotherapy and the activation of the patients' auto reparative processes.

Key Words: multiple sclerosis, electrical stimulation, posture, rehabilitation

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Introduction

Multiple sclerosis (MS) is a chronic, progressive disease of the central nervous system, believed to be caused by an autoimmune process and affecting approximately 2.3 million people worldwide. The most visible disability is impaired mobility, which also profoundly impacts the daily life of people with MS (pwMS)[1].

Impaired mobility is often manifested as foot drop, which causes stumbles, falls, gait instability and decreased gait efficiency. This problem has been commonly solved with the use of an ankle–foot orthosis (AFO) - a passive fixation in dorsiflexion with no movement in the ankle. A recently developed alternative to the AFO is Functional Electrical Stimulation (FES). Even though FES is a promising method, the outcomes from previous research are debatable and there are different views on evaluating the effects of FES. The vast majority of studies showed a positive *orthotic effect* (the immediate change in gait with FES on, compared with FES off)[2-17] of FES in people with MS. Only a few studies [10,18,19] showed *therapeutic* or *training effect* in pwMS, which refers to changes in walking performance after regular, long-term FES use when the measurement is recorded without the device. To our knowledge, no study has evaluated whether an effect persists or is delayed when FES is no longer used.

Little is also known about how FES compares with physiotherapy, or FES combined with physiotherapy treatment of foot drop [2,20]. Standard application of FES (described in detail in Stein et al. [10]) does not work when using physiotherapy on the postural system, but we decided to use key elements from individual physiotherapy developed at our workplace, combined them with standard application of FES, and developed a new FES methodology – *FES in Posturally Corrected Position* (*FES in PCP)*. We expected that in such an application, patients will use their stabilization mechanism and therefore will be able to walk in a more stable manner.

Most studies investigated the effect of FES on walking using self-reported and quantitative outcome measures (5 Minute Walking Test, 6 Minute Walking Test, 10 Meter Walking Test, 2 Minute Walking Test, Timed 25-foot Walk, MSWS-12, MSIS-29) [2-14,16,18,20-29]. We were convinced, and our opinion was in accordance with Barret et al. [3] that confidence with balance during FES application is just as important as the walking speed and distance. This is why balance and walking parameters were chosen as our primary outcomes. As a secondary outcome, mobility, fatigue, cognition and patients' perceptions have been chosen, because little research has been done on the effects of FES on such important aspects of pwMS.

Besides evaluating how FES in a Posturally Corrected Position affects balance and the aforementioned secondary outcome measures, we were also interested in comparing this treatment approach with individual therapy. More specifically, we compared FES in a Posturally Corrected

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Position on the aforementioned outcome measures with individual neuroproprioceptive facilitation physiotherapy, so called Motor Program Activating Therapy (MPAT).

Materials and methods

Trial design

A parallel randomised rater-blinded trial was performed to compare two kinds of foot drop treatment. An independent study coordinator using computer-generated randomization to one of two groups in a 1:1 ratio allocated patients randomly to one of the two treatment groups between May 2015 and May 2017. Subjects in Group 1 used Functional Electric Stimulation in a Posturally Corrected Position for two months in daily life and subjects in Group 2 underwent two months of ambulatory physiotherapy called Motor Programme Activating Therapy. The sample size was estimated using the BBS score change difference as the main endpoint. Based on a previous study [30] with a similar setting and therapy, we estimated the number of participants to be 27 in the Group 1 and 27 in the Group 2 to have 80 % power to detect a difference in BBS ≥ 3 at 5 % level of statistical significance.

Participants

The subjects were recruited from the MS Centres of Hospitals in the Czech Republic by an independent neurologist according to the following inclusion criteria: definite diagnosis of MS [31], stable clinical status in the preceding 3 months, Expanded Disability Status Scale score ≥ 2 and ≤ 6.5, foot drop, no corticosteroid therapy in the preceding month, and no physiotherapy in the previous six months. Patients with factors disturbing mobility (e.g. stroke, pregnancy, fractures) were excluded from the study. All subjects signed an informed consent form approved by the ethics committee of the Kralovske Vinohrady University Hospital in Prague (full trial protocol EK-VP/21/0/2014 is available there).

Interventions

Group 1 (22 subjects) underwent Functional Electric Stimulation in Posturally Corrected Position. First, participants underwent one session (one hour) of MPAT with the aim of correcting them into a postural position where the motor programs for sitting and standing are activated. Next, participants underwent one session (two hours) where the device The WalkAide® System (Innovative Neurotronics Inc., 4999 Aircenter Circle, Suite, 103 Reno, NV 89502, USA) was standardly, according to Stein et al.[10], programmed by a WalkAide® System-certified orthotist and by an educated and experienced professional (MSc., two years' experience with pwMS). The device was programmed to produce electrical stimuli to the common peroneal nerve and anterior calf muscles through surface adherent electrodes to induce muscle contractions that mimic normal voluntary gait movement (lifting the foot during the swing phase of

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gait and achieving correct placement on the ground). Stimulation parameters such as ramp, timing duration, and output levels were adjusted to suit the individual person's needs, in order to provide the most effective gait pattern. Afterwards the subjects received the device to use in daily life (as much as they felt able to). Six subjects had bilateral foot drop and received two FES devices, one for each foot, while 16 subjects had unilateral foot drop and received only one FES device. The next session was provided after fourteen days of FES use and both the orthotist and physiotherapist checked the correction of foot drop. If the correction was not functional, the device was reprogrammed again (one hour). Moreover, the patients underwent postural correction (one hour) by MPAT in sitting and standing. Then, the subjects continued to use the device during daily life activities for the next six weeks. They were given a simple, clear instruction manual, which explained how to set up the system and included a list of safety precautions. The participants were encouraged to contact the physiotherapist immediately if the stimulator was not working well. The number of applied stimuli per day (1190.5 on average) and hours of using the device per day (6.5 hours on average) was monitored by the WalkAide® System. All sessions were led individually face to face at the ambulatory unit of the Department of Neurology, Kralovske Vinohrady University Hospital in Prague.

Group 2 (22 subjects) underwent 16 sessions (1 hour, twice a week for two months) of Motor Programme Activating Therapy (MPAT)[32]. This method falls in the "neuroproprioceptive facilitation and inhibition" category of physiotherapy interventions [33]. We chose this method on the grounds of our clinical experience - it was developed and verified by our team. In this therapy, patients are corrected into a postural position where their joints are functionally centred. Then somatosensory (manual and verbal) stimuli are applied to activate motor programs in the brain, which then lead to the co-contraction of the patient's whole body when the patient is lying, sitting, standing up or moving forward. Activated programs are repeated under various conditions and in different situations and environments, to teach the patients to use the acquired motor skills automatically in daily life [32]. The intensity of load during therapy corresponds to moderate activities [34]. The therapy was led face to face by an educated and experienced professional (MSc., two years' practice with pwMS), specifically trained in MPAT at the ambulatory unit of the Department of Neurology, Kralovske Vinohrady University Hospital in Prague. The treatment was individually designed according to the patient's status, reaction to the therapy, the defined main problem and goal of one therapy session and the whole treatment. The therapist was maximally helpful and abided by the schedule for each patient to undergo all 16 sessions. To increase the adherence to the treatment, patients received a brochure and videotape with instructions on how to sit, stand up and stand correctly. Moreover, the therapist provided effective advice, educated patients about MS and

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PT possibilities, established a confidential relationship and motivated patients to work on themselves.

Outcomes

Relevant demographic and anamnestic data were collected by a neurologist at the beginning of the study, namely gender, age, height, weight (Body Mass Index was calculated), length of disease duration, type of MS (relapsing-remitting, primary or secondary progressive), Expanded Disability Status Scale, use of walking aids, and information about physiotherapy in the past.

A blind assessor (unaware of the assigned intervention of assessed subjects) examined the patients to evaluate primary (gait and balance) and secondary outcomes (mobility, fatigue, cognition and the subject's perceptions) three times: at the beginning of the programme, immediately after its termination (immediate effect), and two months after finishing the program (persistent effect). During the assessment, the subjects were examined with the FES off.

Primary outcomes

Gait was evaluated by a 2-Minute Walk Test (2MWT) [35], Timed 25-Foot Walk test (T25-FW) [36] and by a Multiple Sclerosis Walking Scale-12 (MSWS-12) questionnaire [37].

Balance was evaluated by a Berg Balance Scale (BBS) [38], Timed Up and Go Test (TUG, TUGcogn) [39], Dynamic Gait Index (DGI) [40] and The Activities-specific Balance Confidence Scale (ABC) [41].

Secondary outcomes

Mobility was evaluated by a Five Times Sit to Stand Test (5xSTS), Modified 5-repetition sit-to-stand test (mod5STS) [42], Four Square Step Test (FSST) [43], Rivermead Mobility Index (RMI) [44] and Performance Scale - mobility (PSmob) [45].

Cognition was assessed by a Symbol Digit Modalities Test (SDMT) [46], fatigue and cognition by The Fatigue Scale for Motor and Cognitive Functions (FSMC) [47], subjective assessment of different aspects of daily life by a Euroqol-5 dimensions-5 levels questionnaire (EQ-5D-5L) [48], and the impact of MS on daily life by the Multiple Sclerosis Impact Scale (MSIS-29) [49].

Data Analysis

Continuous data were summarized as means with standard deviations (SD) or medians with interquartile range (IQR) wherever appropriate. Categorical variables were summarized using absolute and relative frequencies. The effect of the therapy was tested using a paired t-test or paired Wilcoxon test (immediate effect of therapy between the second and the first assessment, long-term effect of therapy between the third and the first assessment). A two-sample t-test or Wilcoxon two-sample test (sum rank test) were used to compare continuous variables between therapy groups.

In general, non-parametric techniques (median, Wilcoxon, Kruskall-Wallis) were used with time-related measurements (e.g. the TUG test), otherwise parametric methods were employed. Because of the many tests applied there is a higher chance of Type I error, i.e. rejection of the null

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hypothesis when it is true. To address this issue, p-values were adjusted by the Benjamini-Hochberg method for multiple comparisons.

To check for influence of other factors, namely gender, age, disease duration, BMI, EDSS, use of walking aides and physiotherapy in the past (seven to sixteen months before the beginning of the study), we used linear regression models with a change in the measured variable as the response variable, Group as the independent variable and patients' characteristic as a confounding factor. Possible interactions of Group with the characteristic of the subjects were also explored. All analyses were performed in statistical language and environment R, v. 5.0.3.

Results

Out of 55 people who were assessed for eligibility, 49 were randomized. One drop out was due to an increased number of falls potentially related to the subject's use of FES (adverse event). 44 participants completed the study and underwent a second and third examination (Figure 1). They were on average 48.5 ± 10.2 years old with EDSS 4.7 ± 1.4 and with disease duration 12.8 ± 6.2 years. Both groups were similar in size and all basic characteristics (Table 1).

An effect of FES in PCP (Group 1)

The therapeutic effect of FES in PCP on both primary and secondary outcomes has been confirmed.

Primary outcomes: Immediately after the therapeutic program, BBS (p=0.008) and ABC (p=0.04) significantly improved. The improvement of BBS and a trend for improvement of MSWS-12 did not persist, while in ABC we detected a trend for persistent therapeutic effect (p=0.073).

Secondary outcomes: Significant immediate (EQ-5D-5L mobility, p=0.005; self-care, p=0.019) and persistent (EQ-5D-5L mobility, p=0.001; self-care, p=0.005; usual activities, p=0.029) improvement in several aspects of daily life was documented. Moreover, some parameters improved not immediately after the FES application, but two months later (TUGcogn, p=0.005; SDMT, p=0.053; FSMCcogn, p=0.083; FSMC motor, p=0.082 and FSMCtotal, p=0.074).

An effect of MPAT (Group 2)

The therapeutic effect of MPAT on both primary and secondary outcomes has also been confirmed.

Primary outcomes: MPAT led to a significant immediate effect of BBS (p=0.025), and a trend to immediate improvement of MSWS-12 (p=0.078) that persisted two months after finishing the therapy (p=0.089).

Secondary outcomes: PSmob (p=0.043) and several aspects of daily life (EQ-5D-5L mobility, p=0.046; usual activities, p=0.008; pain discomfort, p=0.008 and health today, p=0.032 – the difference between groups was significant, P=0.038) significantly improved. A trend of improvement of EQ-5D-5L usual activities (p=0.057) persisted.

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Difference between FES in PCP and MPAT

The therapeutic effect of both FES in PCP and MPAT has been confirmed. While an immediate effect is comparable in both groups, in Group 1 a higher persistent and even delayed effect has been documented.

Immediately after the program, Group 2 improved considerably more than Group 1 in the EQ5DL Health today score (t-test p = 0.032, Group 2 mean improvement 12.8, Group 1 mean improvement 2.0). Two months after therapy termination, some changes persisted (EQ-5D-5L self-care, p=0.005; EQ-5D-5L mobility p=0,001). In some outcomes, a statistically important delayed effect (TUGcogn p=0.005; EQ-5D-5L usual activities, p=0.029) and trend for improvement (TUG, SDMT, FSMC cognitive, motor and total, ABC) were documented. Differences were not statistically significant after a multiple comparisons adjustment. The detailed description of the results in each group is in Table 2.

Influence of other factors on the treatment effect

From all covariates (gender, age, disease duration, BMI, EDSS, use of walking aides and physiotherapy in past), only the influence of previous physiotherapy was significant.

As for the effect of MPAT therapy less than 6 months before the experiment, we noted a statistically significant difference in the change of FSMC scores on both motor and cognitive components. While patients without prior therapy stayed the same or slightly worsened, patients with prior therapy improved by a mean -3.6 points in cognitive, -5.2 in motor and -8.8 points in the total score (p = 0.023, 0.001 and 0.004, respectively, significant even after the multiple comparisons adjustment).

Discussion

Study advantages and limitations

This study brings several innovative aspects.

1) It is one of the first studies that confirms a therapeutic effect of FES in pwMS.
2) It verifies a specially developed mode of FES application (FES in Posturally Corrected Position) in pwMS.
3) It examines an extent range of outcomes and as such could provide further important and relevant information to the FES MS users.
4) It compares two different means of foot drop treatment in pwMS - FES in PCP and individual physiotherapy MPAT.
5) In addition to an immediate effect, it analyses a persistent and a delayed effect that could be a consequence of activation of plastic and adaptive processes in the central nervous system.

The study has limitations that should be considered. The biggest is a relatively small sample size, although it is comparable with studies evaluating the effect of FES [2-4,6-8,16,18,20,22,23,25,27,28,45,50]. We

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were willing to reach a higher number of participants (27 – 30 in each cohort), but it was not possible, because of a limited number of devices loaned from the representing company and the demanding character of the individual physiotherapy (it took 2 years to collect data for 22 participants). Moreover, the number of subjects reporting similar problems in each category was small, reducing the statistical significance of the observed affects. Despite these limitations we believe this study provides important results and provides a platform for future studies.

A therapeutic effect of FES in pwMS

In this study, an immediate therapeutic effect on balance has been documented.

This is the only study documenting an improvement of static balance evaluated by BBS. Until now, any other studies looked for an effect on BBS, probably because an effect of standard FES application on BBS was not expected. We are convinced that the special mode of FES application has a higher effect on static balance than a standard application, but this needs to be verified.

Moreover, the improvement of the self-reported confidence evaluated by ABC has been documented in this study, similarly to Renffrew et al. [28]. Other studies Esnouf et al. [20] and Taylor et al. [24] and Gervasoni et al. [19] documented improvement of balance by fewer numbers of falls.

In contrast with studies that documented a therapeutic effect on walking speed and distance [19,51], these parameters did not change in our study. Only subjective feelings on how MS impacts walking ability (MSWS-12) improved, similarly to in other studies [6,7,16,28].

A positive effect of the specially developed FES application – FES in a Posturally Corrected Position

When developing this FES application, we followed the fact that foot drop in MS is very frequently accompanied by clinical problems which lead to decreases in overall balance: an increased hip and knee flexion during the stance phase and a decreased ankle dorsiflexion during the swing phase; a circumduction of the lower limb and a trunk lateral flexion, and a malposition of the foot. We hypothesized that these clinical problems are caused by an insufficient postural function. Moreover, we followed our previous experience with the positive effect of MPAT on clinical functions in pwMS [32,52] and combined key elements from individual physiotherapy MPAT with FES.

This study is unique due to the combination of FES use with postural correction, and as such is not comparable with other studies. We would like to point out that postural correction in our methodology took only two hours in fourteen days. It is surprising that such a short individualized session can sufficiently prepare a person with MS to use FES. The effectiveness of FES may increase the improvement of some clinical problems in individual therapy. For instance, some subjects in our study experienced a knee hyperextension connected with a missed impulse or

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impaired balance – such patients could not use the WalkAide® without individual postural correction (physiotherapy).

Linear regression models also confirmed the role of the postural correction in treating foot drop. The only factor influencing the effectiveness of both MPAT and FES in PCP on FSMC and TUG was the patient's previous exposure to postural correction. To avoid misplacement of therapeutic effects and covariate "physiotherapy in the past", only patients who had not undergone any physiotherapy minimally six months prior to the study were included.

A complex view on therapeutic effect

We were looking not only at walking speed (T25-FW) or walking distance (2MWT), but also on balance (BBS, TUG, DGI), mobility (5xSTS, mod5STS, FSST, RMI), fatigue and cognition (SDMT, FSMC). Moreover, several self-report outcomes (MSWS-12, MSIS-29, ABC, PSmob, EQ-5D-5L) were analysed. We are convinced that this complex view is important for understanding the therapeutic effect.

While some studies have confirmed an effect on MSIS-29 [5,7,10], this study does not support it, similarly to Van der Linden et al. [16] and Taylor et al. [24]. On the other hand, we are in accordance with studies confirming an effect on quality of life [3,7,28]. An effect on fatigue has been documented by several studies [16,28,53]. In contrast, we did not find improvement of FSMC immediately, but noted a trend for improvement two months later, together with cognitive functions (FSMC, SMDT and TUGcogn). To our knowledge, no other study has investigated a potential effect of FES on cognitive functions, not even in a long-term perspective. In this study, we documented a delayed effect of FES in PCP on cognitive functions, which could potentially help pwMS to deal with multiple tasks during walking and everyday activities [54].

Comparison of therapeutic effect of FES with that of physiotherapy

Until now, only a few studies evaluated an effect of physiotherapy or exercise on foot drop and accompanying clinical functions, or even compared the effect of physiotherapy with that of FES. Barrett et al.[2] reported a training effect in the exercise group, and in Burridge's study [4] some patients profited from a short course of physiotherapy. Taylor et al. [24] in the follow up study reported an indication that adding core stability exercises to FES may have been associated with an improved training effect, although no training effect was seen with physiotherapy alone. Also, Esnouf et al. [20] compared a group with FES only to a group with exercise therapy, where subjects received a programme of simple physiotherapy home exercise. The exercise group showed a

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training effect in this study. Taylor's [24] and Esnouf's [20] studies confirmed a higher effect of FES, but noted the importance of combining FES with physiotherapy.

Our results confirmed that foot drop is treatable by an individually guided physiotherapy as well as by FES. The immediate effect of MPAT on clinical functions is comparable or even stronger (the overall significant changes in BBS and EQ-5D-5L components were mainly driven by MPAT) than FES in PCP. On the other side, this study documented minimal persistent and any delayed effect of MPAT.

Immediate, persistent and delayed effect

Most studies evaluated an immediate effect [2-16,18,20-28]. This is the first study documenting a persistent and delayed effect that could be caused by an activation of the plastic and adaptive processes in the central nervous system (CNS). Although our pilot studies [55,56] documented that MPAT activates these processes, from results in this study it seems that FES in PCP activates auto reparative processes strongly - while an immediate effect of both foot drop treatment is comparable, persistent (EQ-5D-5L self-care and mobility) and delayed effect (TUGcognitive and EQ-5D-5L usual activities) has been documented only after FES in PCP. According to Everaert et al. [18] who, based on motor-evoked potentials using transcranial magnetic stimulation over the motor cortex, noticed that FES could modulate the CNS by repetitive stimuli in such a way as to promote plasticity in the cortico-spinal pathways. This promising findings need to be verified.

Conclusions

The new approach combining FES with postural correction of the patients' position has a significant immediate therapeutic effect on the static balance, on the self-reported balance confidence and on several aspects of perceptions of patients with MS. The immediate effect of FES in PCP is comparable with the individualized Motor Program Activating Therapy. A significant therapeutic effect persisted only in Group 1 where the subjects used Functional Electrical Stimulation. Moreover, a delayed effect on cognitive functions and fatigue is documented in this group. The only patient-related factor that predetermined the effectiveness of both individual physiotherapy and FES application was the patients' prior experience with individual physiotherapy. Our results could help to improve the algorithm treatment of foot drop in people with Multiple Sclerosis.

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NOTES

Conflicts of interest. The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Table 1. Baseline characteristic of participants

	Total	Group 1	Group 2	Fisher exact test p-value	t-test p-value
Age [years]	48.5 ± 10.2	50.5 ± 10.8	46.5 ± 9.3		0,201
Sex: female	25 (57%)	12 (55%)	13 (59%)	0.99	
male	19 (43%)	10 (45%)	9 (41%)		
EDSS	4.7 ± 1.4	4.5 ± 1.3	4.9 ± 1.4		0,322
Time since onset [years]	12.8 ± 6.2	12.9 ± 6.8	12.7 ± 5.8		0,939
Type of MS: RR	23 (52%)	12 (55%)	11(50%)	0.99	
SP	17 (39%)	8 (36%)	9(41%)		
PP	4 (9%)	2 (9%)	2 (9%)		
Physiotherapy in past (more than 6 months)	14 (32%)	4 (18%)	10 (45%)	0,104	
Use of walking aids … no aid	13 (32%)	7 (37%)	6 (27%)	0,167	
unilateral	11 (27%)	7 (37%)	4 (18%)		
bilateral	17 (41%)	5 (26%)	12 (55%)		
Use of orthosis	4 (9%)	2 (9%)	2 (9%)	0.99	
BMI	24.3 ± 4.5	24.6 ± 4.4	24.0 ± 4.6		0,643

Table note: N number of participants, BMI = Body Mass Index, EDSS = Expanded Disability Status Scale, Status Scale, Types of Multiple Sclerosis (MS): RR = Relapsing-Remitting, SP = Secondary-Progressive, PP = Primary-Progressive

Fisher exact test was used to compare categorical characteristics between therapy groups t-test was used to compare continuous characteristics between therapy groups

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Table 2: Immediate and persistent treatment effects

	Group 1					Group 2							
Part A: variables where non-parametric approach appropriate	**M1**	**M1 → M2**	**Wilcoxon test**	**M1 → M3**	**Wilcoxon test**	**M1**	**M1 → M2**	**Wilcoxon test**	**M1 → M3**	**Wilcoxon test**	**Difference in immediate therapeutic effect between group 1 and 2**	**Difference in persistent therapeutic effect between group 1 and 2**	**Physiotherapy in past as covariate of effetive therapy**
	median	**median change**	**p-value**	**median change**	**p-value**	**median**	**median change**	**p-value**	**median change**	**p-value**	**W - test**	**W - test**	**W-test**
T25FW [s]*	8,3	0	0,935	-0,1 ↑	0,644	8,9	0	0,946	0,4 ↓	0,349	1	0,3169	0,773
TUG [s]	11,5	-0,6 ↑	0,137	-0,8 ↑	0,064	12,6	-0,7 ↑	0,198	0,1 ↓	0,892	0,954	0,2279	0,288
TUGcogn [s]	12	-0,3 ↑	0,633	-1.0 ↑	**0,005**	13	0,5 ↓	0,225	0,3 ↓	0,329	0,255	**0,0129**	0,46
Part B: variables where parametric approach appropriate	**M1**	**M1 → M2**	**t-test**	**M1 → M3**	**t-test**	**M1**	**M1 → M2**	**t-test**	**M1 → M3**	**t-test**	**Difference in therapeutic effect between group 1 and 2**	**Difference in therapeutic effect between group 1 and 2**	**Physiotherapy in past as covariate of effetive therapy**
	mean	**mean change**	**p-value**	**mean change**	**p-value**	**mean**	**mean change**	**p-value**	**mean change**	**p-value**	**t - test**	**t - test**	**t-test**
FSST [s]	14,1	-1,3 ↑	0,164	-1,2 ↑	0,12	12,3	-0,3 ↑	0,475	-0,5 ↑	0,243	0,292	0,593	0,375
5xSTS [s]	16,3	0,5 ↓	0,583	-0,8 ↑	0,212	16	-0,3 ↑	0,787	0,4 ↓	0,538	0,569	0,545	0,612
mod5STS [s]	15,2	-0,7 ↑	0,158	-1 ↑	0,142	18,7	1,2 ↓	0,372	1,1 ↓	0,158	0,158	0,241	0,313
2MWT [m]*	86,1	0,2 ↑	0,961	-3,1 ↓	0,406	88,9	-0,9 ↓	0,812	2,4 ↑	0,456	0,828	0,57	0,536
BBS*	35,7	2.0 ↑	**0,008**	1,1 ↑	0,528	36,8	2.2 ↑	**0,025**	1,1 ↑	0,361	0,841	0,976	0,928
DGI*	12,9	0,2 ↑	0,591	-0,4 ↓	0,617	15	0,5 ↑	0,241	0,4 ↑	0,315	0,57	0,574	0,062
SDMT	40	2 ↑	0,115	2,8 ↑	0,053	36,7	0,2 ↑	0,915	0,6 ↑	0,73	0,333	0,57	0,629
FSMCcogn	28	-1,5 ↑	0,361	-3,3 ↑	0,083	28,5	0,8 ↓	0,536	-0,1 ↑	0,952	0,278	0,545	**0,023**
FSMCmotor	37,1	-2,1 ↑	0,15	-3 ↑	0,082	35,4	-0,2 ↑	0,867	-0,7 ↑	0,647	0,327	0,57	**0,001**
FSMCtotal	65,1	-3,5 ↑	0,214	-6,1 ↑	0,074	63,9	0,6 ↓	0,799	-0,7 ↑	0,727	0,272	0,545	**0,004**
RMI	12,2	0,2 ↑	0,644	0,4 ↑	0,282	13,1	0,3 ↑	0,468	0,1 ↑	0,895	0,817	0,66	0,667
MSWS-12*	43,2	-5,2 ↑	0,063	-2,5 ↑	0,381	38,3	-3,8 ↑	0,078	1,2 ↓	0,681	0,677	0,574	0,086
PSmob	3,5	-0,1 ↓	0,54	-0,1 ↓	0,266	3,1	0,1 ↑	0,772	0,1 ↑	0,494	0,534	0,545	0,458

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MSIS-29	71,8	-4,3 ↑	0,334	-3,4 ↑	0,456	75,2	-6,2 ↑	**0,043**	-4,4 ↑	0,089	0,717	0,922	0,056
ABC*	45,7	6.1 ↑	**0,04**	6,8 ↑	0,073	60,7	-0,7 ↓	0,796	-4,5 ↓	0,166	0,092	0,18	0,131
EQ-5D-5L mobility	3,4	-0.5 ↑	**0,005**	-0.7 ↑	**0,001**	2,9	-0.5 ↑	**0,046**	-0,1 ↑	0,816	0,941	0,18	0,545
EQ-5D-5L self care	2,4	-0.5 ↑	**0,019**	-0.6 ↑	**0,005**	2,1	-0,3 ↑	0,163	-0,2 ↑	0,331	0,459	0,397	0,538
EQ-5D-5L usual activities	2,7	-0,3 ↑	0,248	-0.5 ↑	**0,029**	2,8	-0.5 ↑	**0,008**	-0,4 ↑	0,057	0,399	0,933	0,854
EQ-5D-5L pain discomfort	2,1	0	1	0	1	2,3	-0.5 ↑	**0,008**	-0,4 ↑	0,149	0,108	0,573	0,263
EQ-5D-5L anxiety and depression	1,5	-0,2 ↑	0,135	-0,1 ↑	0,605	1,6	-0,3 ↑	0,287	0	1	0,896	0,834	0,594
EQ-5D-5L health today	62,1	2 ↑	0,471	2,5 ↑	0,476	66,9	12.8 ↑	**0,032**	-0,6 ↓	0,929	**0,038**	0,782	0,417

Table note: * significant at 0.05, without correction

&primary outcome

25-FW Timed 25-Foot Walk test, TUG Timed Up and Go Test, cogn cognitive, FSST Four Square Step Test, 5xSTS Five Times Sit to Stand Test, mod5STS Modified 5-repetition sit-to-stand test, 2MWT 2-Minute Walk Test, BBS Berg Balance Scale, DGI Dynamic Gait Index, SDMT Symbol Digit Modalities Test, FCMC The Fatigue Scale for Motor and Cognitive Functions, RMI Rivermead mobility index, MSWS-12 Multiple Sclerosis Walking Scale-12, PS mob Performance Scale - mobility, MSIS-29 Multiple Sclerosis Impact Scale, EQ-5D-5L Euroqol-5 dimensions-5 levels questionnaire; ↑ improvement, ↓ worsening

Abbreviations: M1, examination 1 (baseline clinical characteristic); M2, follow up, examination 2 (immediate effect); M3, follow up 2, examination 3 (persistent effect); M1 → M2: difference M2-M1, M1 → M3: difference M3-M1

In case of T25FW avg, TUG and TUGCOGN a nonparametric approach was appropriate. Median was used as a location parameter; paired Wilcoxon test was used to test for change in a measurement and two-sample Wilcoxon test was used to compare differences between therapy groups (Effect of therapy type) and between those with and without prior MPAT therapy (Effect of therapy before).

For other variables, a parametric approach was appropriate. Mean was used as a location parameter, paired t-test was used to test for change in a measurement and two-sample t-test was used to compare differences between therapy groups (Effect of therapy type) and between those with and without prior MPAT therapy (Effect of therapy before).

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