The impact of balance specific physiotherapy, intensity of therapy and disability on static and dynamic balance in people with multiple sclerosis: a multi-centre prospective study

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Abstract

Background: A high-quality research identifying the best physiotherapeutic approach for the improvement of balance in people with multiple sclerosis is missing. This study compared aspects of balance improvement such as therapy specificity to balance, therapy method and category, country, intensity and medical conditions.

Methods: A multicentric randomised rater-blinded controlled trial comprised three different physiotherapy programs (Czech and Italian outpatient or inpatient programs). All patients received 20 therapy sessions. Experimental group underwent balance specific physiotherapy (it was Motor Program Activating Therapy in the Czech cohort and Sensory-motor Integration Training in the Italian cohort), control group underwent non-balance specific physiotherapy (it was Vojta reflex locomotion in the Czech cohort and conventional dynamic strengthening exercises in the Italian cohort, respectively). Static balance was evaluated by Berg Balance Scale and dynamic balance was assessed by Timed Up-and-Go Test.

Results: A total of 149 patients entered the study. Physiotherapy significantly improved static balance ($p < 0.0001$, increase by mean 2.6 points (95% confidence interval 2.0-3.5) in BBS score). Balance specific approach had a higher effect than non-specific balance approach (increase in BBS by 1.9 points, 95 % confidence interval 0.9 to 3.7 points). The intensity of the physiotherapy significantly influenced static balance (BBS by 2.7 points higher in the inpatient setting, $p = 0.007$). Dynamic balance was also improved (TUG decrease by -0.8 s (95% CI -1.4 – -0.1 s, $p = 0.011$)); the balance specificity had no impact. The level of disability played the most important role ($p = 0.022$).

Conclusion: Although the overall changes in static and dynamic balance were statistically significant, they were quite small in a clinical sense. A small statistically significant difference between balance specific and non-specific treatment was found. It seems that a high intensity of the therapy is critical to maximize the effectiveness.

Highlights

- Physiotherapy has a significant effect on balance in people with multiple sclerosis.
- With the same number of sessions, more intense therapy is more effective.
- Physiotherapy improves dynamic balance more in people with more severe disability.
- Outcome is influenced by balance specificity approach but not by different physiotherapeutic categories.

Key words
physiotherapy, static and dynamic balance, multiple sclerosis, intensity of therapy, balance specific approach

1. Introduction

Balance impairment has been reported in 75% of people with multiple sclerosis (MS) and is one of the primary causes of disability limiting their daily life activities (Cattaneo et al., 2002).
Despite the fact that physiotherapy (PT) is an important component of a comprehensive treatment of the people with MS, literature addressing MS balance physiotherapy does not offer clear consensus of the balance management with a significant reduction of falls (Paltamaa et al., 2012, Cattaneo et al., 2018). Several studies confirmed a positive effect of some of the physiotherapeutic methods, for example of balance-based torso-weighting (Gibson-Horn et al., 2008), exercise programs oriented to improve muscle strength, flexibility and endurance (Coote et al., 2013), balance exercises using functional positions (Coote et al., 2013), the Wii balance board (Brichetto et al., 2013), balance control (Smedal et al., 2006) and behavioural approaches that alter the knowledge, skills and attitudes about the control of balance (Finlayson et al., 2009). However, a high-quality research identifying factors influencing the effectiveness of the physiotherapy for balance improvement in people with MS is still missing. To fill this gap, we have used the findings and structure from a pilot project of the Italian co-authors (Cattaneo et al., 2007) to realize a larger study that would, apart from balance specific intervention, target also the treatment intensity and methods as possible intervening factors.
Factors intervening in the efficacy of physiotherapy are a very current topic in MS (Grasso et al., 2005, Liberatore et al., 2014) and other diseases such as stroke (Paolucci et al., 2001) or traumatic spinal cord injury (AlHuthaifi et al., 2017) , however till now there is a dearth of studies investigating possible intervening factors in enhancing efficacy of balance physiotherapy in people with MS.

The objectives of the study were to evaluate the effect of physiotherapy on static and dynamic balance in people with MS and to determine the role of various factors influencing the effectiveness of physiotherapy on balance, namely balance specificity, therapeutic category (neuroproprioceptive "facilitation, inhibition" versus motor/skill acquisitions), intensity of therapy and medical condition.

2. Methods

2.1 Design of the study

Three centers, two from the Czech Republic and one from Italy, participated in the parallel randomised rated blinded controlled trial between March 2011 and October 2014. Patients were recruited from inpatient (IT-1) and/or outpatient (CZ-O, IT-O) programs provided by the participating centers. In each center, a blinded assessor evaluated static and dynamic balance of MS patients before and after the therapeutic programs, respectively. Both inpatients and outpatients programs consisted of 20 treatment sessions but the length of the program differed: twenty consecutive days for inpatients and two months for outpatients. Outpatients in both outpatient locations and inpatients in Italy were allocated into control / intervention groups according to a randomization list aiming at ratio 1:2 (control / intervention). The control group in each of the center underwent their conventional physiotherapy program. The intervention group underwent a physiotherapy program that included a minimum of 25 minutes of specific balance oriented intervention (Table 1). Control treatments, as well as, intervention (balance specific) treatments differed between the centers thus the aim was to explore the effect of a balance-specific intervention within the usual practice of a center. Data from Italian cohorts were also analysed for other hypotheses in Cattaneo et al. (2018), clinical trial registration NCT02390830.

2.2 Participants

Patients with definite MS (Polman et al., 2005) were enrolled into this study based on the inclusion criteria: stable clinical status in the preceding three months, ability to walk for six meters even with an assistive device, ability to maintain a standing position with open eyes for at least 30 seconds, an ability to stand in monopodalic-standing position for 10 seconds, and enough cognitive ability, by clinical judgement, to understand and execute instructions given by the therapist. All subjects signed the informed consent forms approved by the local ethics committees.

2.3 Assessment

Demographic data (age, type and duration of the disease, and the level of disability according to the Expanded Disability Status Scale (EDSS; Kurtzke et al., 1983)) were either assessed by the neurologists at the beginning of the study or the information was retrieved from clinical charts. Static balance was evaluated by Berg Balance Scale (BBS; Berg et al., 1995) while dynamic balance was assessed by Timed Up-and-Go Test (TUG; Schoene et al., 2013). Minimal clinically important change (MCID) for BBS was set at an increase of 3 points or more for inpatients and at 2 points or more for outpatients. MCID for TUG was set at a decrease of 2 seconds and more (Gervasoni et al., 2017). Treatment responders were defined as patients with MCID or a better result. BBS and TUG data were collected before the first session of the therapeutic program (pre-treatment) and without delay after the last session of each therapeutic program (post-treatment).

2.4 Intervention

The treatment of the **Control group** was aimed at the reduction of limitations of the body function and the functional level. Specific treatment of balance was restricted to the maximum of 10 minutes per session. In both IT-1 and IT-O cohorts, the patients underwent **conventional exercises,** including stretching, core stability and light strengthening exercises (Moon et al., 2013). In CZ-O cohort, **Vojta reflex locomotion treatment** (VRL; Vojta, Peters, 2007), a kind of neuroproprioceptive "facilitation, inhibition" (Martinkova et al., 2018), was applied. VRL method is based on the activation of global locomotion patterns by the stimulation of specific zones, with the individual placed in a precisely determined initial position. VRL activates involuntary responses of muscle function necessary for spontaneous movements.

Balance specific treatment was carried out in two IT centers and in the CZ-O. The treatment of the **Intervention group** consisted of at least 25 minutes of balance specific treatment aimed at improving the participant's control of position and movement of the center of mass and body segments during static, dynamic and transitional tasks. Patients in both IT-1 and IT-O cohorts underwent **Sensory-motor Integration Training** (SMIT, Cattaneo et al., 2007), a kind of motor/skill acquisitions (Martinkova et al., 2018). SMIT involves balance exercises in different sensory contexts oriented to the task execution. Patients in CZ-O cohort underwent **Motor Program Activating Therapy** (MPAT, Rasova et al., 2014), a kind of neuroproprioceptive "facilitation, inhibition" (Martinkova et al., 2018). MPAT combines different kinds of afferent somatosensory stimuli (mainly proprioceptive, but also tactile, visual, auditory, etc.) in different functionally centred initial postural positions (sitting, standing) so that it creates an attitude for different movements (standing up, walking).

2.5 Data analysis

Data were analysed using intention-to-treat approach. Based on the previous pilot study, we have estimated the number of participants to be 98 in the intervention and 57 in the control group to have 90 % power to detect a difference in BBS ≥ 3 at 5 % level of statistical significance.

Categorical variables (sex, type of MS, use of assistive devices, proportion of responders) were summarized as absolute and relative frequencies. Continuous variables (age at recruitment, EDSS, disease duration, pre-treatment BBS score and TUG) were summarized either as means with standard deviation (SD) or as medians with interquartile range (IQR), depending on the character of the variable. For initial comparisons of continuous variables between study groups, Wilcoxon two-sample test was used to compare the Czech and Italian cohort and Kruskall-Wallis test to compare the three study groups (IT-I, IT-O, CZ-O). For the same comparisons of categorical variables Fisher exact test was used.

The effectiveness of treatment was examined through BBS score / TUG change computed as a difference of post-treatment value minus pre-treatment value. Presence of any change across groups was tested using one-sample t-test in case of BBS change and one-sample Wilcoxon sum rank test in case of TUG (because of the character of TUG data). The overall difference in the therapy effect between intervention and control groups and between inpatient and outpatient settings was tested using two-sample t-test for BBS score and Wilcoxon test for TUG. For the possible difference in the proportion of responders Fisher exact test was used. In order to account for the multicenter design of the study linear ANOVA models for BBS and TUG change were constructed, with intervention/control as a main factor and center (IT-I, IT-O and CZ-O) as a covariate. For the proportion of responders, Cochran-Mantel-Haenszel test was used. The proportion of responders (i.e. patients with BBS score change ≥ MCID) was assessed only for patients with pre-treatment BBS score ≤ 53 (potential responders). Such patients could potentially improve their BBS score by at least MCID.

The influence of other factors (gender, type of disease, EDSS, use of assistive devices, age, disease duration) on the changes in TUG score and in BBS score were further modelled using multiple linear regression model with interactions between the control/intervention status and the factor. The possible influence of other factors on the proportion of responders was assessed through multiple logistic regression models with interactions. The comparison of various types of physiotherapy categories (motor/skill acquisitions / neuroproprioceptive "facilitation, inhibition" / non-specific) were carried out using Tukey post-hoc in the linear regression model. Two outlying TUG change measurements (-50 s, -32 s) were excluded from relevant regression models as they heavily influenced the linear model testing.

The level of statistical significance was set to 0.05. The analyses were carried out in the statistical environment and language R, version 3.2.2.

3. Results

3.1 Participants

Out of 178 eligible MS patients that were randomised, 149 MS patients (84 %) finished the study (for the flow of participants see Figure 1). There was an issue with the Italian cohort's compliance in TUG tests. TUG measurements were missing from 31 patients (21%), mostly from the Italian inpatient group (22, i.e. 52%) and, more importantly, from the Italian inpatient control group (10, i.e. 83%). Therefore we decided to include only the Italian outpatient group (9, i.e. 16% TUG measurement missing) into the analysis of the TUG measurements. The analysis of the BBS scores was performed as planned initially, using all the Czech and Italian outpatient and inpatient data.

While the participating centers did not differ in the male/female ratio and age of participants, there was a main source of heterogeneity in the severity of the disease, mainly between Italian and Czech centers. Italian patients had more severe EDSS than Czech patients (by 1 point, median 5.5 vs. 4.5, p = 0.002, Wilcoxon two-sample test) and they also had a slightly but non-significantly longer disease duration (14.4 vs. 12 years, p = 0.168, Wilcoxon two-sample test). Czech patients mostly suffered from relapse-remittent MS while the Italian ones, namely patients in IT-1 center, had more secondary progressive MS and used more assistive devices. These factors may have influenced the slight difference in the pre-treatment BBS and TUG scores between the Czech and Italian patients (median BBS 49 vs. 47 points, p = 0.071, median TUG 10.2 vs. 12.5 s, p = 0.045, Wilcoxon two-sample test), respectively (for detailed characteristics of the participants see Table 2).

3.2. Static balance – Berg Balance Scale scores

Overall, the physiotherapy improved the static balance measured by BBS by mean 2.6 points (95%CI 2.0-3.5, $p < 0.0001$. Of the 127 potential responders (i.e. patients with the pre-treatment BBS score ≤ 53), 54 % (69) were true BBS responders, i.e. improved by 3 or more points if inpatients and 2 or more points if outpatients. (Table 3, Figure 2A). There was no statistically significant difference in the overall improvement between countries. The heterogeneity in the disease type and severity hence did not have a significant effect (t-test $p = 0.22$).

We observed a statistically significant mean difference of 1.9 points (95 % confidence interval (CI): 0.9 to 3.7 points, t-test $p = 0.039$, Table 3, Figure 2B) favouring intervention (balance specific) groups over the control (balance non-specific). This observation was weakened when adjusting for country and intensity of therapy; the regression estimate of a difference being 1.6 (95 % CI: -0.1 to 3.4 points, $p = 0.071$). In terms of clinically meaningful improvement, there were 59 % (49 out ot 83) responders in the intervention group and 46 % (20 out of 44) responders in the control group; however, the difference was not statistically significant (Fisher exact test $p = 0.18$).

As the Italian cohort was (a) more homogeneous in a sense of disease type and severity, (b) used the same methods in both intensity arms and (c) directly followed up our previous Italy-based pilot study (Cattaneo et al., 2007), we have performed the tests separately for the Italian patients. There was a statistically significant difference of 2.6 (95 %CI 0.5 – 4.9) points in improvement in BBS scores in the Italian intervention group, irrespective of the intensity of therapy (overall $p = 0.015$, adjusted $p = 0.020$, Table 3, Figure 2C). In terms of responsivity to the treatment, there were 60 % (39 out ot 65) responders in the intervention group and 38 % (11 out of 29) responders in the control group but the difference was not statistically significant (Fisher exact test $p = 0.07$).

There was a statistically significant difference of 2.9 (95 %CI 1.0 – 4.7, $p = 0.007$) in BBS improvement between the inpatient facility (IT-1, mean 4.6) and outpatient facilities (IT-O and, mean 1.7). The patients with more intense therapy improved more (Table 3). Looking at the clinically meaningful improvement in the inpatient setting (MCID 3 points or more), there were 52 % responders, while in the outpatient care (MCID 2 points or more) there were 55 % responders ($p = 0.85$, Fisher exact test).

Neither patient's age, gender, type of the disease, disease severity (EDSS), disease duration nor the use of assistive devices influenced differences between pre-therapy and post-therapy measurements. As for the different categories of the therapy used throughout the experiment, the motor/skill acquisitions had slightly higher, but non-significant, effect in comparison with the neuroproprioceptive "facilitation, inhibition" on static balance ($p = 0.062$, Tukey post-hoc test in linear regression model, Figure 2A).

3.3 Dynamic balance – Timed Up-and-Go test

The TUG measurements were analysed for the Czech and Italian outpatient cohorts due to a large proportion of missing data in the inpatient cohorts.

Overall, the physiotherapy improved the dynamic balance measured by TUG by median -0.8 s (95% CI -1.4 – -0.1 s, $p = 0.011$). Of the 91 patients, 27 (30 %) patients improved in dynamic balance (i.e. had shorter time in TUG test) by 2 seconds or more (Table 4, Figure 3A). There was no statistically significant difference in the overall improvement between countries (Wilcoxon test $p = 0.12$).

We didn't observe any statistically significant difference between intervention and control groups (overall $p = 0.74$, adjusted $p = 0.51$, Table 4, Figure 3B). Similarly, the percentage of improved patients did not differ between control and intervention groups (p = 0.65, Table 4). There was no difference in TUG change between control and intervention group in the Italian subset (p = 0.77).

The most important factor influencing the treatment-related TUG change was the EDSS score prior to the therapy. It best explained changes in the dynamic balance: by mean -0.6 s shorter time post therapy for 1 EDSS point (p = 0.022, 95 %CI -1.1 to -0.1, model controlled for country). Similarly, the probability of response in dynamic balance (TUG decrease by 2 s and more) increased by 53% with each EDSS point (p = 0.037, OR = 1.53, 95 %CI 1.01 to 2.32, model controlled for country). Otherwise neither patient's age, gender, type of the disease, disease duration nor the use of assistive devices influenced the differences between pre-therapy and post-therapy measurements. Also, there was no particular effect of therapy category on TUG or TUG responsivity.

4. Discussion

This multicenter study investigated the effectiveness of physiotherapy on balance in MS people and it compared aspects of its effectiveness such as therapy specificity to balance, therapy method and category, country, intensity and medical conditions.

As expected, the balance-specific intervention led to a higher improvement of the static balance compared to the standard therapy, in terms of the BBS score change. This confirms the results from the pilot study (Cattaneo et al., 2007). Numerically, about 60 % of patients responded to the treatment in the intervention group compared to less than a half in the control group. On the contrary, there was only a minor change in dynamic balance measured with the TUG test and no statistically significant differences were found between the balance-specific and standard program. This different result for the dynamic balance may be influenced by the fact that only the lower intensity groups had the TUG test measured in the present study.

Several factors modulating the effects of physiotherapy and the number of responders to the physiotherapy were explored in this study. One of the most important factors was the setting of the physiotherapy procedure. Inpatient physiotherapy provides higher intensity of treatment and a more comprehensive and multi-professional approach to the whole process. This confirms our observations from the pilot study (Cattaneo et al., 2007). Treatment intensity was a key factor although differences in drug prescription and other concomitant therapies (e.g. cognitive rehabilitation) not acounted for in the study may have influenced the results (Slade et al., 2002, Grasso et al., 2005). Similar proportion of responders in the inpatient and outpatient setting supports the distinction of Minimal Clinically Meaningful Difference on the BBS according to therapy intensity as proposed by Gervasoni et al., 2017.

Apart from the treatment intensity the next factor was the disease progression , with more severely disabled MS subjects showing more improvement in motor and balance skills. This is in accordance with former studies by Liberatore et al. (2014) and by Grasso and al. (2005) who found better response in those with a more severe balance dysfunction at baseline. In this study, 37 % (55) patients had BBS higher or equal to 50 points at baseline with 10 of them reaching the maximum score before physiotherapy, thus reducing the possibility of an observable response to physiotherapy.

Finally, two different categories (neuroproprioceptive "facilitation, inhibition" and motor/skill acquisitions physiotherapy categories) were compared in this study. In the motor/skill acquisitions the MS patients learned by repeating a given specific task in the different environments/under different conditions while in the neuroproprioceptive "facilitation, inhibition", afferent inputs were applied to facilitate and improve the quality of motor patterns (Rasova et al., 2010, Martinkova et al., 2018).

Motor/skill acquisitions approach to balance physiotherapy (methods used in Italy) had higher but not statistically significant effect on static balance. This is in contrast with findings of Wiles et al. (2001) and Lord et al. (1998) that did not find any difference in the effect of facilitation and task oriented approach in MS patients.

There were several limitations to the study. First, some patient characteristics differed between centers and programs (3.1 Participants), namely in disease type and severity. On the other hand, the differences between patients in inpatient and outpatient programs within the same country cohort were minimal and we accounted for them in the regression analyses. The other important issue is a problem with the Italian inpatient cohort's compliance in TUG tests. TUG measurements were missing from 22, i.e. 52% of Italian inpatients,therefore we could only evaluate the intervention effect for the outpatient programs. Further studies with a bigger number of participants in the inpatient group and with more measures of dynamic balance would be indicated.

Other possible limitation lies in the tools used to measure balance improvement. In this study we used the TUG and the BBS as measures of dynamic and static balance. It is known that the BBS suffers from a ceiling effect, so a different balance scale might better capture changes in balance in response to physiotherapy in persons with MS with lower EDSS scores (e.g. Mini-BESTest, Ross et al, 2016). Also, TUG test may be too rough to capture improvements compared to other walking ability tests (Pearson et al, 2015). Fatigue, mood and cognitive reserve, not measured in the present study, are other factors that might influence outcome of physiotherapy for people with multiple sclerosis and should be included in future prospective randomized studies.

Also, the use of different physiotherapy methods may be seen as a limitation. Our previous study (Martinkova et al, 2018) showed that there is a large variety in particular method preferences among centers, both on regional and individual levels. This experience is thus reflected in the present study – the goal was to see whether the intervention defined as "balance specific approach within the usual practice of the center" is able to improve the patients' balance expressed through BBS/TUG measurements.

5. Conclusions

Physiotherapy had a beneficial effect on static balance improvement in persons with MS, with a better outcome when balance specific approaches were used. The major factors associated with the effectiveness of the therapy aiming at improving balance are the intensity of the therapy and the degree of disability. This is a fundamental information for clinicians planning physiotherapy approaches tailored to an individual person with MS.

REFERENCES

AlHuthaifi F, Krzak J, Hanke T, Vogel LC. Predictors of functional outcomes in adults with traumatic spinal cord injury following inpatient rehabilitation: A systematic review. The journal of spinal cord medicine. 2017;40(3):282-94.

Berg K, Wood-Dauphinee S, Williams JI. The Balance Scale: reliability assessment with elderly residents and patients with an acute stroke. Scandinavian journal of rehabilitation medicine. 1995;27(1):27-36.

Brichetto G, Spallarossa P, de Carvalho ML, Battaglia MA. The effect of Nintendo(R) Wii(R) on balance in people with multiple sclerosis: a pilot randomized control study. Multiple sclerosis (Houndmills, Basingstoke, England). 2013;19(9):1219-21.

Cattaneo D, De Nuzzo C, Fascia T, Macalli M, Pisoni I, Cardini R. Risks of falls in subjects with multiple sclerosis. Archives of physical medicine and rehabilitation. 2002;83(6):864-7.

Cattaneo D, Jonsdottir J, Zocchi M, Regola A. Effects of balance exercises on people with multiple sclerosis: a pilot study. Clinical rehabilitation. 2007;21(9):771-81.

Cattaneo, D.; Řasová, K.; Gervasoni, E.; Dobrovodská, G.; Montesano, A.; Jonsdottir, J.: Falls prevention and balance rehabilitation in multiple sclerosis: a bi-centre randomised controlled trial. Disability and Rehabilitation, 2018, 40(5): 522-526.

Coote S, Hogan N, Franklin S. Falls in people with multiple sclerosis who use a walking aid: prevalence, factors, and effect of strength and balance interventions. Archives of physical medicine and rehabilitation. 2013;94(4):616-21.

Finlayson M, Peterson EW, Cho C. Pilot study of a fall risk management program for middle aged and older adults with MS. NeuroRehabilitation. 2009;25(2):107-15.

Gervasoni E, Jonsdottir J, Montesano A, Cattaneo D. Minimal Clinically Important Difference of Berg Balance Scale in People With Multiple Sclerosis. Arch Phys Med Rehabil. 2017; 98(2):337-340

Gibson-Horn C. Balance-based torso-weighting in a patient with ataxia and multiple sclerosis: a case report. Journal of neurologic physical therapy: JNPT. 2008;32(3):139-46.

Grasso MG, Troisi E, Rizzi F, Morelli D, Paolucci S. Prognostic factors in multidisciplinary rehabilitation treatment in multiple sclerosis: an outcome study. Multiple sclerosis (Houndmills, Basingstoke, England). 2005;11(6):719-24.

Herman T, Giladi N, Hausdorff JM. Properties of the 'Timed Up and Go' Test: More than Meets the Eye. Gerontology. 2011;57(3):203-10.

Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983;33(11):1444-52.

Liberatore G, Clarelli F, Nuara A, Ungaro D, Gatti R, Rovaris M, et al. Predictors of effectiveness of multidisciplinary rehabilitation treatment on motor dysfunction in multiple sclerosis. Multiple sclerosis (Houndmills, Basingstoke, England). 2014;20(7):862-70.

Lord SE, Wade DT, Halligan PW. A comparison of two physiotherapy treatment approaches to improve walking in multiple sclerosis: a pilot randomized controlled study. Clinical rehabilitation. 1998;12(6):477-86.

Martinková, P; Freeman, J; Drabinová, A; Erosheva, E; Cattaneo, D; Jonsdottir, J; Baert, I; Smedal, T; Romberg, A; Feys, P; Alves-Guerreiro, J; Habek, M; Henze, T; Santoyo Medina, C; Beiske, A; Van Asch, P; Bakalidou, D; Salci, Y; Dimitrova, En; Pavlíková, M; Řasová, K. Physiotherapeutic interventions in multiple sclerosis across Europe: Regions and other factors that matter. Multiple Sclerosis and Related Disorders. 2018, 22(May), 59-67.

Moon HJ, Choi KH, Kim DH, Kim HJ, Cho YK, Lee KH, et al. Effect of Lumbar Stabilization and Dynamic Lumbar Strengthening Exercises in Patients With Chronic Low Back Pain. Annals of Rehabilitation Medicine. 2013;37(1):110-7.

Paltamaa J, Sjogren T, Peurala SH, Heinonen A. Effects of physiotherapy interventions on balance in multiple sclerosis: a systematic review and meta-analysis of randomized controlled trials. Journal of rehabilitation medicine. 2012;44(10):811-23.

Paolucci S, Grasso MG, Antonucci G, Bragoni M, Troisi E, Morelli D, et al. Mobility status after inpatient stroke rehabilitation: 1-year follow-up and prognostic factors. Archives of physical medicine and rehabilitation. 2001;82(1):2-8.

Pearson M, Dieberg G, Smart N. Exercise as a therapy for improvement of walking ability in adults with multiple sclerosis: a meta-analysis. Arch Phys Med Rehabil. 2015 Jul;96(7):1339-1348.

Rasova K, Feys P, Henze T, van Tongeren H, Cattaneo D, Jonsdottir J, et al. Emerging evidence-based physical rehabilitation for multiple sclerosis - towards an inventory of current content across Europe. Health Qual Life Outcomes. 2010;8:76.

Rasova K, Havrdova E, Brandejsky P, Zalisova M, Foubikova B, Martinkova P. Comparison of the influence of different rehabilitation programmes on clinical, spirometric and spiroergometric parameters in patients with multiple sclerosis. Multiple Sclerosis. 2006;12(2):227-34.

Rasova K, Prochazkova M, Tintera J, Ibrahim I, Zimova D, Stetkarova I. Motor programme activating therapy influences adaptive brain functions in multiple sclerosis: clinical and MRI study. International journal of rehabilitation research Internationale Zeitschrift fur Rehabilitationsforschung Revue internationale de recherches de readaptation. 2014.

Ross E, Purtill H, Uszynski M, Hayes S, Casey B, Browne C, Coote S. Cohort Study Comparing the Berg Balance Scale and the Mini-BESTest in People Who Have Multiple Sclerosis and Are Ambulatory. Phys Ther. 2016 Sep;96(9):1448-55.

Schoene D, Wu SM, Mikolaizak AS, Menant JC, Smith ST, Delbaere K, et al. Discriminative ability and predictive validity of the timed up and go test in identifying older people who fall: systematic review and meta-analysis. Journal of the American Geriatrics Society. 2013;61(2):202-8.

Slade A, Tennant A, Chamberlain MA. A randomised controlled trial to determine the effect of intensity of therapy upon length of stay in a neurological rehabilitation setting. Journal of rehabilitation medicine. 2002;34(6):260-6.

Smedal T, Lygren H, Myhr KM, Moe-Nilssen R, Gjelsvik B, Gjelsvik O, et al. Balance and gait improved in patients with MS after physiotherapy based on the Bobath concept. Physiotherapy research international: the journal for researchers and clinicians in physical therapy. 2006;11(2):104-16.

Vojta V, Peters, A. Das Vojta-Prinzip. Heidelberg: Springer; 2007.

Wiles C, Newcombe R, Fuller K, Shaw S, Furnival-Doran J, Pickersgill T, et al. Controlled randomised crossover trial of the effects of physiotherapy on mobility in chronic multiple sclerosis. Journal of Neurology, Neurosurgery, and Psychiatry. 2001;70(2):174-9.

Figure 1: CONSORT diagram of the flow of patients through the trial

Figure 2: BBS score change by intensity of therapy and treatments (A) and by Intervention / Control status, for the whole set (A, N = 149) and the Italian set only (C, N = 99). Figures show boxplots (median, 1st and 3rd quartile, outliers) and respective mean and median changes, within intensity + treatment groups and within control / intervention group. Overall p-values correspond to two-sample t-test. Multicentric p-values correspond to ANOVA F-test with respect to country and setting as covariates. Used abbreviations: in = inpatient, out = outpatient, SMIT = Sensory-motor Integration Training, VLR = Vojta Reflex Locomotion, MPAT = Motor Program Activating Therapy

Figure 3: TUG change by intensity of therapy and treatments (A) and by Intervention / Control status, for the whole outpatient set (A, N = 91) and the Italian outpatient set only (C, N = 48). Figures show boxplots (median, 1st and 3rd quartile, outliers) and respective mean and median changes, within intensity + treatment groups and within control / intervention group. Overall p-values correspond to Wilcoxon two-sample test. Multicentric p-values correspond to ANOVA F-test with respect to country and setting as covariates. For the calculation of TUG mean and ANOVA, two extreme observations were excluded. Used abbreviations: in = inpatient, out = outpatient, SMIT = Sensory-motor Integration Training, VLR = Vojta Reflex Locomotion, MPAT = Motor Program Activating Therapy

Table 1: Study design, methods overview and number of patients in each center and control/intervention arm

Country	Code name	Name of the center	Type of facility	Total N	Conventional (control) program	N	Balance intervention	N
Italy	IT-1	Department of neurorehabilitation, Milan	inpatient	42	**conventional lumbar dynamic strengthening exercises** (muscle re-education approach) aimed at improving the neuromuscular control, strength, and endurance of the muscles (Moon et al., 2013)	12	**SMIT: Sensory-motor Integration Training** (motor/skill acquisition) that involves balance exercises in different sensory contexts. It is aimed at subject's needs and sensory-motor disorders underlying the task execution (Cattaneo et al., 2007)	30
Italy	IT-O	Department of neurorehabilitation, Milan	outpatient	57		20		37
Czech Republic	CZ-O	Faculty hospitals Motol and Royal Vineyard, Prague	outpatient	50	**Vojta Reflex Locomotion** (neuroproprioceptive "facilitation, inhibition") that activate global locomotion patterns by stimulation of specific zones, with the individual placed in a precisely determined initial position (Vojta V., 2007)	23	**Motor Program Activating Therapy** (neuroproprioceptive "facilitation, inhibition") corrects patient's position according to ontogenesis and uses somatosensory stimuli to activate motor programs in the brain which then leads to the co-contraction of the patient's whole body (Rasova et al., 2015)	27
Total number of patients in the study				149	In the conventional (control) arm	55	In the intervention arm	94

Table 2: Group characteristics by center (N = 149)

Characteristic	Italian Cohort		Czech Cohort	p-value Fisher test # or KW test
	IT-1 (inpatients)	IT-O (outpatients)	CZ-O (outpatients)	
Number of participants	42	57	50	
Age [years] - Median (IQR)	45.5 (14.5)	48.9 (16.9)	45.5 (19.0)	0.083
Sex Male / Female N (%)	12 (29%) / 30 (71%)	21 (37%) / 36 (36%)	18 (22%) / 39 (78%)	0.248 #
Type of MS: Primary progressive - N (%)	2 (5%)	8 (17%)	2 (4%)	
Relapse-remittent - N (%)	17 (43%)	25 (52%)	30 (60%)	0.072 #
Secondary progressive - N (%)	21 (52%)	15 (31%)	18 (36%)	
Use of assistive device: None - N (%)	33 (79%)	35 (61%)	43 (86%)	
Unilateral - N (%)	5 (12%)	16 (28%)	1 (2%)	0.003 #
Bilateral / rollator / wheelchair - N (%)	4 (9%)	6 (11%)	6 (12%)	
EDSS [score] - Median (IQR)	5.5 (1.5)	5.5 (1.6)	4.5 (2.4)	0.006
MS duration [years] - Median (IQR)	14.9 (10.0)	13.9 (12.0)	12.0 (8.5)	0.287
Pre-treatment TUG [s] - Median (IQR) *	excluded	12.5 (6.8)	10.2 (6.6)	0.045
Pre-treatment BBS [score] - Median (IQR)	45.0 (8.8)	49.0 (8.0)	49.0 (12.0)	0.008
Pre-treatment BBS ≤ 53 - N (%)	42 (100%)	52 (91%)	32 (66%)	< 0.001 #
Pre-treatment fall rate - N (%)	18 (46%)	17 (30%)	12 (24%)	0.095 #

SD = standard deviation, IQR = interquartile range, KW = Kruskal-Wallis ANOVA test, MS = Multiple Sclerosis, EDSS = Expanded Disability Status Scale, TUG = Timed Up-and-Go, BBS = Berg Balance Scale

fall rate = fell at least once in the last two months

p-values correspond to comparisons between the four groups, # groups compared by Fisher exact test

* Pre-treatment TUG measurements are missing from 31 patients (21%), mostly from the Italian inpatient group (22, i.e. 52%). All the TUG related Italian inpatient data were hence excluded from the analysis

Table 3: Static balance (measured by BBS) results, overall and by study groups (control vs. interventions by centers, inpatient vs. outpatient)

Control vs. Intervention			**Valid N**	**Mean pre-treatment BBS score (SD)**	**Mean post-treatment BBS score (SD)**	**Mean BBS score change (SD)**	**Comparison of mean change** **Control vs. Intervention**	**Potential responders $** **N**	**Responders: BBS change ≥ 3 / 2 points $$ n (%)**	**Comparison of responders' proportions** **Control vs. Intervention**
Italian Cohort	Inpatients	Control	12	40.3 (9.5)	41.9 (9.4)	1.6 (1.5)		12	3 (25%)	
	Inpatients	Intervention	30	43.9 (6.5)	49.7 (4.6)	5.8 (6.5)	**All patients** Overall test * p = 0.039 Multicenter test ** p = 0.071	30	19 (63%)	**All patients** Overall test # p = 0.19 Multicenter test ## p = 0.18
	Outpatients	Control	20	44.5 (11.6)	45.2 (11.3)	0.8 (6.0)		17	8 (47%)	
	Outpatients	Intervention	37	47.4 (5.6)	49.8 (4.2)	2.4 (4.2)	**Italian cohort only** Overall test * p = 0.015 Multicenter test ** p = 0.020	35	20 (57%)	**Italian cohort only** Overall test # p = 0.07 Multicenter test ## p = 0.08
Czech Cohort	Outpatients	Control	23	48.5 (8.5)	50.3 (7.9)	1.8 (6.3)		15	9 (60%)	
	Outpatients	Intervention	26	42.6 (14.2)	42.9 (14.9)	1.6 (3.8)		18	10 (56%)	
Inpatient vs. outpatient							**Inpatients vs. outpatients**			**Inpatients vs. outpatients**
All inpatients			42	42.9 (7.5)	47.5 (7.2)	4.6 (5.8)	p = 0.007 *	42	22 (52%)	p = 0.85 #
All outpatients			106	45.9 (10.2)	47.3 (10.3)	1.7 (5.0)		85	47 (55%)	
Overall effect							**Overall effect**			
All patients			148	45.1 (9.6)	47.4 (9.5)	2.6 (5.4)	p < 0.0001 ***	127	69 (54%)	

* overall test = two-sample t-test, ** multicenter = ANOVA with respect to country and setting as covariates
# overall test = Fisher exact test, ## multicenter = Mantel-Haenszel test with respect to country and setting
$ Potential responders: patients with valid BBS pre-treatment score ≤ 53
$$ Minimal clinically important change defined as 3 for inpatients and 2 for outpatients
*** one sample t-test with $\mu = 0$ as null hypothesis

Table 4: Static balance (measured by TUG) results, overall and by study groups (control vs. interventions by centers)

Control vs. Intervention			Valid N	Median pre-treatment TUG [s] (IQR)	Median post-treatment TUG [s] (IQR)	Median TUG change [s] (IQR)	Comparison of median change Control vs. Intervention	Responders: TUG change ≤ -2s n (%)	Comparison of responders proportions Control vs. Intervention
Italian Cohort	Outpatients	Control	18	12.0 (7.8)	11.5 (11.0)	-0.2 (3.0)	**All outpatients** Overall test * p = 0.74 Multicenter test ** p = 0.51	6 (33%)	**All outpatients** Overall test # p = 0.65 Multicenter test ## p = 0.86
	Outpatients	Intervention	30	13.0 (6.0)	12.0 (4.0)	-0.1 (4.8)		10 (33%)	
Czech Cohort	Outpatients	Control	23	9.6 (4.6)	9.3 (5.1)	-0.7 (2.6)	**Italian outpatients only** Overall test * p = 0.77	2 (22%)	**Italian outpatients only** Overall test # p = 1.0
	Outpatients	Intervention	20	12.3 (14.3)	9.8 (8.6)	-1.0 (3.4)		6 (30%)	
Overall effect							**Overall effect**		
All patients			91	12.0 (6.4)	11.0 (5.0)	-0.8 (3.0)	p < 0.011 ***	27 (30%)	

Only outpatient data are included because of a large proportion of missing data in the Italian inpatient cohort
* overall test = two-sample Wilcoxon test, ** multicenter = ANOVA with respect to country and as covariate, extreme changes of -50 s and -32 s excluded
# overall test = Fisher exact test, ## multicenter = Mantel-Haenszel test with respect to country