The effects of mechanical focal vibration on walking impairment in multiple sclerosis patients: A randomized…

Data · September 2016

CITATIONS
0

READS
28

9 authors, including:

Emanuele Spina
University of Naples Federico II
17 PUBLICATIONS **30** CITATIONS
SEE PROFILE

Antonio Carotenuto
University of Naples Federico II
40 PUBLICATIONS **75** CITATIONS
SEE PROFILE

Ilaria Cerillo
University of Naples Federico II
10 PUBLICATIONS **2** CITATIONS
SEE PROFILE

Rosa Iodice
University of Naples Federico II
48 PUBLICATIONS **266** CITATIONS
SEE PROFILE

Restorative Neurology and Neuroscience 34 (2016) 869–876
DOI 10.3233/RNN-160665
IOS Press

The effects of mechanical focal vibration on walking impairment in multiple sclerosis patients: A randomized, double-blinded vs placebo study

Emanuele Spina, Antonio Carotenuto, Maria Gabriella Aceto, Ilaria Cerillo, Francesco Silvestre, Francesco Arace, Paolo Paone, Giuseppe Orefice and Rosa Iodice*
Department of Neurosciences, Odontostomatological and Reproductive Sciences, University of Naples "Federico II", Naples, Italy

Abstract.
Background: Multiple Sclerosis is a heterogeneous disorders involving in early stage gait and balance. Together with immunomodulating therapies, rehabilitation had a crucial role in improving motor tasks and quality of life. Between the emerging techniques, Focal Vibrations (FV) could play a role, but they have been used in MS only to reduce muscle tone and fatigue alone or together with botulinum toxin.
Objective: To assess whether FV is effective on walking impairment in a cohort of MS patients.
Methods: We performed a single-centre randomized, double-blind, sham-controlled study to investigate efficacy of FV vs sham vibration in 20 RR MS patients. Ten patients received treatment with the active device and ten patients sham treatment. Demographical, clinical and gait instrumental data analysis have been collected for each patient at baseline (T0), after treatment (T1) and after three weeks of wash out (T2).
Results: Both groups were clinically and demographically comparable. Treated patients showed significant improvements during the first right step (FRS) ($p = 0.007$), average stride lenght (ASL) ($p = 0.012$), double support right (DSRT) ($p = 0.016$) and left (DSLT) ($p = 0.003$) time. Non-treated patients didn't show any significance for any dynamic variables. Moreover, on posturographic measurements we registered only a trend towards significance in swing area with eyes open (SAEO) ($p = 0.087$). We also found in treated group significant improvements in FRT ($p = 0.018$); BBS ($p = 0.037$) and FSS scales ($p = 0.038$) between T1 and T0. Lastly, we found a significant inverse correlation in the treated group between disease duration and percentage of improvement for DSLT ($r = –0.775$; $p = 0.014$) in T1 vs T0 and percentage of improvement of FSS, with an inverse correlation with both disease duration ($r = –0.775$; $p = 0.014$) and AGE ($r = –0.733$, $p = 0.025$) in T1 vs T0
Conclusion: Our results suggest a beneficial effect of FV on walking impairment in MS patients suffering from spasticity and/or postural instability, which partially lasted until follow up.

Keywords: Multiple sclerosis, neurorehabilitation, focal vibrations, gait analysis

1. Introduction

Subjects with multiple sclerosis (MS) experience gait dysfunction due to balance disorders, spasticity and mobility impairment (Feinstein, Freeman, & Lo, 2015) even in the very early stages (Martin et al., 2006). A range of interventions aimed at enhancing

*Corresponding author: Rosa Iodice, Department of Neurosciences, Odontostomatological and Reproductive Sciences, University of Naples "Federico II" – Via Pansini, 5, 81025 Naples, Italy. Tel./Fax: +39 0817464348; E-mail: rosaiodice81@gmail.com.

walking ability are used in clinical practice, the most common between them is physiotherapy (Paltamaa, Sjögren, Peurala, & Heinonen, 2012). Recently, several studies tested the effects of intervention such as treadmill or robotic assisted training (Swinnen et al., 2012; Straudi et al., 2016) with promising results. Further more, the whole body vibration (WBV) training has been used to improve walking endurance in MS patients with low disability status (Kantele, Karinkanta, & Sievänen, 2015). Focal vibrations (FV) are widely used in neurologic rehabilitation as supportive treatment of stroke, cerebral infantile palsy (CIP), movement disorders and hemineglect. Through their dual action, both spinal modulation (Alfonsi et al., 2015) and intracortical facilitation, FV found applications in improving spasticity, motor control, gait, in facilitating muscle contraction and in stimulating proprioceptive system (Murillo et al., 2014). Until now, there is just one article about the clinical application of FV (Paoloni et al., 2013) in reducing muscle tone and fatigue alone or together with botulinum toxin in MS patients. However, no exhaustive evidence is available to establish if FV are effective in restoring walking impairment due to postural instability and/or spasticity in a cohort of MS patients. Equistasi® is a registered (class 1, ministerial code n. 342577 on 05/08/2010) medical device consisting in a rectangular plate measuring $10 \times 20 \times 0.5$ mm and with a weight of 0.17 gr. The device is exclusively composed by nanotechnology fibers that transform the body temperature into mechanical vibratory energy (0.8 N, 9000 Hz) able to generate a variation of muscle length of max 0.02 mm (Necking et al., 1996) by far within the safety limit (0.12 mm) found to be harmful for human muscles. We, therefore, performed a trial to assess the efficacy of Equistasi® in improving gait, balance, spasticity and fatigue in MS patients.

2. Matherials and methods

This is a pilot placebo-controlled, randomized, longitudinal, interventional trials aimed to evaluate the effect of Equistasi® in 20 MS patients with walking impairment due to postural instability, impaired balance, associated or not to spasticity. The trial was approved by the CE of University Federico II num.71/15. Written informed consent was obtained prior to procedures from each patient. The study was performed according to the declaration of Helsinki.

2.1. Participants

All participants have been recruited from Department of Neurosciences, Odontostomatological and Reproductive Sciences, University Federico II of Naples, over a six months period. Inclusion criteria were: 1) MS diagnosis defined by the McDonald revisited criteria (Polman et al., 2011); 2) age between 18 and 65; 3) Expanded Disability Status Scale (EDSS) (Kurtzke, 1984) less than 5.5; 4) subjects complaining of impaired balance and postural instability, assessed by clinical examination; 5) remitting phase of disease; 6) subjects able to sign an informed consent. Exclusion criteria were: 1) symptoms or sign suggestive of peripheral neuropathy or other superimposed neurological or psychiatric condition that could affect walking; 2) medical condition preventing the use of the device; 3) pregnancy; 4) cognitive impairment as assesed by a score on Mini Mental State Examination (MMSE) of less than 24; 5) use of antidepressant drugs or antispastic medication. Disease modifying therapies were not modified during the study or during the previous 3 months.

2.2. Study procedures and outcome measures

At baseline (T0) we collected demographic and clinical features, (age, gender, body mass index (BMI), disease duration and course, EDSS scale). Each patient underwent clinical and instrumental evaluation of balance, stability and spasticity. As primary outcome, we selected stabilometric and dynamic gait parameters as assessed by freeMED® 120×50 cm baropodometric platform (produced by Sensor Medica, Guidonia Montecelio, Roma, Italy) in combination with FreeStep® software (http://www.sensormedica.com/site/en/software/software-forbiomechanic-analysis). During analysis, patients were in standing position on a stable platform and without ankle foot orthosis. Acquisition was performed during upright stance with the patient barefoot and the feet splayed out at 30 degrees, while keeping the arms alongside the body and staring at a fixed point marked on the wall at a distance of one meter at the height of the glabella. During stabilometric analyses data acquisition was performed for 51 seconds under each condition [with eyes open (EO) or closed (EC)]. The oscillations of the center of gravity, or center of pressure (mm/sec), are expressed graphically by the "ball", which indicates the movement of the center of gravity by measuring sway area (SA) amplitude (mm^2), length of path (LP)

(mm), and maximum swing (MaS) (mm) (Corradini, Fioretti, Leo, & Piperno, 1997). Dynamic measures were collected as follows: the dynamic ambulation of the patient on the FreeStep platform allows to record the mechanisms of balance control and informations on the gait cycle. The patient, standing and firm on the platform, performed a step forward with the first right step (FRS) (cm) and with the same method, with the first left step (FLS) (cm). When patients walked down the platform 10 times consecutively, FreeStep calculated the average stride length (ASL) (cm) (Martin et al., 2006) and double support left time (DSLT) (ms) and right (DSRT) (ms) (Martin et al., 2006). All information have been recorded on a central database allowing the storage and monitoring. As secondary outcomes, clinical data about motor impairment were evaluated as follows: Berg Balance Scale (BBS) (Berg, Wood-Dauphinee, & Williams, 1995) Dynamic Gait Index (DGI) (Dibble, Lopez-Lennon, Lake, Hoffmeister, & Gappmaier 2013; Forsberg, Andreasson, & Nilsagard, 2013), Functional Reach Test (FRT) (Duncan, Weiner, Chandler, & Studenski, 1990), Timed 25-foot Walk (25FWT) (Larson,Larson, Baumgartner, & White, 2013), Multiple Sclerosis walking scale (MSWS-12) (Hobart, Riazi, Lamping, Fitzpatrick, & Thompson, 2003), Modified Ashworth Spasticity scale (MAS) (Bohannon & Smith, 1987), Fatigue Severity Scale (FSS) (Krupp, La Rocca, Muir-Nash, & Steinberg, 1989). Each kit of active and sham devices was associated to a random number between 1 and 300, by a third-party. At enrollment, blinded investigators assigned to each patient an active or sham device randomly. Both active and placebo devices were identical and did not cause any recognizable sensory sensation, thus guarantying patients' blindness. Each patient applied Equistasi® devices or placebo ones one hour per day, five days per week, with interruption during the fourth and the seventh days of the week for three weeks. The devices were applied on the patient's skin with a common patch, according to the prevailing disorder. Given the heterogeneity in the clinical presentation of the disease, it was impossible to forecast a single application schema of the devices. Medical Investigator and Physiotherapist detected the best location of device taking into account the prevailing impairment for each patient. In patients suffering exclusively from balance disorders, without impairment of the pyramidal system, the devices were applied at the seventh cervical vertebra and at the triceps surae tendon bilaterally (3 devices weared contemporarly) (Volpe, Giantin, & Fasano, 2014; Valkovic, Krafczyk, & Botzel, 2006; Valkovic, Krafczyk, Saling, Benetin, & Botzel, 2006). In patients showing an involvement of pyramidal system in at least one limb, the pattern of application was the following: all 3 devices weared on the affected limb or most affected by hypertonus, one in correspondence of triceps surae to reduce spasticity and increase proprioceptive inflow, one on the patellar tendon to improve weakness of the quadriceps muscle and prevent classic hyperextension of the knee, and the last one on the medius gluteus to improve weakness and reduce the sign of Trendelenburg (Volpe et al., 2014; Paoloni et al., 2013; Alfonsi et al., 2015). During the first application at T0, each patient and a family member or other care-giver were trained to use and handle the device in order to apply it by them at home Additionally, the patient and his family filled a form on a daily basis, in which they wrote if the application had taken place and the expected timing. After three weeks of treatment, the patients were fully re-evaluated (T1) as baseline. Finally, after an additional three weeks, without wearing any device, active or placebo, it was carried out the final evaluation (T2). During study period all patients underwent to their conventional rehabilitative program consisting of balance exercises, coordination, postural re-education associated with active mobilization and cognitive exercises for control of the gait phases.

2.3. Statistical analysis

This trial used a sample of convenience, with the assumption that 20 patients were enough to detect significance. Given the small sample and the lack of normal distribution of variables on Shapiro-Wilk test, nonparametric statistics were performed. Comparisons between groups at T0, T1 and T2 were explored by means of Mann-Whitney U test, while treatment effect across time were explored by means of the Friedman analysis of variance by ranks, with Wilcoxon signed rank test as *post hoc* analysis. Categorical variables were compared using a chi-square test, while to compare severity, type of disturbance and clinical modifications Spearman correlations coefficients were used. Furthermore, at baseline we performed analysis of correlation by Spearman's rho between demographic, dynamic, posturographic variables and scales, to assess associations potentially affecting results. In each obtained significance at comparison of means and

Table 1a
Demographic and clinical variables comparison at baseline

	EG mean (dvst)	PG mean (dvst)	*p*-value*	
HEIGHT (mt)	1,65 (0,07)	1,70 (0,13)	ns	
WEIGHT (kg)	65,55 (9,46)	67,1 (8,08)	ns	
BMI	24,25 (4,01)	23,34 (2,35)	ns	
EDSS BASELINE	3,88 (1,31)	3,7 (1,13)	ns	
YEARS OF DESEASE (years)	7,55 (5,76)	6,4 (8,88)	ns	
AGE (years)	47 (12,17)	48 (12,34)	ns	
SM TYPE	Relapsing-Remitting (n° of patients)	Primary-Progressive (n° of patients)	Secondary-Progressive (n° of patients)	
EQUISTASI GROUP	4	2	3	*p*-value**
PLACEBO GROUP	6	1	3	ns
TREATED LIMB	DX	SX	C7	
EQUISTASI GROUP	2	3	4	*p*-value**
PLACEBO GROUP	2	2	6	ns

*Mann Whitney U-Test. **Chi.Square – Test.

explored with *post-hoc* analysis we performed another analysis of correlation between demographical variables and percentage of improvement, in order to identify which kind of patients could be more likely to have benefits from treatment. XSTAT software (Addinsoft SARL, New York) was used for all statistical analysis. All tests were two-sided with a level of significance set at $P < 0.05$.

3. Results

Clinical and demographic characteristics are summarized in Table 1a. Ten patients (seven female) received Equistasi® (EG, equistasi group) and ten patients (five female) were assigned to the placebo group (PG). One male patient of EG were not included into analysis due to a relapse between T0 and T1, and dropped out from trial. At baseline (T0) the two groups were comparable for demographic (sex, age, height, weight, BMI, disease duration) and clinical features (subtype of MS, limbs affected), evaluation scales (EDSS, BBS, DGI, MSWS-12, FRT, T25WT, FSS, MASS) and for the following stabilometric and dynamic features: sway area (SA), lenght of path (LP), maximum swing (MaS) both EO and EC and RFS. EG and PG significantly differed on the following dynamic measurements: FLS ($p = 0.015$), ASL ($p = 0.042$), DSRT ($p = 0.036$) and DSLT ($p = 0.035$) [Table 1b]. About analysis of correlation at baseline between clinical data and dynamic and posturographic variables we found: for BMI, a direct correlation with age ($r = 0.485$, $p = 0.035$) without any other correlation with dynamic and posturographic measures; for EDSS, a direct correlation with LPEO ($r = 0.472$, $p = 0.041$) and an inverse correlation with DGI ($r = –0.57$, $p = 0.011$) without any correlation with dynamic variables, no correlation for disease duration with any variable; for age an inverse correlation with ASL ($p = –0.603$, $p = 0.06$) and DGI ($r = –0.523$, $p = 0.022$).

Table 1b
Gait analysis data and scales at baseline

	EG		PG		*p*-value*
	mean	dev st	mean	dev st	
LPEO (mm)	1401.83	558.22	1244.49	571.82	ns
SAEO (mm^2)	196.83	246.39	432.60	492.21	ns
MaSEO	7.72	4.26	6.49	2.82	ns
LPEC (mm)	1452.80	561.38	1313.88	479.07	ns
SAEC (mm^2)	457.59	633.72	563.75	554.01	ns
MaSEC	9.57	6.46	12.91	7.59	ns
FRS cm	36.27	3.33	42.8	11.13	ns
FLS cm	37.04	6.99	44.1	8.20	0.015
ASL cm	36.78	5.73	43.9	9.71	0.042
DSRT ms	400.73	265.08	199.97	233.52	0.036
DSLT ms	400.18	278.44	248.89	258.48	0.035
DGI	15.56	3.88	15.4	4.65	ns
MSWS-12	40.44	10.16	40.2	10.96	ns
FRT	18.61	6.14	22.97	6.79	ns
T25FW	22.97	13.61	17.66	9.38	ns
BBS	45.33	6.18	42.7	7.53	ns
FSS	50.56	11.01	49.4	9.16	ns

3.1. Primary outcome

At Friedman comparisons of means in dynamic variables EG patients showed significant improvement in FRS ($p = 0.007$), with *post-hoc* significance on T1 vs T0 ($p = 0.012$) and on T2 vs T0 ($p = 0.017$); ASL ($p = 0.012$) with *post-hoc* significance on T1 vs T0 ($p = 0.011$); DSRT ($p = 0.016$), with *post-hoc* significance on T1 vs T0 ($p = 0.011$) and on T2 vs T0 ($p = 0.038$) and DSLT ($p = 0.003$), with *post-hoc*

Table 2
Static and Dynamic variables at three time points with Friedman comparison and *post-hoc* analysis between groups

	group	T0		T1		T2		Friedman	*p* value**	*p* value**	*p* value**
		mean	sd	mean	sd	mean	sd	test*	T0-T1	T0-T2	T1-T2
LPEO	Equistasi Group	1.401.82	558.22	1.242.80	377.60	1.242.60	366.78	0.324	0.639	0.677	0.993
	Placebo Group	1.244.49	571.22	1.190.44	359.26	1.105.42	420.71	0.655	0.720	0.698	0.922
SAEO	Equistasi Group	196.83	246.39	372.35	391.04	143.99	114.35	0.087	0.061	0.621	0.083
	Placebo Group	432.60	492.20	502.62	651.15	472.54	575.53	0.720	0.566	0.897	0.701
MaSEO	Equistasi Group	7.72	4.26	6.84	3.08	6.16	2.57	0.332	0.887	0.744	0.931
	Placebo Group	6.49	2.82	10.35	14.69	5.64	4.06	0.466	0.402	0.871	0.339
LPEC	Equistasi Group	1.452.80	561.38	1.341.48	334.75	1.317.67	518.86	0.239	0.571	0.883	0.943
	Placebo Group	1.313.87	479.06	1.276.92	361.97	1.187.58	430.10	0.561	0.604	0.378	0.469
SAEC	Equistasi Group	457.59	633.72	282.20	283.06	391.77	700.69	0.129	0.101	0.573	0.378
	Placebo Group	563.75	554.01	581.81	373.50	368.60	373.50	0.766	0.893	0.467	0.399
MaSEC	Equistasi Group	9.57	6.46	12.81	8.35	9.33	5.91	0.724	0.683	0.992	0.489
	Placebo Group	12.90	7.59	17.23	12.71	15.66	21.93	0.461	0.398	0.832	0.488
FRS	Equistasi Group	36.26	3.32	42.88	5.13	43.55	6.09	0.007	0.012	0.017	0.596
	Placebo Group	42.80	11.13	45.40	13.36	44.90	10.47	0.438	0.733	0.802	0.855
FLS	Equistasi Group	37.03	6.99	43.61	9.07	39.77	5.61	0.134	0.0514	0.572	0.203
	Placebo Group	44.10	8.19	43.85	11.68	44.50	9.31	0.376	0.844	0.934	0.783
ASL	Equistasi Group	36.77	5.73	39.77	6.42	39.66	6.16	0.012	0.011	0.127	0.953
	Placebo Group	43.90	9.71	43.40	12.91	43.80	10.67	0.977	0.872	0.902	0.921
DSRT	Equistasi Group	400.72	265.07	288.63	209.73	319.30	306.72	0.016	0.011	0.038	0.432
	Placebo Group	199.96	122.08	303.24	233.52	251.38	171.86	0.073	0.058	0.229	0.663
DSLT	Equistasi Group	400.18	278.43	274.77	198.41	318.40	287.40	0.003	0.008	0.038	0.515
	Placebo Group	248.89	258.48	304.87	232.98	279.29	231.71	0.239	0.433	0.881	0.922

*p value - **Bonferroni correction $\alpha = 0{,}017$.

significance on T1 vs T0 ($p = 0.008$) and on T2 vs T0 ($p = 0.038$). Only one dynamic variable, FLS, didn't show significance at Friedman comparison of means but at *post-hoc* analysis we detected a trend towards significance on T0 vs T1 ($p = 0.051$). Conversely, PG patients didn't show any significance for any dynamic variabile. Moreover, on posturographic measurements SAEO, SAEC, LPEO, LPEC, MaSEO, MaSEC we didn't register any significance in both groups, aside from trend towards significance in Friedman comparison of means in SAEO ($p = 0.087$), confirmed at *post-hoc* analysis between T1 and T0 ($p = 0.061$) [Table 2].

Lastly, regarding primary outcome, we found in EG group a significative correlation between disease duration and percentage of improvement for DSLT ($r = –0{,}724$; $p = 0.028$) in T1 vs T0 [Fig. 1].

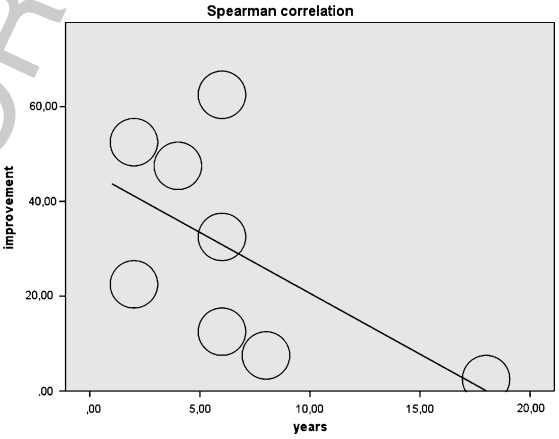

Fig. 1. Spearman correlation between disease duration and % of improvement in DSLT. Rho Spearman = –0.724 - p value 0.028.

3.2. Secondary outcome

Regarding self-rating scale and physician-administered one we observed in EG group significant improvements between means only in FRT ($p = 0.018$), with *post-hoc* significance on T1 vs T0 ($p = 0.012$); BBS ($p = 0.037$) with *post-hoc* significance on T1 vs T0 ($p = 0.017$) and FSS ($p = 0.038$), with *post-hoc* significance on T1 vs T0 ($p = 0.025$) scales without any significance in EDSS, DGI, MSWS-12, T25WT, MASS. No differences among three time points have been found in PG group [Table 3]. Moreover, we found a significative correlation in EG group regarding FSS, with an inverse correlation with both disease duration ($r = –0.775$; $p = 0.014$) and AGE ($r = –0.733$, $p = 0.025$) in T1 vs T0 [Fig. 2].

4. Discussion

Walking is a complex task involving strength, coordination and sensation. A sufficient balance control

Table 3
Self administered scales and physician-ones at three time points with Friedman comparisons and *post-hoc* analysis between groups

	group	T0		T1		T2		Friedman test*	*p* value**	*p* value**	*p* value**
		mean	sd	mean	Sd	mean	sd		T0-T1	T0-T2	T1-T2
DGI	Equistasi Group	15.55	3.87	16.33	4.63	16.33	5.65	0.366	0.671	0.560	0.821
	Placebo Group	15.40	4.64	15.80	5.55	16.13	5.35	0.631	0.555	0.621	0.733
MSWS-12	Equistasi Group	40.44	10.16	35.88	9.41	39.88	13.74	0.326	0.192	0.891	0.201
	Placebo Group	40.21	10.96	40.12	12.91	40.45	13.82	0.873	0.992	0.990	0.891
FRT	Equistasi Group	18.61	6.13	23.02	5.22	23.77	4.86	0.018	0.012	0.066	0.996
	Placebo Group	22.97	6.78	22.90	9.58	24.60	7.46	0.893	0.802	0.488	0.401
MASSQR	Equistasi Group	3.75	0.89	3.81	0.75	3.86	0.38	0.793	0.890	0.755	0.902
	Placebo Group	4.15	0.47	4.30	0.48	4.25	0.61	0.642	0.906	0.782	0.882
MASSQL	Equistasi Group	3.69	0.88	3.81	0.75	3.71	0.76	0.366	0.673	0.922	0.801
	Placebo Group	3.95	0.83	3.90	0.74	4.17	0.75	0.821	0.944	0.803	0.882
MASSIR	Equistasi Group	3.88	0.64	3.50	0.53	3.88	0.63	0.329	0.344	1.00	0.588
	Placebo Group	3.85	0.82	4.00	0.67	3.67	1.03	0.471	0.670	0.872	0.622
MASSIL	Equistasi Group	3.75	0.71	3.38	0.92	3.88	0.83	0.811	0.489	0.724	0.901
	Placebo Group	3.50	1.00	3.80	0.79	3.92	0.66	0.489	0.302	0.722	0.799
MASSTAR	Equistasi Group	4.00	0.76	3.75	0.46	3.88	0.35	0.561	0.481	0.498	0.498
	Placebo Group	4.05	0.60	4.10	0.74	3.58	1.02	0.892	0.891	0.387	0.420
MASSTAL	Equistasi Group	3.56	1.29	4.00	0.53	3.88	0.64	0.308	0.398	0.573	0.450
	Placebo Group	3.75	1.01	4.00	0.67	3.83	0.75	0.391	0.388	0.891	0.670
T25FW	Equistasi Group	22.97	13.61	17.83	4.15	20.15	7.33	0.773	0.167	0.722	0.455
	Placebo Group	17.65	9.37	17.32	5.49	16.55	5.97	0.892	0.881	0.471	0.600
BBS	Equistasi Group	45.33	6.18	47.67	7.24	47.00	8.44	0.037	0.017	0.343	0.675
	Placebo Group	42.70	7.52	41.80	7.80	44.33	6.96	0.703	0.476	0.378	0.582
FSS	Equistasi Group	50.55	11.01	43.11	11.68	44.33	11.68	0.038	0.025	0.334	0.843
	Placebo Group	49.42	9.15	45.19	15.27	46.55	11.73	0.572	0.329	0.670	0.392

*p value - **Bonferroni correction $\alpha = 0{,}017$. MASSQR/L = Modified Ashworth Spasticity Scale Quadriceps femoris right/left; MASSIR/L = Modified Ashworth Spasticity Scale Ileopsoas right/left; MASSTAR/L = Modified Ashworth Spasticity Scale Tibialis anterior right/left.

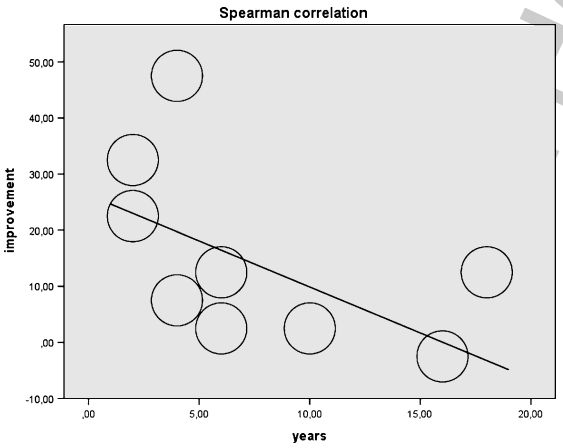

Fig. 2. Spearman correlation between disease duration and % of improvement in FSS. Rho Spearman = –0.775 - p value 0.014.

is crucial to all daily activities and a proper ambulation is essential to improve quality of life, to avoid risks of falls or orthopedic morbidity. In neurorehabilitation, focal vibration was already used to reduce upper limb spasticity and improve gait in stroke patients, to enhance attention in hemi-neglect, to facilitate motor control tasks (Murillo et al., 2014) and to improve stability and to reduce falls rate in PD (Volpe et al., 2014). In MS WBV has been widely used with contrasting results showing effects only on walking endurance without any effects on walking speed and balance (Kantele et al., 2015). With regards to FV, only a single study (Paoloni et al., 2013) showed that it may improve spasticity and fatigue with or without botulinum toxin in MS patients. To our knowledge, this is the first trial assessing the efficacy of focal vibration on walking impairment in MS patients with postural instability with or without spasticity. The main finding of our study is that FV might add further benefits in restoring walking impairment. At baseline, there are no demographic differences between the two groups, but, over time, age, disease duration and EDSS could influence primary and secondary outcome. However, although the placebo group had best performances at baseline compared to Equistasi group, we found improvements on dynamic gait measurements only in the second one that, at least in part, lasted over time. The significantly reduction in double support time bilaterally and increase in LFS, suggested that

MS patients walked with a faster velocity and cadence took longer steps over a shorter time interval (Motl, Sandroff, Suh & Sosnoff 2012). Instead, we didn't find any improvement in stabilometric parameters. It is not surprising because it is already been demonstrated that in MS patients dynamic balance, rather than static measures, may lead to a better understanding of walking mechanism and identification of how the human body compensates for balance or strength deficits (Fritz, Jiang, Keller, & Zackowski, 2015). A previous study showed that deficit in static balance linked with reduced walking speed and muscle strength, as well as fall risk (Fritz et al., 2015). Interestingly, among stabilometric measure only one measure of static balance, SAEO, showed a trend to significance, in line with improvement in postural stability as recorded through FRT and BBS, although it deteriorated over time. We also found a positive effect on FSS underling the impact on psychological well-being dependent of treatment effectiveness. This effect is likely mediated by proprioceptive circuits linked to Ia and II afferences of muscle spindles, able to interfere on central fatigue pathways (Alfonsi et al., 2015). Although Fritz et al found the relationship between T25FWT and balance measures (Fritz et al., 2015) we found no effects on this scale, maybe because MS patients needs a long-distance test in detecting improvement after rehabilitation (Gijbels, Dalgas, & Romberg, 2012). At same time, we failed to find a FV efficacy on DGI, MSWS12 and MASS. It could be due to the fact that, as most clinical assessment, several scales suffering of ceiling effects and are not responsive enough to measure small progress (Kieiseier & Pozzilli, 2012) As mentioned above, we observed that shorter disease duration correlate with a better performance in EG group at DSLT and FSS. This suggests that FV could be more effective if applied before accumulation of irreversible damage occurs. These evidences underline the need of early rehabilitative support, in order to preserve and optimize the residual functional gait ability of MS patients

5. Conclusion

This study suggests that FV has a potential in improving walking in MS patients with postural instability and/or spasticity. Limitations could be identified in a too small sample size, moreover too heterogeneous in its clinical features and treated for far too little time. Statistical differences at baseline required, besides a wider sample, tighter inclusion criteria to minimize the risks, and a directly measure of spasticity (e.g. H/M ratio) that would correlate to degree of impairment could be results more reliable. Therefore, further well-designed, long term RCTs with adequate sample size and more sensitive measurement methods are needed.

References

Alfonsi, E., Paone, P., Tassorelli, C., De Icco, R., Moglia, A., Alvisi, E., … & Sandrini G. (2015). Acute effects of high-frequency microfocal vibratory stimulation on the H reflex of the soleus muscle. A double-blind study in healthy subjects. *Functional Neurology*, *30*(4), 269-274

Berg. K., Wood-Dauphinee, S., & Williams, J.I. (1995). The Balance Scale: Reliability assessment with elderly residents and patients with an acute stroke. *Scandinavian Journal of Rehabilitation Medicine*, *27*, 27-36.

Bohannon, R.W., & Smith, M.B. (1987). Interrater reliability of a modified Ashworth scale of muscle spasticity. *Physical Therapy*, *67*(2), 206-207.

Corradini, M.L., Fioretti, S., Leo, T., & Piperno, R. (1997). Early recognition of postural disorders in multiple sclerosis through movement analysis: A modeling study. *IEEE Transaction on Biomedical Engineering*, *44*, 1029-1038.

Dibble, L.E., Lopez-Lennon, C., Lake, W., Hoffmeister, C., & Gappmaier, E. (2013). Utility of disease specifics measures and clinical balance tests in prediction of falls in persons with multiple sclerosis. *Journal of Neurologic Physical Therapy*, *37*(3), 99-104.

Duncan, P.W., Weiner, D.K., Chandler J., & Studenski S. (1990) Functional reach: A new clinical measure of balance. *Journal of Gerontology*, *45*, M192-M197.

Feinstein, A., Freeman, J., & Lo, A.C. (2015). Treatment of progressive multiple sclerosis: What works, what does not, and what is needed. *Lancet Neurology*, *14*(2), 194-207. doi: 10.1016/S1474-4422(14)70231-5

Forsberg, A., Andreasson, M., & Nilsagard, Y.E. (2013). Validity of the dynamic gait index in people with multiple sclerosis. *Physical Therapy Journal*, *93*(10), 1369-1376.

Fritz, N.E., Jiang, A., Keller, J., & Zackowski, K.M. (2015). Utility of the six-spot step test as a measure of walking performance in ambulatory individuals with multiple sclerosis. *Archives of Physical Medicine and Rehabilitation*, *97*(4), 507-512. doi: 10.1016/j.apmr.2015.10.100

Gijbels, D., Dalgas, U., Romberg, A. (2012) Which walking capacity test to use in Multiple Sclerosis? A multicentre study providing the basis for a core set. *Multiple Sclerosis*, *18*, 364-371.

Hobart, J.C., Riazi, A., Lamping, D.L, Fitzpatrick, R., & Thompson, AJ. (2003). Measuring the impact of MS on walking ability: The 12-Item MS Walking Scale (MSWS-12). *Neurology*, *14*, 60(1), 31-36.

Kantele, S., Karinkanta, S., & Sievänen, H. (2015). Effects of long-term whole-body vibration training on mobility in patients with multiple sclerosis: A meta-analysis of randomized

controlled trials. *Journal of the Neurological Sciences*, *15*, 358(1-2), 31-37.

Kieiseier, B.C. & Pozzilli, C. (2012) Assessing walking disability in multiple sclerosis. *Multiple Sclerosis*, *18*(7), 914-924.

Krupp, L.B., La Rocca, N.G., Muir-Nash J., & Steinberg AD. (1989). The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Archives of Neurology*, *46*(10), 1121-1123

Kurtzke, J.F. (1983). Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). *Neurology*, *33*(11), 1444-1452.

Larson, R.D., Larson, D.J., Baumgartner, T.B., & White L.J. (2013). Repeatability of the timed 25–foot walk test for individuals with multiple sclerosis. *Clinical Rehabilitation*, *27*(8), 719-723.

Martin, C.L., Phillips, B.A., Kilpatrick, T.J., Butzkueven, H., Tubridy, N., McDonald, E., & Galea, M.P. (2006). Gait and balance impairment in early multiple sclerosis in the absence of clinical disability. *Multiple Sclerosis*, *12*, 620-628.

Motl, R.W., Sandroff, B.M., Suh, Y., & Sosnoff, J.J. (2012). Energy cost of walking and its association with gait parameters, daily activity, and fatigue in persons with mild multiple sclerosis. *Neurorehabilitation and Neural Repair*, *26*(8), 1015-1021.

Murillo, N., Valls-Sole, J., Vidal, J., Opisso, E., Medina, J., & Kumru, H. (2014). Focal Vibration in Neurorehabilitation. *European Journal of Physical and Rehabilitation Medicine*, *50*(2), 231-242.

Necking, L.E., Lundström, R., Dahlin, L.B., Lundborg, G., Thornell, L.E. & Fridèn, J (1996). Tissue displacement is a causative factor in vibration-induced muscle injury. *Journal of Hand Surgery British*, *21*(6), 753-757.

Paltamaa, J., Sjögren, T., Peurala, S.H., & Heinonen, A. (2012). Effects of physiotherapy interventions on balance in multiple sclerosis: A systematic review and meta-analysis of randomized controlled trials. *Journal of Rehabilitation Medicine*, *44*(10), 811-823.

Paoloni, M., Giovannelli, M., Mangone, M., Leonardi, L., Tavernese, E., Di Pangrazio, E., ... & Pozzilli, C. (2013). Does giving segmental muscle vibration alter the response to botulinum toxin injections in the treatment of spasticity in people with multiple sclerosis? A single-blind randomized controlled trial. *Clinical Rehabilitation*, *27*(9), 803-812.

Polman, C.H., Reingold, S.C., Banwell, B., Clanet, M., Cohen, J.A., Filippi, M., ... & Wolinsky, J.S. (2011). Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Annals of Neurology*, *69*(2), 292-302.

Sensor Medica FreeStep Sofware. http://www.sensormedica.com/site/en/software/software-forbiomechanic-analysis

Straudi, S., Fanciullacci, C., Martinuzzi, C., Pavarelli, C., Rossi, B., Chisari, C., & Basaglia N. (2016). The effects of robot-assisted gait training in progressive multiple sclerosis: A randomized controlled trial. *Multiple Sclerosis*, *22*(3), 373-384.

Swinnen, E., Beckwée, D., Pinte, D., Meeusen, R., Baeyens, J.P., & Kerckhofs, E. (2012). Treadmill training in multiple sclerosis: Can body weight support or robot assistance provide added value? A systematic review. *Multiple Sclerosis*, Int.;240274.

Valkovic, P., Krafczyk, S., & Botzel, K. (2006). Postural reactions to soleus muscle vibration in Parkinson's disease: Scaling deteriorates as disease progresses. *Neurosciences Lett*, *401*, 92-96.

Valkovic, P., Krafczyk, S., Saling, M., Benetin, J., & Botzel, K. (2006). Postural reactions to neck vibration in Parkinson's disease. *Movement Disorders Journal*, *21*, 59-65

Volpe, D., Giantin, M.G., & Fasano, A. (2014). A wearable proprioceptive stabilizer (equistasi®) for rehabilitation of postural instability in Parkinson's disease: A phase II randomized double-blind, double-dummy, controlled study. *PloS One*, *17*, 9(11), e112065.