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Percutaneous Venous Angioplasty in Patients With Multiple Sclerosis And Chronic Cerebrospinal Venous Insufficiency: A Randomized Wait List Control Study

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Short title: Angioplasty In Patients with Multiple Sclerosis.

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ABSTRACT

Objectives Venous percutaneous transluminal angioplasty (vPTA) in patients with multiple sclerosis (MS) and chronic cerebrospinal venous insufficiency (CCSVI) have shown contradictory results. Aim of the study is to evaluate the efficacy of the procedure in a randomized wait list control study.

Materials: 66 adults with neurologist-confirmed diagnosis of MS and sonographic diagnosis of CCSVI were allocated in to vPTA-yes group (n=31) or vPTA-not group (n=35, control group). Venous PTA was performed immediately 15 days after randomization in PTA-yes group and 6 months later in the control group.

Methods: Evoked potentials (EPs), clinical-functional measures (CFM) and upper limb kinematic measures (ULKM) were measured at baseline (T0) and six months after in both groups, just before the venous angioplasty in vPTA-not group (T1).

Results: Comparing vPTA-yes and vPTA-not group, the CFM derived composite functional outcome showed 11(37%) versus 7(20%) improved, 1(3%) versus 3(8%) stable, 0 versus 7(20%) worsened and 19(61%) versus 18(51%) mixed patients (χ^2=8.71, df=3, p=0.03). Unadjusted and adjusted (for baseline confounding variables) OR at 95% confident interval (95%CI) were respectively 1.93(1.3-2.8) *P*-value 0.0007 and 1.85(1.2-1.7) *P*-value 0.002. EPs and ULKM derived composite functional outcome showed no significant difference between the two groups.

Conclusions: Venous angioplasty can positively impact a few CFM especially for the quality of life, but achieving disability improvement is unlikely.

Keywords: Multiple Sclerosis; Chronic Cerebrospinal Venous Insufficiency; Angioplasty; Endovascular Procedures

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system with a disabling progressive course. Chronic Cerebrospinal Venous Insufficiency (CCSVI) has been recognized as truncular venous lesions with obstructing characteristics localized in the territory of internal jugular veins (IJVs) and/or vertebral veins (VVs)[1]. Available clinical studies, about the CCSVI and the potential effects of corrective venous PTA, show contradictory results and do not provide evidence of the efficacy of the treatment[2-6]. Only a few randomized sham-controlled intervention studies have been published[7-8]. Furthermore, improvement has been reported relating to subjective symptoms such as headache, fatigue and depression, which could not be detected with the commonly used expanded disability status scale (EDSS)[9-12]. Following the resolution issued by the Italian Superior Health Council in February 2011 and spurred by public opinion, the Directorate of tertiary referral center activated a care pathway aimed at clarifying the clinical effectiveness of venous Percutaneous Transluminal Angioplasty (vPTA) in patients with MS and CCSVI. A local collaborative team constituted by specialists relating to neurology (FS, TB), neuro-rehabilitative section (MCC, RB), radiology (VN, DC), interventional radiology (OP, RC), statistic (RM) and vascular surgery (RB, MM, NM, CC, MF) units was endorsed. A randomized controlled clinical study was carried out once local ethical committee approved the study protocol.

METHODS

Design

This study was a randomized and wait list, not-sham (not intervention) controlled clinical study to evaluate the efficacy of vPTA in patients with MS and CCSVI. A wait list design was conceived: half of the participants were randomly assigned to receive vPTA early (vPTA-yes group) and half of the participants were randomly assigned to receive it later (vPTA-not group) (Fig 1). Simple type 1:1 randomization was performed by an external structure. All patients had a baseline evaluation (T0) and the second evaluation (T1) six months after in both groups, just before the venous angioplasty in vPTA-not group. The clinical study started in September 2011 and closed in September 2016. For clinical study safety the stopping rules included serious adverse events and their types and grades are reported according to the Good Clinical Practice guidelines.

Patients

418 patients requesting vPTA were registered, but only in 161(38.5%) the diagnosis of MS was confirmed by neurologists following McDonald criteria[13].

A total number of 161 patients underwent echo-color Doppler (ECD) ultrasonography in sitting and supine position. The ECD examination protocol for the diagnosis of CCSVI was obtained following the methodology proposed by Zamboni [14-16]. Out of 161 patients, 47(29.2%) had normal ultrasonographic findings, and 114 patients (70.8%) had CCSVI. Out of these 114 participants, 48(42.1%) declined to participate, so 66(57.9%) were included in the randomization phase; MS course of the enrolled patients was: relapsing-remitting (RR) 37(56.1%), secondary progressive (SP) 13(19.7%) and primary progressive (PP) 16(24.2%) (Fig 1).

The inclusion criteria were: age within 18-65 years; diagnosis of MS with any kind of disease course and any disability level[16-18]; diagnosis of CCSVI by ECD exam[14-16]. The exclusion criteria were: age less than 18 years or more than 65 years; patients unable to provide informed consent; the presence of other pathologies of the central nervous system other than MS; clinical relapses and therapy with steroids in the 30 days before the procedure; patients not willing to strictly adhere to the study design and to follow the expected controls; the presence of pregnancy or lactation; life expectancy of less than one year; inadequate temporal acoustic window at intracranial ECD exam; the arbitrary use of new pharmacological treatments. Previous vPTA was not considered an exclusion criterion.

Ultrasonographic diagnosis of CCSVI

CCSVI assessment was performed by a single operator (VN) certificated at Zamboni's center training. All the ultrasound examinations were carried out using CCSVI Protocol MyLab Vinco (Esaote S.p.A, Florence, Italy) equipped with a linear transducer of 3.5–10MHz for extracranial veins evaluation and a phased array transducer of 2,0-3,3 MHz for intracranial veins assessment. The presence of at least 2 of 5 Zamboni's morpho-functional specific criteria related to internal jugular veins (IJVs) or vertebral veins (VVs) visualized in both supine and sitting positions was used to diagnose CCSVI and select patients for the randomization procedure[19-20].

Therefore the presence of the five ultrasound diagnostic criteria, such as:

1) reflux in the IJVs and/or VVs,

2) reflux in the intracranial veins,

3) high-resolution B-mode evidence of IJVs stenosis and/or other B-mode anomalies,

4) absence of flow in the IJVs and/or VVs,

5) cross-sectional area (CSA) of the IJV measured in sitting position larger than to that obtained in supine position,

was investigated in all MS patients. No muscular entrapment was detected.

Patients were submitted the day after the procedure and after 30 days to an ultrasound examination to exclude complication such as vein thrombosis.

Technical and inter-procedural details of the vPTA

Patients allocated into vPTA-yes group received the dilative vPTA immediately 15 days after randomization and the patients allocated into control, not-sham, group underwent interventional procedure 6 months later.

The interventional procedures were executed using two angiographic device (GE INNOVA 4100 Cath/Angio Suite and GE Healthcare InnovaTM IGS 540 Image Guided System) in a room prepared for angiography and interventional radiology. This device allowed the acquisition of multiple two-dimensional images along a circular trajectory greater than 180°.

The same team whose members were certificated at Zamboni's center training carried out all the interventional procedures (OP, RC). Local anesthesia at venous access site was performed in all patients. The 2D projections obtained were converted in axial images similar to those of the TC with a reconstruction algorithm 3D cone-beam. Patient preparation was considered completed only when the informed consent was obtained and local anesthesia in groin area and systemic heparinization (5000 UI of sodium heparin in 48/55 patients and 7500 UI in 7/55 patients) were administrated.

Diagnostic procedure was made up of:

1) placement of a 15 cm long valvular introducer 7-9 Fr (Cordis®, AVANT+ introducer, Cordis Cashel, chair Road Cashel. Co Tipperary. Ireland) in the femoral vein with Seldinger technique;

2) ascending catheterization (recommended with catheter 4Fr Radifocus® Glidecath® - Hydrophilic Angiographic Catheter, Vertebral/ Simmons/Sidewinder1; Cordis®, SIM 1, Super Torque®; Cordis®, H1, Super Torque®) of the left ileolumbar (IL) vein followed by the phlebography (mdc injection: 20-30 ml, 4 ml/s) of the lumbar district in postero-anterior projection which aims to study the paravertebral vein circulation. If the catheterization of the left IL is complicated, could be catheterized a lateral sacral vein or directly a lumbar vein;

3) superior vena cava (SVC) catheterization and manometry;

4) azygos vein catheterization, manometry and phlebography in postero-oblique projection (mdc injection: 10-30 ml, 3-8 ml/s);

5) internal jugular vein (IJV) manometry, and phlebography in postero-anterior and oblique projection after the placement of the catheter at the level of the mandibular angle (mdc injection: 8 ml, 3 m/s). It was advisable to let the patient breathe deeply and make the Valsalva maneuver, because these procedures help the venous outflow and the valves opening;

6) vertebral veins retrograde catheterization and phlebography with manual injection.

The vPTA was executed with adequate size compliant balloon catheters at level of stenosis in extra cranial and azygos veins. In case of significative stenosis was performed an invasive evaluation of the pressure and the trans-stenotic pressure gradient.

The interventional procedure of azygos vein was made up of:

1) vPTA with compliant balloon catheters (Wanda™ PTA Balloon / Atlas® GOLD PTA Dilatation Catheters): 8-12 mm (caliber), 2-4 cm (length) inflated with a maximum of 14-18 atm, the insufflation lasts for 30-60 sec and is repeated several times;

2) phlebography and manometry control of the azygos after the vPTA.

The interventional procedure of internal jugular veins was carried out by:

1) PTA with compliant balloon catheters (Wanda™ PTA Balloon / Atlas® GOLD PTA Dilatation Catheters): 10-22 mm (caliber), 2-6 cm (lenght) inflated with a maximum of 18 atm,

2) dilatation with not compliant balloons (Atlas® GOLD PTA Dilatation Catheters) inflated with high pressure (18-20 atm), the insufflation lasts for 30-60 sec and it is repeated several times if post-procedure result was not sufficient; phlebography and control manometry of the jugular veins after the angioplasty was performed.

The interventional procedure of vertebral veins was carried out by means of vPTA with compliant balloon catheters (Wanda™ PTA Balloon/ Atlas® GOLD PTA Dilatation Catheters): 8-10 mm (caliber), 2-4 cm (length) inflated with a maximum of 8 atm. We used balloons with length between 20-60 mm (mean 45 mm; median 40 mm) and caliber between 8-22 mm (mean 12 mm; median 10 mm), in all patients after the procedure a pressure evaluation was performed in basal conditions and during Valsalva maneuver.

Functional Outcome

Several neurophysiological and functional tests were used to consider the efficacy of the vPTA. Three categories of tests were arranged: (1) evoked potentials (EPs) tests, (2) clinical-functional measures (CFM) and (3) upper limb kinematic measures (ULKM).Evoked potentials (EPs) evaluation was performed by both visual evoked potentials (VEPs) and motor evoked potentials (MEPs). An independent blinded neurological assessor was involved for each category of tests (EPs, CFM and ULKM).

Each single test was classified as worsened, improved or stable on the basis of the relative change (arbitrarily set at 20%) found at T1 when compared to T0; a test was improved or worsened if the variation was at least 20%, stable if otherwise.

A derived composite functional outcome for each category of EPs, CFM, and ULKM tests was designed by aggregating similar single functional tests in the same category. Thus, a composite functional endpoint for EPs, CFM and ULKM tests was used and accordingly each of enrolled patient could be classified as worsened (W) if some tests showed worsening, stable (S) if no change in all tests, improved (I) if some tests showed improvement and mixed (M) if there was a mixture of worsened and improved tests. The proportion of improved patients from each derived composite functional outcome was estimated between the two groups of treatment.

Statistical analysis

Analysis was carried out on an intention-to-treat basis. The effect of vPTA versus control on each EPs, CFM and ULKM composite functional outcome was assessed by comparing the proportion of improved patients at T1 in both vPTA-yes and vPTA-not groups. Significance of differences in proportion was assessed by χ^2 test.

As the estimate of the effect size, odds ratio (OR) at 95% confident interval (95%CI) was considered appropriate to verify the relationship between treatment group predictor variables and response outcome variables. For each EPs, CFM and ULKM composite functional outcome, both unadjusted and adjusted OR were assessed. Adjusted logistic model was used for gender, MS course, both T0 and T1 EDSS raw data scores, both T0 and T1 EDSS >3.5 and interactions. Possible co-existing correlation between rate of EDSS variation and Venous Hemodynamic Insufficiency Severity Score (VHISS) variation after vPTA was not assessed.

Detailed results concerning baseline tests values (raw data scores) at T0 and T1 for components of each EPs, CFM and ULKM composite functional outcome in vPTA-yes group were also evaluated. Both matched-pairs t-test and Wilcoxon signed-rank test with continuity correction were used to compare pre- and post-vPTA measurements in paired observation.

For statistical significance *P*-value <0.05 and two-sided test were used. Adjusting for multiple comparisons using Hommel method (reported as adjusted *P*-value) was applied when components of each derived composite functional outcome was analyzed[21].

All statistical analyses were carried-out with JMP 7.0 (2007 SAS Institute Inc.) and R 3.3 software[22, 23].

RESULTS

Baseline patients' characteristics did not show difference between the two groups (Table 1). Sites for venous angioplasty in vPTA-yes group were: monolateral jugular vein 5(16%); bilateral jugular veins 26(84%); jugular plus azygos veins 2(6%). No venous angioplasty was performed in vertebral veins.

Results for each EPs, CFM and ULKM composite functional outcome are summarized in Table 2. When EPs and its derived composite functional outcome in the vPTA-yes versus vPTA-not group were analyzed, unadjusted and adjusted OR (95% CI) for treatment group predictor variable were respectively 1.03 (*P*-value 0.82) and 1.26 (*P*-value 0.18). However, while at final logistic adjusted model the treatment group predictor variable had no significant effect, but the MS course (especially the PP phenotype), both T0 and T1 EDSS raw data scores, EDSS >3.5 at T1 showed significant effect: OR=1.7(*P*-value 0.03) (MS course PP/RR); OR=2.1 (*P*-value 0.007) (MS course PP/SP); OR=4.04(*P*-value 0.0019) (T0 EDSS raw data scores); OR=0.14(*P*-value 0.0001) (T1 EDSS raw data scores); OR=4.4(*P*-value 0.0004) (EDSS>3.5 at T1).

The CFM and its derived composite functional outcome in the vPTA-yes versus vPTA-not group showed an unadjusted and adjusted OR (95% CI) for treatment group predictor respectively of 1.93(*P*-value 0.0007) and 1.85(*P*-value 0.002). However, at final logistic adjusted model both T0 and T1 EDSS raw data scores were also significant predictors: OR=4.03(*P*-value 0.007)(T0 EDSS raw data scores); OR=0.22(*P*-value 0.003)(T1 EDSS raw data scores).

The ULKM and its derived composite functional outcome in the vPTA-yes versus vPTA-not group showed an unadjusted and adjusted OR (95% CI) for treatment group predictor variable respectively of 1.16(P-value 0.5) and 1(P-value 0.96). While at final logistic adjusted model the treatment group predictor variable was not significant however both T1 EDSS raw

data scores and EDSS>3.5 at T1 had a significant main effect: OR=1.3(P-value 0.008)(T1 EDSS raw data scores); OR=0.28(P-value 0.01)(EDSS>3.5 at T1).

Detailed results for each EPs, CFM and ULKM composite functional outcomes are provided in Table 3, 4, 5.

Both paired-t-test and Wilcoxon signed rank test with continuity correction for matched pairs in the PTA-yes group demonstrated significant results for urinary urgency (#31 test), quality of life (QoL) physical (#43 test) and mental (#44 test), and MDE with right arm (#45 test). However only the mental QoL test remained significant after *P*-value adjustment for multiple comparisons.

DISCUSSION

The vPTA has been proposed as a valid treatment option in patients with MS and CCSVI. This procedure has been suggested to potentially improve the clinical course of MS (relapse rate) and quality of life. Positive aspects emerging from current evidence are the improvement of MS course and potential modulation of MR lesion dissemination and activity 6 months after treatment. Defined negative aspects include inadequate disability improvement[8]. vPTA might be a useful intervention for treating patients with persistent headaches[10]. These changes cannot be detected with the commonly used EDSS score system for disability. Recognized drawbacks are its ineffective role in restoring blood flow in nearly half the patients in case of muscular entrapment or compression, hypoplasia, very long abnormal leaflets as well as restenosis. Finally effects could be not long lasting[24].

The present study was conceived to verify the efficacy of vPTA in patients having both MS and CCSVI in terms of different clinical outcomes and to offer free services for MS patients in highly specialized center, which would otherwise have been provided by many hospitals for a fee, both in Italy and in other countries. The randomization and a wait list allowed

generating the control group (vPTA-not group, n=35) and treatment group (vPTA-yes group n=31). In fact within the time of the wait list all patients allocated in the control group underwent two consecutive measurements of outcome (T0 and T1) before the completion of vPTA, while all patients allocated in the treatment group underwent a baseline evaluation (T0) before vPTA and the second evaluation (T1) after vPTA. Therefore the only difference between the two groups was the completion of the radiological procedure in the treatment group and the lack of the vPTA in the control group.

Our results concerning CFM derived composite functional outcome showed significant improvements of some clinical functional aspects, such as fatigue, pain, quality of life both mental and physical, anxiety, depression, attention and urinary urgency. There was no improvement in motor function after treatment, except for TUG test. These results confirm a previous study, where vPTA had no positive effects on motor disability[8]. However, other studies demonstrated improvement in fatigue, numbness, balance, concentration and memory, and mobility[10-12] as well as in physical and psychological performance items of the MSIS-29[9, 25]. Although 6 months follow-up was performed in both studies, in Sadovnick's study[24]the improvements were transient and progressively decreased, while in Hubbard's study[9] they were maintained. These studies were based on the patients' self-reported outcome instead of objective outcomes derived from physicians' clinical scales. However, the improvement priority and aim could be unequal in physician or patients' points of view. A recent study[26] reported that patients' concerns about quality of life are not always the same as the physicians'. In another study[27], MS patients considered pain the most relevant aspect about health perception, which was followed by gait impairment and fatigue. The authors concluded that what they supposed to be the "invisible disability" could be more relevant to health perception than motor disability in MS patients.

One point of strength of our study is the neurophysiological assessment. To the best of our knowledge published results about the behaviour of VEPs in MS patients who had venous angioplasty have not previously been evaluated, and only one case report has assessed MEPs changes over time[28]. Classically, VEPs and MEPs are considered functional predictive biomarkers for therapeutic responses because neurophysiological scores are bi-directional, covering both improvement and deterioration[29]. Overall, EPs evaluation may help to provide early differentiation between possibly effective and needless interventions in phase-II clinical trials[30-33]. Despite a slight tendency to improvement when some tests were analysed separately, EPs composite functional outcome did not significantly change. That seems to fit with the lack of a clear disability improvement in clinical scales.

In our study the MS course was not considered an exclusion criteria and there are not any significantly unbalanced proportion between the two groups. Nevertheless our results showed a significant effect of MS course, especially the PP phenotype, when EPs and its derived composite functional outcome in the vPTA-yes group at final adjusted logistic model was considered (OR=1.7, P-value 0.03, MS course PP/RR and OR=2.1, P-value 0.007, MS course PP/SP). However caution in the interpretation is needed taking into account of the small number of cases enrolled.

Medical therapy was not included as predictor in the adjusting logistic model; therapy with steroids in the 30 days before the procedure and the arbitrary use of new pharmacological treatments were exclusion criteria.

Venous angioplasty for CCSVI is considered a safe procedure but adverse events can occur[24,34-37]. In our study vPTA produced major complications such as acute in-segment IJV thrombosis in 3(9.6%) cases, minor complications such as puncture site bleeding in 1(3%) case. There were no serious adverse events. These cases of acute IJV segment thrombosis referred to patients in whom either complete stenosis with no valid hemodynamic flow or

hypoplasia was revealed at catheter phlebography and ECD. Since we prolonged the time of heparin administration from 15 to 40 days such a complication was solved without clinical consequences. Hypoplasia of IJV segments is considered a relative contraindication to venous angioplasty because of scarce angiographic response and high thrombotic risk. Open surgery has been invoked as alternative procedures[38]. Coagulation activation and endothelial dysfunction could have also played a significant role in this particular complication[39].

Several limitations of this study should be considered. Both difficulties in enrolling a sufficient sample size, despite 5 years devoted to that purpose with high cost, and lack of blinding or not-sham control could entail underpowered and biased results. Sham control trials and wait list control trial could be considered similar in that there are often potential problems of lack of blinding. It was thought that patients of sham control group could realize that their intervention time was different from standard procedure, despite the radiologists' best efforts to mask it, and from there deduce that they had received placebo. Besides, patients allocated in sham control group had to undergo a potential harmful procedure.

Although frequently used for ethical advantages, a wait list design can pose several issues in this particular clinical setting: first, the effects of being in a wait list control condition in interventional procedure research have not previously been evaluated[40]; second, participants who are going to receive their treatment sooner could be better motivated and comply better with the treatment programs and report better outcomes[41-42].

Finally, another limitation of our study is the lack of an adequate follow-up, which needed to be consistent and long enough to verify the progression of the disease. The improvements we found were only present at one month after procedure and nothing can be said about the long-term effects and restenosis of vPTA in MS patients with CCSVI.

In conclusion, patients with MS and CCSVI treated with vPTA showed significant improvements of some clinical functional aspects, such as fatigue, pain, quality of life both

mental and physical, anxiety, depression, attention and urinary urgency. Evoked potentials and upper limb kinematic measures were not significant enough to allow the evaluation of the efficacy of the procedure. vPTA can have a positive impact on a few neurological tests including quality of life but achieving disability improvement is unlikely.

IRB Approval: The Ethical Committee Institutional Review Board of the University of Pisa named Comitato Etico Area Vasta Nord Ovest (CEAVNO), approved the study on May 26, 2011.

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Conflicts of Interest: none.

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517 **Legends for tables**

518 Table 1. Demographic and clinical features of vPTA-yes and vPTA-not groups.

519 Table 2. Results for Evoked Potentials (EPs), Clinical-Functional measures (CFM) and Upper
520 Limb Kinematic Measures (ULKM) derived composite functional outcomes.

521 Table 3. Detailed results for single components of Evoked Potentials (EPs) composite
522 functional outcome.

523 Table 4. Detailed results for single components of Clinical-Functional Measures (CFM)
524 composite functional outcome.

525 Table 5. Detailed results for single components of Upper Limb Kinematic Measures (ULKM)
526 composite functional outcome.

527

528 **Legends for illustrations**

529 Figure 1. Flow Diagram of participants.

530

Tables

Table 1. Demographic and clinical features of PTA-yes and PTA-not groups.

	N (%) *		
	PTA-yes	PTA-not	
Characteristics	**(n = 31)**	**(n = 35)**	***P*-value**
Female	16 (51.6)	18 (51.4)	0.9
Age, mean (SD), y	47.8 (10.2)	46.7 (11.7)	0.6
EDSS score			
≥ 3.5	18 (58.1)	19 (54.3)	
< 3.5	13 (41.9)	16 (45.7)	
MS course			
Remitting Relapsing (RR)	16 (51.6)	21 (60)	0.6
Primary Progressive (PP)	6 (19.4)	7 (20)	
Secondary Progressive (SP)	9 (29)	7 (20)	

Footnotes:
* Percentage of column within group.

Table 2. Results for Evoked Potentials (EP, Clinical-Functional measures (CFM) and Upper Limb Kinematic Measures (ULKM) derived composite functional outcomes.

	No. (%) [•]					
Finding	PTA-yes (n = 31)	PTA-not (n = 35)	*Unadjusted Estimated Effect of Venous PTA OR (95% CI)* [†]	*P*-value	*Adjusted Estimated Effect of Venous PTA OR (95% CI)* [‡]	*P*-value
a. EPs derived composite functional outcome [§]						
Improved	11 (35)	7 (20)	1.03 (0.7-1.3)	0.82	1.26 (0.9-1.8)	0.18
Stable	6 (19)	7 (20)	NA			
Worsened	2 (6)	3 (9)	NA			
Mixed	12(39)	18 (51)	NA			
b. CFM derived composite functional outcome [‖]						
Improved	11 (35)	7 (20)	1.93 (1.3-2.8)	0.0007	1.85 (1.2-2.7)	0.002
Stable	1 (3)	3 (9)				
Worsened	0	7 (20)				
Mixed	19 (61)	18 (51)				
c. ULKM derived composite functional outcome [••]						
Improved	9 (29)	10 (29)	1.16 (0.7-1.8)	0.5	1 (0.6-1.5)	0.96
Stable	5 (16)	8 (23)				
Worsened	2 (6)	0				
Mixed	15 (48)	17 (49)				

Footnotes:

[•] Percentage of column within group.

[†] Unadjusted OR for PTA-yes group improvement at 95%CI and *P*-value from logistic model.

[‡] Adjusted logistic model was used for gender, MS course, both T0 and T1 EDSS raw data scores, both T0 and T1 EDSS ≥ 3.5 and interactions.

[§] All EPs single tests are included to obtain the EPs composite functional outcome.

[‖] CFM composite functional outcome is composed by the following tests: test #19, Trial Making Test-A (TMT-A); test #31, urinary urgency; test #35, Timed Up and Go (TUG); test #38, Fatigue Severity Scale (FSS); test #39, Numerical Rating Scale for pain (NRS); test #40, Hospital Anxiety-Depression Scale (HADS); test #41,HADS-depression; test #43, physical Multiple Sclerosis Quality of life (MSQoL); test #44 mental MSQoL.

[••] ULKM derived composite functional outcome is composed by the following tests: test #45, MDE, right arm; test #47, PTV, right arm; test #49, AI, right arm; test #55, MDE, left arm; test #57, PTV, left arm; test #59, AI, left arm; test #63, MT, left arm.

Table 3. Detailed results for single components of Evoked Potentials (EPs) composite functional outcome.

		T1 * N (%) †			T0 Score		T1 Score	
Functional Assessment	N	I	S	W	Median (range)	Mean (SD)	Median (range)	Mean (SD)
test #1, VEP.Right Eye.60'								
PTA-yes group	31	5 (16)	24 (77)	2 (6)	121 (113-129)	125 (19)	122 (115-135)	126 (18)
PTA-not group	35	5 (14)	25 (71)	5 (14)	115 (105-125)	117 (15)	119 (103-128)	119 (19)
test #2, VEP.Left Eye.60'								
PTA-yes group	31	6 (19)	19 (61)	6 (19)	119 (113-135)	127 (21)	117 (110-133)	122 (16)
PTA-not group	35	8 (23)	24 (69)	3 (9)	115 (105-122)	118 (17)	119 (110-130)	121 (18)
test #3, VEP.Right Eye.15'								
PTA-yes group	31	8 (26)	17 (55)	6 (19)	119 (113-131)	125 (20)	119 (113-141)	126 (19)
PTA-not group	35	7 (20)	20 (57)	8 (23)	117 (105-130)	120 (18)	118 (105-126)	119 (19)
test #4, VEP.Left Eye.15'								
PTA-yes group	31	6 (19)	18 (58)	7 (23)	121 (112-139)	126 (21)	119 (109-132)	112 (15)
PTA-not group	35	9 (26)	19 (54)	7 (20)	116 (105-128)	119 (17)	119 (110-132)	121 (18)
test #5, MEP.TMCT. Right upper arm								
PTA-yes group	31	5 (16)	20 (64)	6 (19)	23 (21-28)	25 (6)	22 (21-26)	24 (5)
PTA-not group	35	4 (11)	30 (86)	1 (3)	21 (20-25)	23 (5)	23 (19-28)	24 (6)
test #6, MEP.TMCT. Left upper arm								
PTA-yes group	31	3 (10)	19 (61)	9 (29)	24 (21-28)	25 (6)	22 (19-27)	24 (6)
PTA-not group	35	5 (14)	26 (74)	4 (11)	22 (20-26)	24 (5)	25 (20-27)	25 (6)
test #7, MEP.TMCT. Right lower leg								
PTA-yes group	31	7 (23)	20 (64)	4 (13)	35 (29-44)	38 (10)	37 (31-47)	39 (9)
PTA-not group	35	5 (14)	27 (77)	3 (9)	35 (29-44)	36 (10)	36 (29-44)	37 (11)
test #8, MEP.TMCT. Left lower leg								
PTA-yes group	31	4 (13)	21 (68)	6 (19)	34 (31-48)	39 (9)	36 (30-46)	38 (19)
PTA-not group	35	4 (11)	25 (71)	6 (17)	33 (28-38)	35 (9)	35 (27-51)	37 (13)
test #9, MEP.dCMCT. Right upper arm								
PTA-yes group	31	3 (10)	25 (81)	3 (10)	9 (8-15)	12 (5)	10 (8-13)	12 (5)
PTA-not group	35	3 (9)	31 (89)	1 (3)	9 (7-11)	10 (5)	10 (7-13)	11 (5)
test #10, MEP.dCMCT. Left upper arm								
PTA-yes group	31	1 (3)	27 (87)	3 (10)	11 (7-14)	12 (6)	10 (7-14)	11 (5)
PTA-not group	35	5 (14)	28 (80)	2 (6)	9 (7-13)	10 (5)	11 (7-14)	12 (6)

Table 3. Continuing

test #11, MEP.dCMCT. Right lower leg								
PTA-yes group	31	7 (23)	20 (64)	4 (13)	21 (14-30)	22 (9)	20 (16-32)	24 (9)
PTA-not group	35	4 (11)	26 (74)	5 (14)	20 (14-31)	22 (9)	22 (14-28)	22 (9)
test #12, MEP.dCMCT. Left lower leg								
PTA-yes group	31	4 (13)	21 (68)	6 (19)	20 (16-32)	23 (9)	19 (14-33)	22 (10)
PTA-not group	35	5 (14)	24 (69)	6 (17)	20 (13-24)	21 (9)	19 (14-30)	22 (10)
test #13, MEP.iCMCT. Right upper arm								
PTA-yes group	31	12 (39)	16 (51)	3 (10)	8 (6-12)	10 (5)	12 (8-14)	12 (5)
PTA-not group	35	11 (31)	20 (57)	4 (11)	7 (5-8)	8 (5)	13 (7-16)	12 (5)
test #14, MEP.iCMCT. Left upper arm								
PTA-yes group	31	9 (29)	17 (55)	5 (16)	9 (6-12)	11 (6)	12 (8-14)	12 (7)
PTA-not group	35	9 (26)	23 (66)	3 (9)	8 (6-11)	9 (4)	12 (7-15)	11 (4)
test #15, MEP.iCMCT. Right lower leg								
PTA-yes group	31	8 (26)	22 (71)	1 (3)	16 (15-28)	19 (8)	16 (15-28)	21 (9)
PTA-not group	35	9 (26)	25 (71)	1 (3)	19 (12-27)	19 (8)	18 (16-22)	20 (7)
test #16, MEP.iCMCT. Left lower leg								
PTA-yes group	31	5 (16)	22 (71)	4 (13)	18 (14-24)	19 (6)	17 (15-28)	21 (9)
PTA-not group	35	9 (26)	23 (66)	3 (9)	18 (11-21)	17 (6)	17 (14-24)	20 (8)

Footnotes:

* All *P*-value are > 0.95 after adjustament for multiplicity with Hommel method.

† Row percentage.

Abbreviations. I: Improved; S: Stable; W: Worsened; VEP: visual evoked potential; 60': 60 degree; 15': 15 degree; MEP: motor evoked potential; TMCT; total motor conduction time; dCMCT: direct central motor conduction time; iCMCT: indirect central motor conduction time.

Table 4. Detailed results for single components of Clinical-Functional Measures (CFM) composite functional outcome.

		T1 • N (%) †			T0		T1	
Functional Assessment	**N**	**I**	**S**	**W**	**Median (range)**	**Mean (SD)**	**Median (range)**	**Mean (SD)**
test #19, TMT-A								
PTA-yes group	31	15 (48)	8 (26)	8 (26)	58 (50-75)	63 (21)	54 (42-76)	63 (35)
PTA-not group	35	8 (23)	20 (57)	7(20)	61 (53-87)	81 (68)	61 (52-74)	69 (33)
test #31, Urinary urgency								
PTA-yes group	31	8 (26)	22 (71)	1 (3)	NA	NA	NA	NA
PTA-not group	35	6 (17)	28 (80)	1 (3)	NA	NA	NA	NA
test #35, TUG								
PTA-yes group	31	9 (29)	19 (61)	3 (10)	10 (8-30)	23 (22)	10 (8-25)	21 (22)
PTA-not group	35	5 (14)	27 (77)	3 (9)	11 (9-13)	19 (26)	10 (8-14)	19 (28)
test #38, FSS								
PTA-yes group	31	6 (19)	23 (74)	2 (6)	47 (39-56)	45 (13)	44 (37-50)	42 (13)
PTA-not group	35	5 (14)	24 (69)	6 (17)	47 (26-55)	40 (17)	46 (23-56)	41 (18)
test #39, NRS for pain								
PTA-yes group	31	12 (39)	14 (45)	5 (16)	2 (0-5)	3 (3)	1.5 (0-3)	2 (2)
PTA-not group	35	6 (17)	18 (51)	11 (31)	0.5 (0-3)	2 (2)	0 (0-5)	2 (3)
test #40, HADS-anxiety								
PTA-yes group	31	12 (43)	7 (25)	2 (32)	5 (2-8)	6 (4)	4 (3-6)	5 (3)
PTA-not group	35	12 (36)	8 (24)	13 (39)	5 (3-8)	6 (4)	6 (3-8)	6 (4)
test #41, HADS-depression								
PTA-yes group	31	14 (45)	8 (26)	9 (29)	6 (4-9)	6 (4)	5 (3-7)	5 (3)
PTA-not group	35	17 (49)	7 (20)	11 (31)	8 (5-10)	7 (3)	6 (4-10)	7 (4)
test #43, MSQoL-physical								
PTA-yes group	31	8 (26)	22 (71)	1 (3)	52 (38-59)	48 (19)	55 (37-65)	53 (21)
PTA-not group	35	1 (3)	28 (80)	6 (17)	49 (38-71)	53 (21)	47 (36-73)	53 (23)
test #44, MSQoL-mental								
PTA-yes group	31	9 (29)	20 (64)	2 (6)	62 (44-76)	59 (20)	69 (51-83)	66 (20)
PTA-not group	35	4 (11)	23 (66)	8 (23)	62 (50-79)	64 (18)	65 (47-78)	61 (24)

Footnotes:

• All *P*-value are > 0.05 after adjustament for multiplicity with Hommel method.

† Row percentage.

Abbreviations. I: Improved; S: Stable; W: Worsened; TMT-A: Trial making tests-A; TUG: Timed Up and Go; FSS: Fatigue Severity Scale; NRS: Numerical Rating Scale for pain; HADS: Hospital Anxiety-Depression Scale; MSQoL: Multiple Sclerosis Quality of Life.

Table 5. Detailed results for single components of Upper Limb Kinematic Measures (ULKM) composite functional outcome.

		T1 * N (%) †			T0		T1	
Functional Assessment	**N**	**I**	**S**	**W**	**Median (range)**	**Mean (SD)**	**Median (range)**	**Mean (SD)**
test #45, MDE.Right								
PTA-yes group	31	14 (45)	10 (32)	7 (23)	4 (2-8)	6 (6)	3 (1-5)	4 (3)
PTA-not group	35	10 (29)	18 (51)	7 (20)	3 (2-6)	6 (7)	3 (1-6)	5 (5)
test #47, PTV.Right								
PTA-yes group	31	8 (26)	15 (48)	8 (26)	1122 (890-1656)	1339 (738)	1138 (880-1711)	1346 (769)
PTA-not group	35	9 (26)	15 (43)	11 (31)	1238 (906-1685)	1282 (476)	1105 (761-1643)	1228 (582)
test #49, AI.Right								
PTA-yes group	31	5 (16)	22 (71)	4 (14)	0.9 (0.7-1)	0.9 (0.2)	0.9 (0.7-1)	0.9 (0.2)
PTA-not group	35	9 (26)	23 (66)	3 (9)	0.9 (07-1)	0.9 (0.3)	0.8 (0.7-1)	0.9 (0.3)
test #55, MDE.Left								
PTA-yes group	31	11 (35)	10 (32)	10 (32)	-1.6 [(-4) - (-0.6)]	- 1.9 (4)	-1.3 [(-4) - (-0.6)]	-1.7 (4)
PTA-not group	35	8 (23)	18 (51)	9 (26)	-3.2 [(-7) - (-2)]	-5 (6)	-3 [(-7) - (-0.5)]	-4 (5)
test #57, PTV.Left								
PTA-yes group	31	9 (29)	17 (55)	5 (16)	1103 (768- 1816)	1282 (701)	1260 (779-1819)	1544 (1214)
PTA-not group	35	8 (23)	13 (37)	14 (40)	1209 (852-1688)	1311 (497)	1140 (852-1688)	1214 (603)
test #59, AI.Left								
PTA-yes group	31	6 (19)	20 (64)	5 (16)	0.8 (0.6-1)	0.8 (0.2)	0.9 (0.8-1)	0.9 (0.2)
PTA-not group	35	10 (28)	22 (63)	3 (9)	0.8 (0.6-0.9)	0.9 (0.3)	0.8 (0.7-0.9)	0.8 (0.3)
test #63, MT.Left								
PTA-yes group	31	7 (23)	24 (77)	0	730 (585-1145)	972 (533)	829 (587-1131)	886 (398)
PTA-not group	35	4 (11)	22 (63)	9 (26)	825 (636-1037)	842 (245)	930 (689-1036)	952 (404)

Footnotes:

* All *P*-value are > 0.35 after adjustament for multiplicity with Hommel method.

† Row percentage.

Abbreviations. I: Improved; S: Stable; W: Worsened; MDE: medium directional error; PTV: peak of tangential velocity; AI: asymmetry index; MT: movement time.

Tables

Table 1. Demographic and clinical features of PTA-yes and PTA-not groups.

	N(%)*		
Characteristics	***PTA-yes (N=31)***	***PTA-not (N=35)***	***P-value***
Female	*16 (51.6)*	*18 (51.4)*	*0.9*
Age, mean (SD), y	*47.8 (10.2)*	*46.7 (11.7)*	*0.6*
EDSS score			
≥ 3.5	*18 (58.1)*	*19 (54.3)*	
< 3.5	*13 (41.9)*	*16 (45.7)*	
MS course			
Remitting Relapsing (RR)	*16 (51.6)*	*21 (60)*	*0.6*
Primary Progressive (PP)	*6 (19.4)*	*7 (20)*	
Secondary Progressive (SP)	*9 (29)*	*7 (20)*	
Footnotes: **Percentage of column within group*			

Table 2. Results for Evoked Potentials (EP, Clinical-Functional measures (CFM) and Upper Limb Kinematic Measures (ULKM) derived composite functional outcomes.

	No. (%)*					
Finding	**PTA-yes (n=31)**	**PTA-not (n =35)**	**Unadjusted Estimated Effect of Venous PTA OR (95% CI) ᴪ**	**P-value**	**Adjusted Estimated Effect of Venous PTA OR (95% CI) ᶲ**	**P-value**
a. EPs derived composite functional outcome$^{\varpi}$						
Improved	11 (35)	7 (20)	1.03 (0.7-1.3)	0.82	1.26 (0.9-1.8)	0.18
Stable	6 (19)	7 (20)	NA			
Worsened	2 (6)	3 (9)	NA			
Mixed	12 (39)	18 (51)	NA			
b. CFM derived composite functional outcome$^{\theta}$						
Improved	11 (35)	7 (20)	1.93 (1.3-2.8)	0.0007	1.85 (1.2-2.7)	0.002
Stable	1 (3)	3 (9)				
Worsened	0	7 (20)				
Mixed	19 (61)	18 (51)				
c. ULKM derived composite functional outcome**						
Improved	9 (29)	10 (29)	1.16 (0.7-1.8)	0.5	1 (0.6-1.5)	0.96
Stable	5 (16)	8 (23)				
Worsened	2 (6)	0				
Mixed	15 (48)	17 (49)				

Footnotes:

*Percentage of column within group

ᴪ Unadjusted OR for PTA-yes group improvement at 95%CI and P-value from logistic model.

ᶲ Adjusted logistic model was used for gender, MS course, both T0 and T1 EDSS raw data scores, both T0 and T1 EDSS ≥

3.5 and interactions

[ϖ] All EPs single tests are included to obtain the EPs composite functional outcome

[θ] CFM composite functional outcome is composed by the following tests: test#19, Trial Making Test-A (TMT-A); test #31, urinary urgency; test#35, Timed Up and Go (TUG); test#38, Fatigue Severity Scale (FSS); test#39, Numerical Rating Scale for pain (NRS); test#40, Hospital Anxiety-Depression Scale (HADS); test#41, HADS depression; test#43, physical Multiple Sclerosis Quality of life (MSQoL); test#44 mental MSQoL.

[**] ULKM derived composite functional outcome is composed by the following test: test#45, MDE, right arm; test #47, PTV, right arm; test#49, AI, right arm; test#55, MDE, left arm; test#57, PTV, left arm; test#59, AI, left arm; test#63, MT, left arm.

Table 3. Detailed results for single components of Evoked Potentials (EPs) composite functional outcome.

	T1* **N(%)[φ]**				**T0** **Score**		**T1** **Score**	
Functional assessment	**N**	**I**	**S**	**W**	**Median (range)**	**Mean (SD)**	**Median (range)**	**Mean (SD)**
Test#1, VEP. Right Eye.60'								
PTA-yes group	31	5 (16)	24 (77)	2 (6)	121 (113-129)	125 (19)	122 (115-135)	126 (18)
PTA-not group	35	5 (14)	25 (71)	5 (14)	115 (105-125)	117 (15)	119 (103-128)	119 (19)
Test#2, VEP. Left Eye.60'								
PTA-yes group	31	6 (19)	19 (61)	6 (19)	119 (113-135)	127 (21)	117 (110-133)	122 (16)
PTA-not group	35	8 (23)	24 (69)	3 (9)	115 (105-122)	118 (17)	119 (110-130)	121 (18)
Test#3, VEP. Right Eye.15'								
PTA-yes group	31	8 (26)	17 (55)	6 (19)	119 (113-131)	125 (20)	119 (113-141)	126 (19)
PTA-not group	35	7 (20)	20 (57)	8 (23)	117 (105-130)	120 (18)	118 (105-126)	119 (19)
Test#4, VEP. Left Eye. 15'								
PTA-yes group	31	6 (19)	18 (58)	7 (23)	121 (112-139)	126 (21)	119 (109-132)	112 (15)
PTA-not group	35	9 (26)	19 (54)	7 (20)	116 (105-128)	119 (17)	119 (110-132)	121(18)
Test#5, MEP.								

TMCT. Right upper arm								
PTA-yes group	31	5 (16)	20 (64)	6 (19)	23 (21-28)	25 (6)	22 (21-26)	24 (5)
PTA-not group	35	4 (11)	30 (86)	1 (3)	21 (20-25)	23 (5)	23 (19-28)	24 (6)
Test#6, MEP. TMCT. Left upper arm								
PTA-yes group	31	3 (10)	19 (61)	9 (29)	24 (21-28)	25 (6)	22 (19-27)	24 (6)
PTA-not group	35	5 (14)	26 (74)	4 (11)	22 (20-26)	24 (5)	25 (20-27)	25 (6)
Test#7, MEP. TMCT. Right lower leg								
PTA-yes group	31	7 (23)	20 (64)	4 (13)	35 (29-44)	38 (10)	37 (31-47)	39 (9)
PTA-not group	35	5 (14)	27 (77)	3 (9)	35 (29-44)	36 (10)	36 (29-44)	37 (11)
Test#8, MEP. TMCT. Left lower leg								
PTA-yes group	31	4 (13)	21 (68)	6 (19)	34 (31-48)	39 (9)	36 (30-46)	38 (19)
PTA-not group	35	4 (11)	25 (71)	6 (17)	33 (28-38)	35 (9)	35 (27-51)	37 (13)
Test#9, MEP. dCMCT. Right upper arm								
PTA-yes group	31	3 (10)	25(81)	3 (10)	9 (8-15)	12 (5)	10 (8-13)	12 (5)
PTA-not group	35	3 (9)	31 (89)	1 (3)	9 (7-11)	10 (5)	10 (7-13)	11 (5)
Test#10, MEP.dCMCT. Left upper arm								
PTA-yes group	31	1 (3)	27 (87)	3 (10)	11 (7-14)	12 (6)	10 (7-14)	11 (5)
PTA-not group	35	5 (14)	28 (80)	2 (6)	9 (7-13)	10 (5)	11 (7-14)	12 (6)
Test#11, MEP.dCMCT.								

Right lower leg								
PTA-yes group	31	7 (23)	20 (64)	4 (13)	21 (14-30)	22 (9)	20 (16-32)	24 (9)
PTA-not group	35	4 (11)	26 (74)	5 (14)	20 (14-31)	22 (9)	22 (14-28)	22 (9)
Test#12, MEP.dCMCT. Left lower leg								
PTA-yes group	31	4 (13)	21 (68)	6 (19)	20 (16-32)	23 (9)	19 (14-33)	22 (10)
PTA-not group	35	5 (14)	24 (69)	6 (17)	20 (13-24)	21 (9)	19 (14-30)	22 (10)
Test#13, MEP.iCMCT. Right upper arm								
PTA-yes group	31	12 (39)	16 (51)	3 (10)	8 (6-12)	10 (5)	12 (8-14)	12 (5)
PTA-not group	35	11 (31)	20 (57)	4 (11)	7 (5-8)	8 (5)	13 (7-16)	12 (5)
Test#14, MEP. iCMCT. Left upper arm								
PTA-yes group	31	9 (29)	17 (55)	5 (16)	9 (6-12)	11 (6)	12 (8-14)	12 (7)
PTA-not group	35	9 (26)	23 (66)	3 (9)	8 (6-11)	9 (4)	12 (7-15)	11 (4)
Test#15, MEP. iCMCT. Right lower leg								
PTA-yes group	31	8 (26)	22 (71)	1 (3)	16 (15-28)	19 (8)	16 (15-28)	21 (9)
PTA-not group	35	9 (26)	25 (71)	1 (3)	19 (12-27)	19 (8)	18 (16-22)	20 (7)
Test#16, MEP. iCMCT. Left lower leg								
PTA-yes group	31	5 (16)	22 (71)	4 (13)	18 (14-24)	19 (6)	17 (15-28)	21 (9)
PTA-not group	35	9 (26)	23 (66)	3 (9)	18 (11-21)	17 (6)	17 (14-24)	20 (8)

Footnotes:

* All P-value are >0.95 after adjustment for multiplicity with Hommel method

ᵠ Row percentage

Abbreviations. I:Improved; S:Stable; W:Worsened; VEP: Visual Evoked potential; 60': 60 degree; 15':15 degree; MEP: Motor Evoked potential; TMCT: total motor conduction time; dCMCT: direct central motor conduction time; iCMCT: indirect central motor conduction time

Table 4. Detailed results for single components of Clinical-Functional Measures (CFM) composite functional outcome.

	T1* **N(%)**[φ]				**T0** **Score**		**T1** **Score**	
Functional assessment	**N**	**I**	**S**	**W**	**Median (range)**	**Mean (SD)**	**Median (range)**	**Mean (SD)**
Test#19, TMT-A								
PTA-yes group	31	15 (48)	8 (26)	8 (26)	58 (50-75)	63 (21)	54 (42-76)	63 (35)
PTA-not group	35	8 (23)	20 (57)	7 (20)	61 (53-87)	81 (68)	61 (52-74)	69 (33)
Test#31, Urinary Urgency								
PTA-yes group	31	8 (26)	22 (71)	1 (3)	NA	NA	NA	NA
PTA-not group	35	6 (17)	28 (80)	1 (3)	NA	NA	NA	NA
Test#35, TUG								
PTA-yes group	31	9 (29)	19 (61)	3 (10)	10 (8-30)	23 (22)	10 (8-25)	21 (22)
PTA-not group	35	5 (14)	27 (77)	3 (9)	11 (9-13)	19 (26)	10 (8-14)	19 (28)
Test#38, FSS								
PTA-yes group	31	6 (19)	23 (74)	2 (6)	47 (39-56)	45 (13)	44 (37-50)	42 (13)
PTA-not group	35	5 (14)	24 (69)	6 (17)	47 (26-55)	40 (17)	46 (23-56)	41(18)
Test#39, NRS								

for pain								
PTA-yes group	31	12 (39)	14 (45)	5 (16)	2 (0-5)	3 (3)	1.5 (0-23)	2 (2)
PTA-not group	35	6 (17)	18 (51)	11 (31)	0.5 (0-3)	2 (2)	0 (0-5)	2 (3)
Test#40, HADS-anxiety								
PTA-yes group	31	12 (43)	7 (25)	2 (32)	5 (2-8)	6 (4)	4 (3-6)	5 (3)
PTA-not group	35	12 (36)	8 (24)	13 (39)	5 (3-8)	6 (4)	6 (3-8)	6 (4)
Test#41, HADS-depression								
PTA-yes group	31	14 (45)	8 (26)	9 (29)	6 (4-9)	6 (4)	5 (3-7)	5 (3)
PTA-not group	35	17 (49)	7 (20)	11 (31)	8 (5-10)	7 (3)	6 (4-10)	7 (4)
Test#43, MSQoL-physical								
PTA-yes group	31	8 (26)	22 (71)	1 (3)	52 (38-59)	48 (19)	55 (37-65)	53 (21)
PTA-not group	35	1 (3)	28 (80)	6 (17)	49 (38-71)	53 (21)	47 (36-73)	53 (23)
Test#44, MSQoL-mental								
PTA-yes group	31	9 (29)	20 (64)	2 (6)	62 (44-76)	59 (20)	69 (51-83)	66 (20)
PTA-not group	35	4 (11)	23 (66)	8 (23)	62 (50-79)	64 (18)	65 (47-78)	61 (24)

Footnotes:

* All P-value are >0.05 after adjustment for multiplicity with Hommel method

ᵠ Row percentage

Abbreviations. I:Improved; S:Stable; W:Worsened; TMT-A: trial making tests-A; TUG: timed up and go; FSS: fatigue severity scale; NRS: Numerical rating scale for pain; HDS:Hospital Anxiety-Depression Scale; MSQoL; Multiple Sclerosis Quality of Life.

Table 5. Detailed results for single components of Upper Limb Kinematic Measures (ULKM) composite functional outcome.

	T1* **N(%)$^{\varphi}$**				**T0** **Score**		**T1** **Score**	
Functional assessment	**N**	**I**	**S**	**W**	**Median (range)**	**Mean (SD)**	**Median (range)**	**Mean (SD)**
Test#45, MDE. Right								
PTA-yes group	31	14 (45)	10 (32)	7 (23)	4 (2-8)	6 (6)	3 (1-5)	4 (3)
PTA-not group	35	10 (29)	18 (51)	7 (20)	3 (2-6)	6 (7)	3 (1-6)	5 (5)
Test#47, PTV. Right								
PTA-yes group	31	8 (26)	15 (48)	8 (26)	1122 (890-1656)	1339 (738)	1138 (880-1711)	1346 (769)
PTA-not group	35	9 (26)	15 (43)	11 (31)	1238 (906-1685)	1282 (476)	1105 (761-1643)	1228 (582)
Test#49, AI. Right								
PTA-yes group	31	5 (16)	22 (71)	4 (14)	0.9 (0.7-1)	0.9 (0.2)	0.9 (0.7-1)	0.9 (0.2)
PTA-not group	35	9 (26)	23 (66)	3 (9)	0.9 (0.7-1)	0.9 (0.3)	0.8 (0.7-1)	0.9 (0.3)
Test#55, MDE. Left								
PTA-yes group	31	11 (35)	10 (32)	10 (32)	-1.6 [(-4)-(-0.6)]	-1.9 (4)	-1.3 [(-4)-(-0.6)]	-1.7 (4)
PTA-not group	35	8 (23)	18 (51)	9 (26)	-3.2 [(-7)-(-2)]	-5 (6)	-3 [(-7)-(-0.5)]	-4 (5)

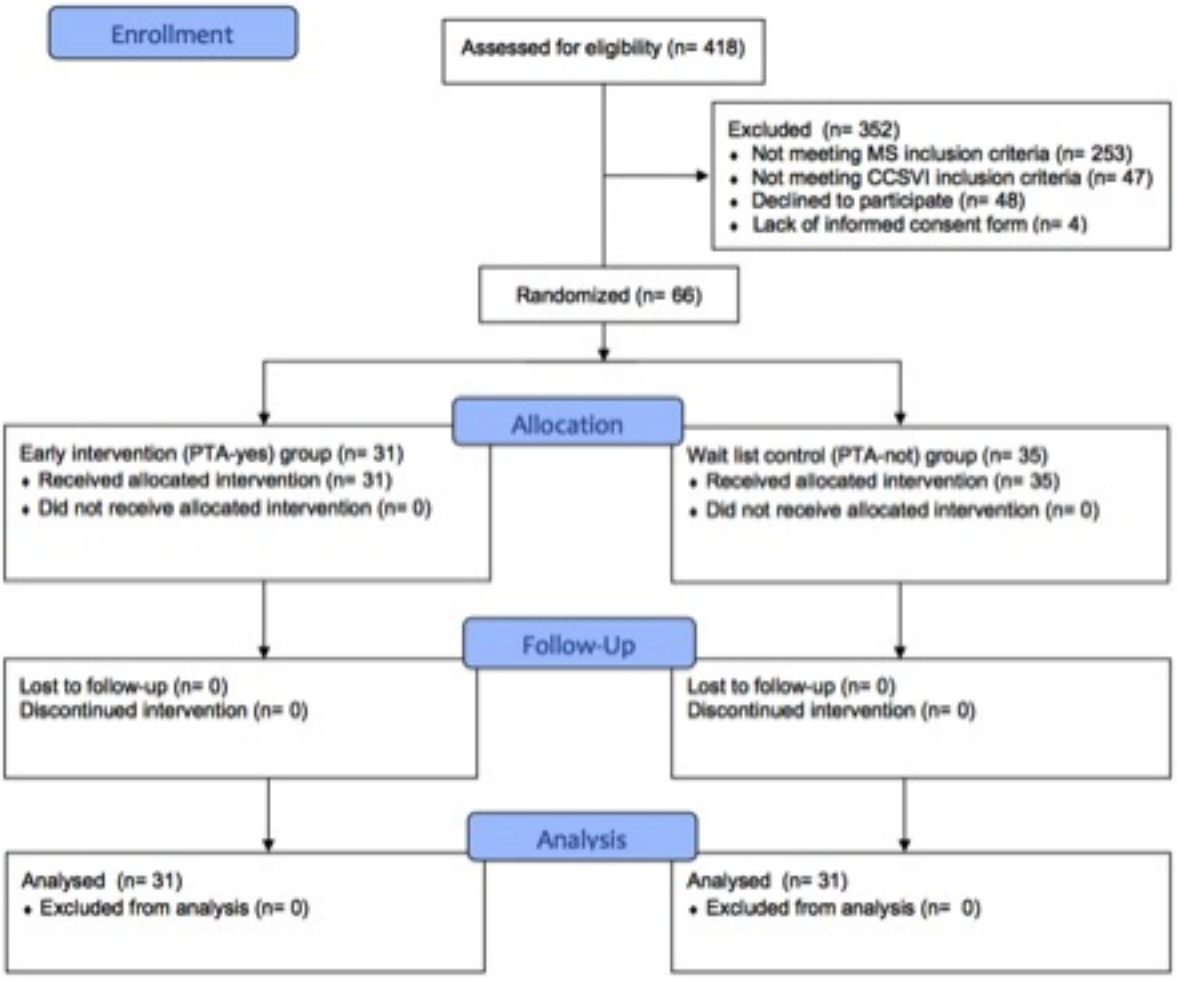
Test#57, PTV. Left								
PTA-yes group	31	9 (29)	17 (55)	5 (16)	1103 (768-1816)	1282 (701)	1260 (779-1819)	1544 (1214)
PTA-not group	35	8 (23)	13 (37)	14 (40)	1209 (852-1688)	1311 (497)	1140 (852-1688)	1214 (603)
Test#59, AI. Left								
PTA-yes group	31	6 (19)	20 (64)	5 (16)	0.8 (0.6-1)	0.8 (0.2)	0.9 (0.8-1)	0.9 (0.2)
PTA-not group	35	10 (28)	22 (63)	3 (9)	0.8 (0.6-0.9)	0.9 (0.3)	0.8 (0.7-0.9)	0.8 (0.3)
Test#63, MT. Left								
PTA-yes group	31	7 (23)	24 (77)	0	730 (585-1145)	972 (533)	829 (587-1131)	886 (398)
PTA-not group	35	4 (11)	22 (63)	9 (26)	825 (636-1037)	842 (245)	930 (689-1036)	952 (404)

Footnotes:

* All P-value are >0.35 after adjustment for multiplicity with Hommel method

ᵠ Row percentage

Abbreviations. I:Improved; S:Stable; W:Worsened; MDE: medium directional error; PTV: peak off tangential velocity; AI: Asymmetry index; MT: movement time.


Enrollment
Assessed for eligibility (n= 418)
Excluded (n= 352)
• Not meeting MS inclusion criteria (n= 253)
• Not meeting CCSVI inclusion criteria (n= 47)
• Declined to participate (n= 48)
• Lack of informed consent form (n= 4)
Randomized (n= 66)
Allocation
Early intervention (PTA-yes) group (n= 31)
• Received allocated intervention (n= 31)
• Did not receive allocated intervention (n= 0)
Wait list control (PTA-not) group (n= 35)
• Received allocated intervention (n= 35)
• Did not receive allocated intervention (n= 0)
Follow-Up
Lost to follow-up (n= 0)
Discontinued intervention (n= 0)
Lost to follow-up (n= 0)
Discontinued intervention (n= 0)
Analysis
Analysed (n= 31)
• Excluded from analysis (n= 0)
Analysed (n= 31)
• Excluded from analysis (n= 0)