The effects of robot-assisted gait training in progressive multiple sclerosis: A randomized controlled trial

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ABSTRACT

Background: Gait and mobility impairments are common in progressive multiple sclerosis (MS), leading to reduced quality of life (QoL).

Objective: In this randomized controlled study, we tested the effects of robot-assisted gait training (RAGT) and compared it to conventional physiotherapy, measuring walking ability, depression, fatigue, and QoL in patients with progressive MS and severe gait disability.

Methods: Fifty-two participants (Expanded Disability Status Scale score 6–7) completed the study protocol. They received two sessions/week over 6weeks of RAGT or conventional walking therapy. Outcome measures were Six-Minute Walk Test, Ten-Meter Walk Test, Timed Up and Go Test, Berg Balance Scale, Fatigue Severity Scale, Patient Health Questionnaire, and Short Form 36. They were performed pre-treatment, post-treatment, and at 3months.

Results: Walking endurance (p<0.01) and balance (p<0.01) were improved among those in the RAGT group. Positive effects on depression in both treatment groups were highlighted. However, only among those in the RAGT group was perceived physical functioning QoL increased. No significant effects on fatigue were found.

Conclusion: RAGT is a treatment option in progressive MS patients with severe gait impairments to induce short-lasting effects on mobility and QoL.

Keywords: Robot-assisted gait training, rehabilitation, multiple sclerosis, gait, QoL

Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease commonly related to motor impairments, and 80% of sufferers experience gait and mobility impairments, while 75% suffer from balance disorders.1 Furthermore, MS might affect either cognitive or emotional domains with subsequent deterioration of perceived quality of life (QoL).2 Psychological wellbeing has been described as related to impairment and more specifically to disease progression; however, several studies demonstrated QoL improvements with exercise training, independent of symptom regression, thus emphasizing the importance of considering this aspect in the global assessment of a patient's functional status.3,4 The majority of people with progressive MS did not receive specific medications.1 Moreover, the high prevalence of motor disorders underlines the need for rehabilitative care in longterm management. Several studies tested the effects of interventions such as treadmill training,5 bodyweight-supported training on a treadmill (BWSTT),6,7 robot-assisted gait training (RAGT),8–13 or a combination of RAGT and BWSTT within a single session,14 reporting small but positive effects on functional status5,6,8,9,11–14 or QoL3,7 in heterogeneous samples of MS patients. However, no exhaustive evidence is available to establish which rehabilitative approaches are more effective in restoring gait and mobility in progressive MS and how they affect subjective perceptions of well-being.3,7 On this basis, the aim of this randomized controlled study was to test the effects of RAGT and compare it to conventional physiotherapy in terms of improving

- gait speed and endurance,

- balance and mobility, and

- fatigue, depression, and QoL in patients with progressive MS and severe gait disabilities.

Materials and methods

This multicenter, randomized, single-blinded, controlled study (NCT01435694) has been reviewed by theFerrara and Pisa University Hospital Ethics Committees. Written informed consent was obtained prior to procedures. Inclusion criteria were:

- aged 18 years or more,

- diagnosis of primary or secondary progressive MS according to McDonald et al.15 criteria, and

- severe gait impairments as evidenced by a rating on the Expanded Disability Status Scale (EDSS) between 6.0 and 7.0.16

Exclusion criteria were

- neurologic conditions in addition to MS,

- severe medical conditions, and

- impaired cognitive functioning as evidenced by a score on the Mini Mental Status Examination of less than 24.

Participants were randomized to RAGT or conventional walking therapy (CWT) through a randomization stratification approach. Patients were grouped into strata defined by the severity of gait disability (EDSS rating: scores 6, 6.5, and 7) and then randomized separately within each stratum according to a block randomization of 4. Two random lists were generated for each treatment center (Ferrara and Pisa). Each list was managed by an administrator external to the research groups to prevent selection bias. The randomization scheme was generated using the website http://www.
randomization.com. Each patient received 12 sessions over 6weeks (two sessions/week).

To calculate sample size, we used data from our pilot study.12 Compared to the control group, the RAGT effect size was shown to be 1.19 based on the SixMinute Walk Test (6MWT). Given an equal allocation between treatment and control arms, 90% power, and an alpha of 1%, we needed 46 patients (23 per arm) to complete the study. Conservatively, we expected a 10% drop-out rate; thus, the sample size was increased by 10% to 52 patients (26 per arm). Finally, to account for unexpected factors, we increased the sample size further to 58 patients.

Each patient wore a harness attached to a system providing body weight support and walked on a treadmill with the help of a robotic-driven gait orthosis (Lokomat; Hocoma, Switzerland). Legs were guided according to a physiological gait pattern. The torques of the drives on the knees and hips were adjustable between 100% and 0%, as was the body weight support. The speed of the treadmill was varied between 0.1 km/h and approximately 3km/h. During
the first session, the training parameters were set according to the subjects' characteristics and demand levels (starting with 100% guidance and 50% body weight support). As training progressed, adjustments (10% each) to the assistance provided by the drivengait orthosis, the amount of body weight support, and treadmill speed were made. Training sessions lasted for 1hour, half of which was used as walking time.

Patients received 1 hour of CWT in each session. During the first 10–15 minutes, they performed lower limb and core stretching exercises to increase muscle flexibility. This was followed by lower limb muscle strengthening (10minutes), motor coordination, and gait and balance exercises (30minutes) tailored to the patient's baseline.

Outcome measures were assessed prior to treatment initiation (T0), after 3weeks (T1), after the end of
treatment (T2), and at 3-month follow-up (T3) by a clinician blinded to the treatment received. As primary outcomes, we selected gait speed and endurance improvements after treatments. Gait speed was measured using a standardized procedure for the Ten-Meter Walk Test (10MWT), which has high inter-rater and intra-rater reliabilities in MS patients.17 Walking endurance was measured using the 6MWT, a feasible, reproducible, and reliable measure in MS patients.18 The Berg Balance Scale (BBS) was used to assess the ability to maintain balance, either statically or while performing

functional movement. It comprises 14 life tasks, each measured on a 5-point ordinal scale.19 The Timed Up and Go (TUG) test, that measures mobility, was administered, giving patients verbal instructions to stand up from a chair, walk 3m, cross a line marked on the floor, turn around, walk back, and sit down.20 The Fatigue Severity Scale (FSS) was used to allow the patient to rate his or her own level of fatigue (from 1 to 7) through a short questionnaire. The Patient Health Questionnaire (PHQ-9), a 9-item mood scale, was used to measure the severity of depression and response to treatment.21 The Short Form 36 (SF-36), a widely used instrument, was used to evaluate healthrelated QoL. It consists of eight subscales: physical functioning, physical role functioning, bodily pain, general health perceptions, vitality, social functioning, emotional role functioning, and mental health, as well as two synthetic indices: the physical component summary and the mental component summary.22 Patient treatment acceptance was tracked using a visual analog scale (VAS; 0–10). Clinical tests and treatments were standardized at each center through specific documents and staff meetings.

Biostatistical analysis

Descriptive statistics were used at T0, T1, T2, and T3. Baseline characteristics and clinical tests were compared between groups to assess the quality of randomization. For continuous variables, we used unpaired *t* tests; for ordinal variables, the Mann–Whitney test; and for categorical variables, the Pearson's chi-square test. To investigate time effects (T0, T1, T2, and T3) within groups, we choose a repeated-measures analysis of variance (RM-ANOVA) and Tukey's post hoc tests for continuous variables or equal-variance data, but the Friedman test followed by the Wilcoxon pairwise comparison test (Bonferroni corrected) for ordinal variables or data with unequal variances. To test differences among groups, unpaired *t* tests (continuous variables and normally distributed data) or Mann–Whitney tests (ordinal variables or non-normal data) were used. Finally, a multiple regression model was used to determine the effects of MS severity and treatment received. A modified intention-to-treat analysis was carried out on all outcome measures, handling missing data with the last observation carried forward approach and excluding the patients who did not receive treatments, withdrew rehabilitation, or were too weak to perform functional tests. To avoid an overestimation of results, for primary outcomes (gait speed and walking endurance), a complete intention-to-treat analysis was performed on all randomized patients assuming a poor outcome (worst-case scenario) for drop-outs. Statistical analysis was performed using STATA 13.1 software. Significance was recognized when $p < 0.05$. Effect sizes for primary outcomes were calculated using Cohen's23 *d.*

Results

We enrolled 58 MS patients from which four (one from the RAGT Group, three from the CWT Group) dropped out because of organization reasons after randomization, two discontinued RAGT (one did not fit into the orthosis and one had scheduling conflicts), and four did not perform functional tests because they were too weak to participate in these assessments (see Figure 1). Clinical and demographic characteristics are summarized in Table 1. The two groups were similar in demographic, functional, and clinical parameters.

Gait speed and endurance

Considering walking endurance, RM-ANOVA revealed that there were significant differences based on time (T0 to T1 and T0 to T2) only in the RAGT group (F =6, df =3,96; p<0.005). Between-groups differences were found at T0 -T1 (p=0.003) and T0 -T2 (p<0.05) in the 6MWT and at T0-T3 (p< 0.05) in the 10MWT (see Tables 2 and 3). For primary outcome measures, the effect sizes (Cohen's *d*s) were calculated: for the RAGT Group (compared to the CWT Group), it was 0.46 (95% confidence interval (CI), -0.11 to 1.03) for the 10MWT and 0.81 (95% CI, 0.21–1.39) for the 6MWT. The effects of both treatment and EDSS rating on the 6MWT (F =91.66, df= 2,185; p<0.001; adjusted $R2$= 0.49) and 10MWT (F=83.50, df=2,181; p<0.001; adjusted $R2$= 0.47) were confirmed using a multiple regression model. An intention-to-treat analysis on all randomized patients (n=58) confirmed

the superiority of RAGT on CWT in improving walking endurance at T0-T1 (p< 0.005) and T0-T2 (p<0.01).

Mobility and balance

The Friedman repeated-measures test highlighted a significant time effect (T0 to T1 and T0 to T2) on balance only in the RAGT group ($\chi 2 = 11.6$, $df = 3$; $p < 0.005$); between-groups differences were found at T0 - T1 ($p < 0.05$). Significant effects on mobility (TUG) were not found in either group (see Tables 2 and 3).

Fatigue and depression

The Friedman repeated-measures test highlighted a significant time effect on depression in both groups (RAGT Group, $\chi 2 = 7.54$, $df = 2$; $p < 0.05$; CWT Group, $\chi 2 = 11.03$, $df = 2$; $p < 0.005$). Specifically, the Wilcoxon pairwise comparison tests underlined a significant improvement in PHQ-9 between T0 and T2 in both groups (RAGT Group, $z = -2.74$; $p < 0.01$; CWT Group, $z = -2.96$; $p < 0.005$) and between T0 and T3 only in the CWT Group ($z = -2.24$; $p < 0.05$). Neither treatment had detrimental or beneficial effects on fatigue, as measured by the FSS. Betweengroups comparisons did not show differences (see Tables 3 and 4).

QoL

The Friedman repeated-measures test highlighted a significant time effect in the RAGT Group on the physical functioning subscale ($\chi 2 = 6.15$, $df= 2$; $p<0.05$) and the mental component summary index ($\chi 2 = 6.204$, $df =2$; $p<0.05$). In the CWT Group, significant differences were found on the mental health subscale ($\chi 2 =11.73$, $df=2$; $p< 0.005$). The Wilcoxon pairwise comparison tests showed a significant improvement (T0 to T2) in the RAGT Group on the mental component summary index (z=-2.68; p <0.01) and in CWT Group on the mental health subscale (z= -3.32; p<0.005) (see Tables 3 and 4). Patient acceptance of treatment (VAS) was well scored in both groups without significant differences between them (RAGT Group, 8.62±1.63; CWT Group, 8.09 ±1.72).

Discussion

The main findings of this clinical trial were that in progressive MS patients with severe gait impairments, RAGT might add further benefits in restoring walking endurance and balance compared to conventional physiotherapy. The diagnosis of progressive MS is correlated with a poor outcome, and disease-modifying drugs have mostly failed as treatments on these subgroups;24 therefore, symptomatic therapies (i.e. for spasticity, fatigue, mood disorders, neurological bladder or pain) and interventions tailored for improving functions are essential for its management.1,25 Thus far, focusing on gait training, several studies tested the effects of BWSTT6,7 and RAGT8–13 in MS patients. The first attempt, made by Giesser et al.,6 found overall improvements in secondary progressive MS patients (EDSS 7–8) after about 40 BWSTT sessions (two sessions/week). Similarly, Pilutti et al.7 reported positive results on QoL, fatigue, and walking mobility after BWSTT training (three sessions/week over 12weeks) in primary progressive MS patients (EDSS 5–8). In the last decade, six randomized controlled trials8–13 fairly demonstrated how RAGT might be feasible and lead to functional gains with positive effects on QoL in the MS population; nevertheless, they failed to verify the superiority of RAGT over other specific gait training with the same amount of practice. Moreover, they used different devices, addressed heterogeneous MS subgroups (RR, PP, SP) with a wide range of gait disabilities (EDSS 3–7.5), and delivered different training protocols (12 15sessions over 3–6weeks). Beer et al.,8 in severe MS patients (EDSS 6–7.5), found an improvement of 22m on the 6MWT after 15 RAGT sessions (five sessions/week over 3weeks) with a large effect size (0.70). Lo and Triche,9 after six sessions of RAGT or BWSTT (two sessions/week over 3weeks), reported overall improvements in walking speed and endurance in both groups (mean

EDSS rating, 4.9). Vaney et al.10 postulated that RAGT is not superior to over-ground walking training after nine sessions (three sessions/week over 3weeks) in MS patients (EDSS 3–6.5). Furthermore, they pooled data8–10 and suggested that patients who can walk 10m in less than 16s might benefit more from over-ground training than RAGT. Conversely, patients who were more impaired should be studied in further randomized controlled trials; according to this hypothesis, our RAGT Group performed the 10MWT in 31.7s. Schwartz et al.11 reported overall improvements in gait speed and walking endurance in those receiving RAGT and conventional walking and found no significant differences between the groups after three sessions/week over 4weeks (EDSS 5.5–7). In a pilot study,12 we observed that patients (EDSS 4.5–6.5) who underwent 12 RAGT sessions (two sessions/week over 6weeks) improved gait speed (0.07m/s) and walking endurance (33.2m) compared to a control group. Gandolfi et al.13 tested an end-effector device, the Gait Trainer, for two sessions/week over 6weeks and found promising effects on balance in MS patients (EDSS 3–5.5). Finally, Ruiz et al.14 recently proposed a novel training paradigm that combines both RAGT and BWSTT within each session and found significant effects on walking endurance (59m) and balance. In this study, a large effect size (0.81) for the 6MWT, compared to that for generic CWT, was found in severely disabled patients with progressive MS.

A multiple regression model revealed how the treatment (RAGT or CWT) and EDSS rating (6, 6.5, or 7) could explain about 49% of the 6MWT performance improvement and 47% of the 10MWT performance improvement.

After RAGT, we found an improvement of 23m (19.2%), slightly above the minimally important change for walking improvement from the patient perspective (22m).26 Furthermore, the increase in walking distance in the 6MWT was correlated with better self-care, mobility, and domestic life27 and reflects habitual walking performance.28 Conversely, no significant difference was found in gait speed as measured by the 10MWT, as was hypothesized. A possible explanation is that long-distance, rather short-distance, tests are more suitable in detecting improvements after rehabilitation or that the Timed 25-Foot Walk, rather than the 10MWT, is more appropriate for measuring walking speed over short distances for MS patients. A significant improvement in balance domains after RAGT13 might corroborate the hypothesis that kneeextensors strength was increased, leading to a better muscle control. We found no beneficial or detrimental effects of our interventions on perceived fatigue, as measured by the FSS. A possible explanation is that they were not as able to reduce fatigue as treadmill training or that this patient-reported questionnaire was not reliable in patients with high levels of fatigue, such as the MS population. We found an improvement of psychological wellbeing, in both groups at the end of the training: this can be interpreted as a positive impact of rehabilitative care on depression, independent of treatment effectiveness, as previously hypothesized by others. On the other hand, the SF-36, a measure of the physical functioning domain, was significantly improved only in the RAGT Group, revealing that specific and effective treatment might have a positive impact on the patient's subjective QoL. This highlights the necessity of shaping rehabilitative interventions around the global needs of the patient. While we found positive effects on walking function, mobility, balance, depression, and QoL, spotty retention at 3months was found, in contrast to our previous study. It can be hypothesized that progressive MS needs longer treatment protocols or a combination of more than one intervention to prevent lack of mobility.1 This study presents several limitations: (1) the groups were time-matched but not intensity-matched, possibly reflecting walking practice that differed consistently between them, thus explaining some part of the superiority found in RAGT to restore walking endurance; furthermore, exercises scheduled during CWT sessions were tailored on patients' preferences and characteristics, affecting reproducibility among them; (2) patients were unblinded to treatment, and this could have reduced internal validity; (3) high missing data percentage (17.25% for functional tests and 10.34% for questionnaires) due to patients who did not start rehabilitation after randomization or discontinued intervention or were too weak to perform functional tests. However, our sample size calculation was conservative and took into account a +20% of the sample required to have an

adequate powered study; (4) even if clinically meaningful changes in MS population are known for the primary outcomes, no information is available for the selected measures of balance, well-being, and QoL. Despite these limitations, this study supports the use of RAGT in patients with progressive MS and severe gait impairments to induce short-lasting effects on walking function and balance.

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