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Does robot-assisted gait training improve ambulation in highly disabled multiple sclerosis people? A pilot randomized control trial

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Abstract

Background: Robotic training is commonly used to assist walking training in patients affected by multiple sclerosis (MS) with non-conclusive results.

Objective: To compare the effect of robot-assisted gait training (RAGT) with that of conventional walking training (CWT) on gait competencies, global ability, fatigue and spasticity in a group of severely affected patients with MS.

Methods: A pilot, single-blind randomized controlled trial was conducted in 43 severe (Expanded Disability Status Scale (EDSS) score of 6–7.5) and non-autonomous ambulant in-patients with MS. Experimental group performed 12 sessions of RAGT, whereas control group performed the same amount of CWT. Primary outcome measures were gait ability assessed by 2 minutes walking test and Functional Ambulatory Category; secondary outcomes were global ability (modified Barthel Index), global mobility (Rivermead Mobility Index), severity of disease (EDSS) and subjectively perceived fatigue (Fatigue Severity Scale).

Results: The number of subjects who achieved a clinical significant improvement was significantly higher in RAGT than in CWT ($p<0.05$ for both primary outcome measures). RAGT also led to an improvement in all the other clinical parameters (global ability: $p<0.001$, global mobility: $p<0.001$, EDSS: $p=0.014$ and fatigue: $p=0.001$).

Conclusions: RAGT improved the walking competencies in non-autonomous ambulant patients with MS, with benefits in terms of perceived fatigue.

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Introduction

People with multiple sclerosis (MS) present a wide range of neurological symptoms related to the varying distribution of demyelization and axonal loss. Reduced mobility and gait dysfunction are two such symptoms that represent key problems, with up to 85% of persons with MS reporting difficulty in walking.[1] In recent years, the treatment of MS gait dysfunction has significantly progressed thanks to various interventions, including robot-assisted approaches.[2] Robot-assisted gait training (RAGT), which is effective in patients with spinal cord injuries,[3] stroke[4] and Parkinson's disease,[5] has more recently been tested for gait rehabilitation purposes in MS. RAGT devices offer an ideal means of facilitating the task-oriented mass practice of walking,[6] which leads to learning-dependent neuroplasticity.[7]

In a recent systematic review, eight studies on treadmill training (TT), body weight–supported treadmill training (BWSTT) and RAGT in MS subjects with walking disabilities were assessed; promising results emerged in terms of gait-related outcomes. However, it is not yet clear what type of device is most effective for the treatment of gait dysfunctions in MS and what level of disability is most responsive to such treatment.[8]

Previous studies on the use of RAGT in MS were focused on less affected subjects, including subjects

who already were able, for example, to walk without any aid or rest at least for 200 m,[6,9–12] and only one research reported the feasibility of the robotic-assisted walking training in patients not autonomous during walking.[13]

Two different approaches are commonly defined for RAGT therapy for walking training: the exoskeleton approach controlling the pelvis and knee kinematic as in the case of Lokomat and an end-effector approach controlling the distal part of the leg by mobile footplates describing a walking cycle as in the case of Gait Trainer. Both are a body weight–supported system as condition sine qua non to allow the walking-like training.[14]

To the best of our knowledge, this is the first trial investigating the robotic therapy using an end-effector approach. These biomechanical differences lead to different walking-like training: end effector, for example, is less constrictive/assistive to pelvis than exoskeleton approach and might allow a major muscle voluntary contraction of proximal leg muscles during walking training.[15]

The primary aim of this study was to investigate whether RAGT performed with an end-effector device is more effective than conventional walking training (CWT) as a means of improving walking capacity in persons with MS with a high disability. The secondary aim of this study was to investigate the effect of RAGT on walking ability, global mobility and ability, as well as on disease severity and symptoms such as fatigue and perceived spasticity.

Materials and methods

Trial design

This study was designed as a single-blind, prospective, randomized controlled trial (RCT) to compare the effects of RAGT with those of CWT in MS patients, adopting a 1:1 allocation ratio. The randomization procedures were carried out thanks to a computer-generated list covered by straps to conceal the allocation.

Participants

A continuous series of in-patients admitted to our institute for research and healthcare between March 2011 and January 2014 were screened for this study.

The inclusion criteria were as follows: diagnosis of MS according to the McDonald criteria,[16] age between 25 and 65 years, high disability (Expanded Disability Status Scale (EDSS) between 6 and 7.5)[17] and a Mini-Mental State Examination score ⩾24.

The exclusion criteria were as follows: other concomitant orthopaedic or neurological diseases that may interfere with ambulation, severe psychiatric impairment, relapses in the month prior to enrolment, MS-related treatment changes, whether symptomatic or preventive, as well as botulin toxin injections performed in the previous 3 months and lower limb spasticity upon admission >3 at the modified Ashworth scale (MAS).[18]

The research was performed in accordance with the Helsinki Declaration and was approved by the ethical committee of our Foundation. Written consent was obtained from all the patients, who were informed of the experimental nature of the study.

Interventions

Enrolled patients performed a standard in-patient rehabilitation programme consisting of at least 2 hours/day of physical therapy (i.e. active and passive range-of-motion exercises, strengthening exercises, hand function, transfer and balance training) as well as occupational, cognitive, respiratory or phoniatric therapy, when necessary. According to scientific evidence, the MS in-patient rehabilitative standard treatment was multidisciplinary and carried out by a team consisting of physicians (i.e. physiatrist, neurologist and cardiologist), a neuropsychologist, nurses, physiotherapists, occupational and speech therapists social services care manager, dietician and support staff.[19] In adjunction to this therapy, RAGT or CWT was administered. RAGT and CWT were performed in the morning, three times a week for 4 consecutive weeks, for a total of 12 sessions lasting 40 minutes each. Before starting the study, the authors designed the RAGT and CWT protocols and instructed the treating physiotherapists (two for each protocol) on how to conduct the training sessions. The RAGT group was treated by means of the electromechanical Gait Trainer GTII® (Reha-Stim, Berlin, Germany), in which patients with MS, supported by a harness and standing with their feet on the motor-driven footplates, practised gait-like movements.[14] Different from previous studies,[20] we have used an electromechanical device that uses an inverse control approach, with end point trajectories' control (end effector). The 40-minute RAGT or CWT sessions comprised 20 minutes of walking, when possible, while the remainder of the time was dedicated to prepare the device (for RAGT), or to prepare the patients for walking.

In the first sessions, training sessions were performed with 40%–50% of the patients' body weight support because of the severity of enrolled patients, whereas in the subsequent sessions, weight support was reduced, as soon as possible. The speed, which was selected so as to be comfortable for the patient, generally ranged between 1.3 and 1.8 km/h. Patients were encouraged to actively 'help' the gait-like movement during RAGT or CWT.[14]

The CWT group received exercises designed to prepare them for walking (i.e. static exercises on the parallel bars for the control and movement of the lower limb load; exercises for the control of the trunk and pelvis; exercises for balance and coordination) and walking exercises on the ground whose difficulty gradually increased. Help provided by the therapists and/or aids, such as a cane, tripod or walker, was allowed.

Outcomes

A blinded examiner performed the pre-treatment (T0) and post-treatment (T1) evaluations. All the patients were examined in the morning.

The primary outcomes of the study were the walking capacity and the walking ability. Walking capacity was measured by the distance covered in 2 minutes by walking (2-minute walking test (2MWT)) and in particular by the number of patients reaching the minimal clinical important difference.[21] Walking ability was assessed by Functional Ambulatory Category (FAC) that categorizes patients according to the basic motor skills required for functional ambulation, with scores ranging from 0 (*non-functional*) to 5 (*independent on level and non-level surfaces*).[22]

Secondary outcomes

Secondary outcomes measures were the global mobility, assessed by means of the Rivermead Mobility Index (RMI), with scores ranging from 0 (*low mobility*) to 15 (*good mobility*).[23] The modified Barthel Index (mBI) was used to assess global ability and independence in activities of daily living, with total scores ranging from 0 to 100 (*total independency*).[24]

The EDSS of Kurtzke was administered to assess the severity of MS. Fatigue was assessed by means of the Fatigue Severity Scale (FSS) and a score >36 was considered significant for perceived fatigue.[25]

Lower limb spasticity was assessed using a 100-mm Visual Analogue Scale (VAS) with anchors ranging from 'no problem' to 'very bad', which is commonly used as a measure of perceived spasticity in patients affected by MS.

Statistical analysis

The sample size has been determined according to previous RCT studies on robotic efficacy in MS in which between 13 and 49 participants were enrolled[9–13] and the estimated drop-out rate was 20%. An intention-to-treat approach was performed in terms of analysing all the patients with respect to their allocation without considering the number of performed sessions of therapy, whereas the drop-out patients not re-assessed at T1 were not included into the analyses according to a plausible assumption about data missing at random.[26]

The mean values and standard deviations were computed to summarize the results. Because most of the variables were ordinal measures (clinical scales), not resulting in normal distribution (Shapiro–Wilk test) and for having a conservative approach due to the given sample size, non-parametric statistic tests were preferred to parametric counterparts. The non-parametric tests used in this study were as follows: χ^2 test for binary variable (including the number of patients who achieved a minimal important clinical difference on the primary outcomes related to walking abilities, in terms of 0.5 points of FAC score and 19.2 m more walking during 2MWT),[27] Wilcoxon signed-rank test for within-subject comparisons, Mann–Whitney *U* test for between-subject comparisons and Spearman coefficient (*R*) for correlations. For all the tests, the threshold of statistical significance was set at 0.05. Analyses were performed using SPSS 17.0.

Results

As shown in the flowchart of Figure 1, 155 patients were assessed, and 50 patients, matching inclusion/exclusion criteria, were enrolled in the study and allocated to either the RAGT or the CWT group. Four patients were lost in RAGT and three patients in CWT group; therefore, 43 patients' data were analysed.

At baseline, the RAGT and CWT groups were significantly different neither in terms of age, gender, course and duration of disease (Table 1) nor in terms of disease severity, global mobility or global ability (T0 in Table 2).

At T1, all the outcomes significantly improved after RAGT with respect to T0, whereas after CWT only

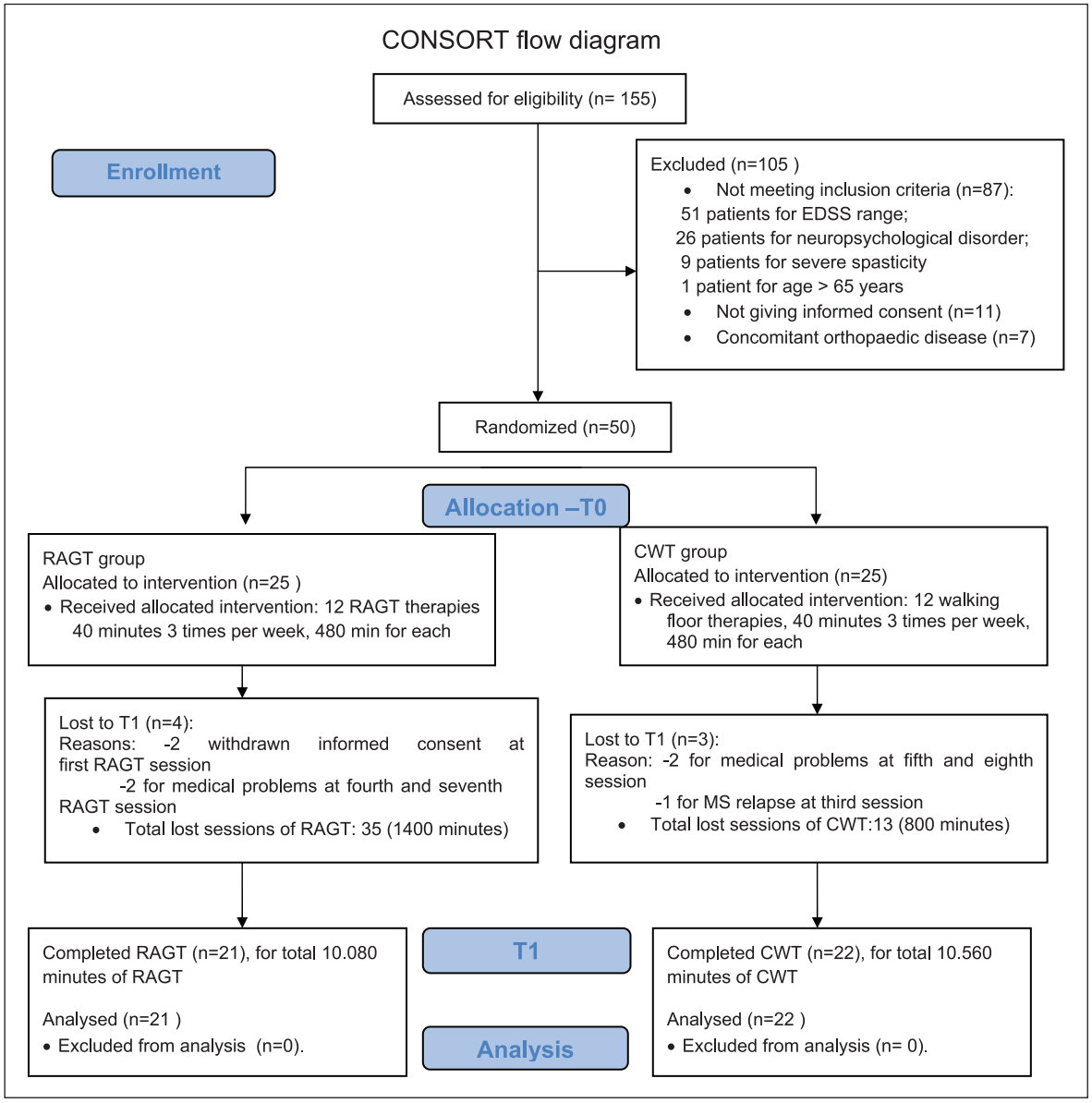

Figure 1. CONSORT flowchart.

Table 1. Summary of patients' features.

Feature	RAGT group	CWT group	*p* value between groups
Number of participants	21	22	–
Disease course (PP/SP)	0/21	3/22	0.101
Gender (female/male)	10/11	12/10	0.650
Age (years)	47.00±11.17	49.86±8.21	0.224
Disease duration (years)	17.05±9.12	14.09±5.71	0.592

RAGT: robot-assisted gait training; CWT: conventional walking training; PP: primary progressive; SP: secondary progressive. Mean and standard deviation are reported for age and disease duration, together with the relevant *p* value of the between-group comparison (χ^2 test for disease course and gender, Wilcoxon signed-rank test for age and disease).

RMI and mBI significantly improved. However, the between-group differences were not statistically significant for the primary outcome measures ($p=0.407$ for FAC, $p=0.798$ for 2MWT). Among the

Table 2. Outcome measures.

Outcomes	RAGT			CWT		
	T0	T1	*p*	T0	T1	*p*
2MWT (m)	33.71±15.43	42.59±20.79	**0.001**	40.91±22.45	43.72±24.50	0.076
FAC	3.10±1.51	3.76±1.04	**0.017**	3.50±1.10	3.50±1.10	0.999
EDSS	6.62±0.42	6.48±0.37	**0.014**	6.50±0.49	6.50±0.49	0.999
FSS	5.31±1.02	3.96±1.19*	**<0.001**	5.40±1.54	5.12±1.46	0.306
RMI	5.76±2.05	7.76±2.62	**<0.001**	6.14±3.11	7.41±2.58	**<0.001**
mBI	63.43±18.51	77.43±15.91	**<0.001**	64.09±20.60	74.10±14.72	**<0.001**
VAS	5.05±1.01	3.40±1.24*	**0.007**	5.31±2.52	5.23±2.29	0.693

RAGT: robot-assisted gait training; CWT: conventional walking training; 2MWT: 2-minute walking test; FAC: Functional Ambulation Category; EDSS: Expanded Disability Status Scale; FSS: Fatigue Severity Scale; RMI: Rivermead Mobility Index; mBI: modified Barthel Index; VAS: Visual Analogue Scale.
Outcome measures assessed at T0 and T1 in the two groups for the clinical scale scores.
p values refer to Wilcoxon signed-rank test of within-group analysis (in bold, if statistically significant), whereas asterisks refer to *p* values <0.05 of between-group analysis obtained with Mann–Whitney *U* test between groups at T1.

other outcome measures, only FSS and VAS scores resulted significantly different between the two groups. In particular, the severity of fatigue and its effect on patients' activities and lifestyle resulted significantly lower in RAGT (−25%±19%) than in CWT (2%±41%) at T1 ($p=0.013$). Interestingly, a significant correlation was found in RAGT between the change in FSS and that in 2MWT ($R=0.493, p=0.045$). The VAS score was computed to assess spasticity in a subgroup of subjects (10 in the RAGT group, 15 in the CWT group). The changes in spasticity resulted statistically significant only after RAGT and not after CWT, and also the between-group comparison resulted statistically significant at T1 ($p=0.048$).

After within- and between-group analyses, we also performed the comparisons of the number of patients who benefited from each treatment, computing the odds ratios (ORs). The number of patients in whom FAC score improved was 7 in RAGT and 0 in CWT ($p=0.0023$, χ^2 test), and the number of patients in whom 2MWT improved of a clinically significant change was 11 in RAGT and 6 in CWT (OR=4.28, 95% confidence interval (95% CI)=1.08–17.00, $p=0.0348$, χ^2 test). The changes in EDSS scores changed in 6 of 21 patients in the RAGT group, but in none of the patients in the CWT group ($p=0.007$, χ^2 test). The EDSS score in the RAGT group dropped from 7.5 to 7 in one patient, from 7 to 6.5 in three patients and from 6.5 to 6 in two patients.

Discussion

This study showed that RAGT in addition to the standard therapy improved walking ability and capacity in people affected by MS with severe limitation on walking. A significant reduction in perceived fatigue (FSS) and in its effects on patient's daily activities was also observed in patients undergoing robotic therapy. As expected, CWT also showed positive benefits for patients, with significant improvements in terms of mobility (RMI score) and independency in activities of daily living (mBI score). These changes were not significantly different from those observed after RAGT. These results are in line with those reported in the literature about conventional therapy in MS, which can be summarized as follows: (1) strong evidences for improved activity and participation, (2) need of exercise-based educational programmes for obtaining significant reduction of fatigue, and (3) inconclusive evidence for other rehabilitation interventions mainly due to limited production of methodologically robust studies.[28]

Some previous studies have suggested that robotic-assisted training improves walking ability and endurance in MS subjects,[8] but the use of robots in patients with MS has been questioned.[29] A recent systematic review of various types of TT highlighted the low power and significance of all previously published articles, which may be attributed to the relatively small sample size and to the wide range of walking disabilities included.[8] We supposed that it was also due to the fact that the previous studies[6,9–12] also enrolled patients already independent in walking.

In contrast to the previous studies, we focused our RCT on patients with severe walking deficits (non-autonomous ambulant patients similar to the study of Beer et al.[13] that instead used exoskeleton), finding significant benefits in terms of walking capacity and reduction in fatigue. The changes in these two

features were significantly correlated after robotic therapy, but not in the group who performed conventional walking therapy.

However, these results should be read at the light of their limitations, especially the absence of statistically significant differences between groups on the primary outcome measures. Despite our sample including only severely affected subjects, their deficits were quite inhomogeneous, and they have probably implied a reduction in the power of between-group analyses. However, when percentage improvements with respect to baseline or when the number of subjects who achieved a minimally clinical important difference were taken into account, the results showed significant differences also between groups.

This result is in line with a previous study on subjects affected by MS at an advanced stage[13] showing that RAGT was found to have a more beneficial effect on gait recovery in more severely affected subjects. In that study,[13] such as in many studies regarding stroke,[20] the used robotic device was an exoskeleton, whereas in our study the used device was an electromechanical end effector. Despite this difference, the findings of our study were in line with those previously published. The use of an end-effector device (Gait Trainer) is innovative because it is not yet documented in MS and is important because this type of devices is usually less expensive and easier to use than robotic exoskeleton already tested in MS.[20]

From our analysis, the reduction in perceived fatigue emerged as an important outcome achieved using RAGT and the benefit obtained on this domain resulted correlated with those obtained on walking capacity. The control group performing CWT did not show any change in fatigue or spasticity. The importance of treating fatigue, which is described as one of the most disabling symptoms in up to 40% of MS people, is evident.[30] Our findings are in agreement with those of previous studies,[31,32] which found an improvement in perceived fatigue. The effects of RAGT on several elements (i.e. physical de-conditioning, evaluated by heart rate and aerobic capacity, and mood) believed to contribute to the genesis of fatigue, whose causes in MS are assumed to be multifactorial, have already been investigated, although with controversial results.[33]

We observed that RAGT led to a significant reduction in lower limb spasticity in our MS sample, whereas CWT did not. Spasticity is a velocity-correlated phenomenon, but the speed at which patients were trained was slow (lower than 0.5 m/s). The literature contains some reports on the effects of RAGT on spasticity. Giesser et al.[33] described reduced spasticity in three of four MS patients treated with BWSTT. The positive effects of RAGT on spasticity, flexor spasms and clonus have also been clearly described in individuals with chronic spinal cord injury[34] and in step-trained spinal animals.[35]

This study has some limitations. One is that a follow-up, which would provide data on the stability of the results, is lacking. Furthermore, a significant number of data on spasticity are missing, which limits the scope for speculation on this interesting finding. Another limitation is the slight difference at baseline between the two groups. Despite the performed randomization, in fact, the RAGT resulted slightly more severely affected. This difference was not statistically significant for any of the clinical assessed measures, but it may question the homogeneity of the two groups at baseline and it may be the cause of lack of between-group differences at T1 for the primary outcome measures. Further studies are hence needed to verify whether RAGT is superior in increasing walking abilities than CWT. Our results support the idea that RAGT is at least not inferior than CWT, but has the advantage of obtaining a gait improvement together with benefits in terms of reduction in both perceived fatigue and spasticity. The fact that these two MS features were favourably influenced by the use of a robot is a new and interesting result deserving further investigations.

In conclusion, we found that RAGT improves walking capacity at least as well as CWT and reduced the perceived fatigue more than CWT. Hence, robotic therapy may be helpful in the rehabilitation field as an add-on treatment to standard therapy for severely affected patients probably primarily favouring a cardiovascular and muscular reconditioning. As already suggested for robots developed for rehabilitation of people with neurological disorders,[36] further studies should investigate the best candidate for RAGT also among patients with MS, and the more effective dose and frequency of the robotic walking training for these patients.

Clinical messages

- Patients with severe MS benefit from robotic therapy in terms of walking ability and capacity.
- There is an amelioration of fatigue in severe subjects with MS after walking robotic training.

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Declaration of Conflicting Interests

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