Robot-assisted gait training in multiple sclerosis: a pilot randomized trial

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Robot-assisted gait training in multiple sclerosis: a pilot randomized trial

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Objective To evaluate feasibility and perform an explanatory analysis of the efficacy of robot-assisted gait training (RAGT) in MS patients with severe walking disabilities (Expanded Disability Status Scale [EDSS] 6.0–7.5) in a pilot trial.

Methods Prospective, randomized, controlled clinical trial comparing RAGT with conventional walking training (CWT) in a group of stable MS patients ($n = 35$) during an inpatient rehabilitation stay, 15 sessions over three weeks. All patients participated additionally in a multimodal rehabilitation program. The primary outcome measure was walking velocity and secondary measures were 6-min-walking distance, stride length and knee-extensor strength. All tests were performed by an external blinded assessor at baseline after three weeks and at follow-up after six months. Additionally, Extended Barthel Index (EBI) at entry and discharge was assessed (not blinded), and acceptance/convenience of RAGT rated by patients (Visual Analogue Scale [VAS]) was recorded.

Results Nineteen patients were randomly allocated to RAGT and 16 patients to CWT. Groups were comparable at baseline. There were 5 drop-outs (2 related directly to treatment) in the RAGT group and 1 in the CWT group, leaving 14 RAGT patients and 15 CWT patients for final analysis. Acceptance and convenience of RAGT as rated by patients were high. Effect sizes were moderate to large, although not significant, for walking velocity (0.700, 95% CI −0.089 to 1.489), walking distance (0.401, 95% CI − 0.370 to 1.172) and knee-extensor strength (right: 1.105, 95% CI 0.278 to 1.932, left 0.650, 95% CI −0.135 to 1.436) favouring RAGT. Prepost within-group analysis revealed an increase of walking velocity, walking distance and knee-extensor strength in the RAGT group, whereas in CWT group only walking velocity was improved. In both groups outcome values returned to baseline at follow-up after six months ($n = 23$).

Conclusions Robot-assisted gait training is feasible and may be an effective therapeutic option in MS patients with severe walking disabilities. Effect size calculation and prepost analysis suggest a higher benefit on walking velocity and knee-extensor strength by RAGT compared to CWT. Due to several limitations, however, our results should be regarded as preliminary. Post hoc power calculation showed that two groups of 106 patients are needed to demonstrate a significant moderate effect size of 0.4 after three weeks of RAGT. Thus, further studies with a larger number of patients are needed to investigate the impact of this new treatment option in MS patients. *Multiple Sclerosis* 2008; **14**: 231–236. http://msj.sagepub.com

Key words: multiple sclerosis; physical therapy; rehabilitation; robot-assisted gait training

Introduction

Gait disturbances are common in MS. In an own population-based study, walking difficulties were found in 78.8% of patients with chronic progressive MS, and in 20.1% with relapsing–remitting MS [1]. Even though walking difficulties are more prevalent in the chronic phase of the disease, subtle changes of gait parameters may be detectable even in the early phase [2]. In general, walking impairments have a high negative impact on personal activities not only restricted to motor domains (i.e., incontinence due to inability to reach a toilet in time) and participation (access to locations) but are also associated with loss of physical quality of life [3,4]. In addition, gait problems increase the risk of falls [5].

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Physical therapy has been shown to be effective in improving gait and mobility, and reducing the risk of falls [6,7]. In patients with more severe gait disabilities, however, over-ground walking training becomes difficult or even impossible. An alternative treatment in these patients is a body-weight-supported treadmill-training (BWSTT), which has been shown to be effective in patients with incomplete spinal cord injuries and stroke [8–10]. In MS patients, BWSTT was investigated only in one small study [11]. BWSTT, however, is physically demanding for treating therapists, who are controlling and assisting walking movements during treadmill walking, and manual simulation of gait pattern is quite rudimental. For these reasons, a robot-driven gait orthosis (Lokomat, Hocoma, Volketswil, Switzerland) was developed and introduced by Colombo *et al*. [12,13]. This robot-assisted gait training (RAGT) allows a more effective support of walking movements and imitation of a nearly normal gait pattern during treadmill training at a higher speed. Until now, there is only one pilot trial studying Lokomat training in a group of stroke patients [14]. The aim of this study was to evaluate feasibility and perform an explanatory analysis of the efficacy of a RAGT in MS patients with severe walking disabilities in an early-phase trial.

Methods

Patients

All MS patients admitted for inpatient rehabilitation were prospectively screened. Inclusion criteria were a stable phase of disease (chronic progressive pattern or relapsing–remitting with no relapse during the last three months), severe walking disabilities (EDSS 6.0–7.5) and written informed consent. Exclusion criteria were major orthopaedic problems or contractures of lower limbs, complete inability to stand or walk for a longer period than three months, significant medical co-morbidities and cognitive or psychiatric problems that might compromise compliance with therapies.

Design and treatment groups

A prospective, randomized controlled design comparing RAGT with conventional walking training (CWT) was used. Block randomization using blocks of two was used. Random numbers were generated with a random generator software (SPSS Version 13.2, Chicago, USA). An independent blinded collaborator who was not involved in the treatment or care of patients performed the randomization. Treatment consisted of 1 h sessions of RAGT and CWT daily, with an effective treatment time of 30 min, five times weekly for three weeks with a total of 15×30 min treatment sessions in both groups. In addition, a specified standardized multimodal rehabilitation program including additional daily physical therapy (no walking activities), standing, water therapy or hippo therapy, training of personal care activities, and group therapies were scheduled, with an identical total treatment time of 16.2 h/week in both groups. Pelvic floor training, occupational therapy or neuropsychological treatment was added, if necessary, excluding standing or walking activities during these sessions. Outside the treatment sessions, patients who were able to walk alone (with or without aids) were allowed, but were not particularly encouraged to do so, and the others were allowed to use a wheelchair. Additional walking training outside the assigned gait training was excluded by using this approach. This is in contrast to our regular rehabilitation procedure in these patients, who normally are walking around with the assistance and support of our attendants.

Robot-assisted gait training and CWT

The RAGT consists of the Lokomat with a robot-driven orthosis and Locobasis for body weight support in combination with a Woodway treadmill system (Weil am Rhein, Germany). During gait training, leg movements are controlled and assisted by robot-driven orthoses with a preprogrammed physiological gait pattern. Treatment was started with an individually adapted body weight support (range 40–80%), and adjusted assistance of leg movements (range 40–100%) at low speed (range 1–1.5 km/h) to assure maximal convenience for the individual patient. During the treatment period, body weight support and walking assistance were gradually reduced and speed increased (up to a maximal speed of 2.8 km/h), thus allowing a more self-dependent and active walking.

In the CWT group walking over ground (with or without walking aids) was trained during the same time (30 min) with assistance of a physical therapist.

Outcome measures and assessment

The primary outcome measure was walking velocity (20-m timed walking). Secondary outcomes were walking distance (6-min walking), stride length (cm), and knee-extensor strength (kp). Assessment was performed by an independent, blinded assessor (E.G.) at baseline, after three weeks, and at follow-up after six months. In addition, Activities of Daily Living (ADL) independence (Extended Barthel Index (EBI) score) [15] was recorded (not blinded). Patients

of the RAGT group were requested to rate the subjective walking safety (VAS) and to score their overall satisfaction (acceptance/convenience) with RAGT (VAS). Treatment-related problems or complications were recorded in both groups by therapists.

Data analysis

All patients, who completed the treatment period, were included for final analysis. The baseline measurements were compared with the three-week measurements and six-month follow-up. The primary focus was on between-group differences, which were analysed with unpaired *t*-test in data with a normal distribution, and Mann–Whitney tests were used for data that were not normally distributed. Prepost differences were tested with paired *t*-test and Wilcoxon. Significance level was set at 0.05. Cohen's standardized effect sizes were calculated with Hedges adjustment. Statistical analysis was performed with SPSS 13.2.

Power calculation was performed after analyses of data, using PS Power and Sample Size Calculations software (Version 2.1.30 alpha = 0.05, power = 0.8)[16].

Results

Thirty-five MS patients (23 females, 12 males) were included in this study. Nineteen patients were assigned to RAGT and 16 to CWT. The baseline values of these patients are presented in Table 1. Groups were comparable at baseline. All but one patient (in RAGT group) were using walking aids.

There were five drop-outs in the RAGT group: two were directly related to treatment (skin irritation by the fixation belt at the knee/lower leg with full recovery), two due to early dismissal for personal/familial reasons and one with respiratory infection. In the CWT group there was one drop-out not related to treatment (urinary infection with incontinence). Finally, 14 patients in the RAGT group and 15 patients in the CWT group completed the treatment and data of these patients could be included for final analysis (Figure 1).

Between-group differences and effect sizes after three weeks are shown in Table 2. In general, effect sizes of differences between RAGT and CWT showed a large effect (>0.6) for walking velocity and knee-extensor strength, and a moderate effect (0.4–0.6) for 6-min walking distance, favouring RAGT. For stride length, there was only a small effect (effect size 0.2–0.4). Inadequate sample size, resulting in insufficient power indicates that the effect sizes may be estimated imprecisely.

A prepost within-group analysis revealed a significant improvement of walking speed in both groups (Table 3). For walking distance and knee-extensor strength, however, differences were only significant in the RAGT, but not in CWT group, supporting the findings in the between-group comparison.

Walking safety was scored lower after RAGT and higher after CWT, with, however, only minimal, not significant, difference (RAGT -1.5 ± 40 versus CWT 4.9 ± 29.9, effect size -0.177). General impression (acceptance/convenience) of RAGT as rated by patients was good (82/100 VAS).

In addition to improvement of walking abilities, there was a significant increase of EBI score in both groups (mean EBI gain +2.2, $P < 0.002$) from entry to discharge, without significant differences between the two groups.

The two patients with RAGT-related skin irritation at the belt fixation side recovered completely.

Table 1 Demographics and baseline values ($n = 35$)

	RAGT ($n = 19$)	CWT ($n = 16$)
Age, years (mean, SD)	49.7 (11.0)	51.0 (15.5)
Gender (men/women)	7/12	5/11
Disease pattern		
–relapsing–remitting	2	1
–secondary progressive	8	10
–primary progressive	9	5
Duration of disease, years (mean, SD)	15 (8)	15 (9)
EDSS (median, range)	6.5 (6–7.5)	6.5 (6 to 7.5)
EBI (mean, SD)	51.9 (7.3)	55.9 (4.7)
20-m-walking velocity, m/s (median, IQR)	0.21 (0.09–0.27)	0.24 (0.17–0.49)
6-min-walking distance, m (median, IQR)	75 (34–97)	95 (62–101)
Stride length, cm (median, IQR)	36.0 (29–47)	36.8 (28–49)
Strength knee-extensor, kp (mean, SD)		
–right	14.3 (7.3)	13.4 (7.0)
–left	12.4 (6.5)	12.8 (9.1)

EDSS, Expanded Disability Status Scale; EBI, Extended Barthel Index.

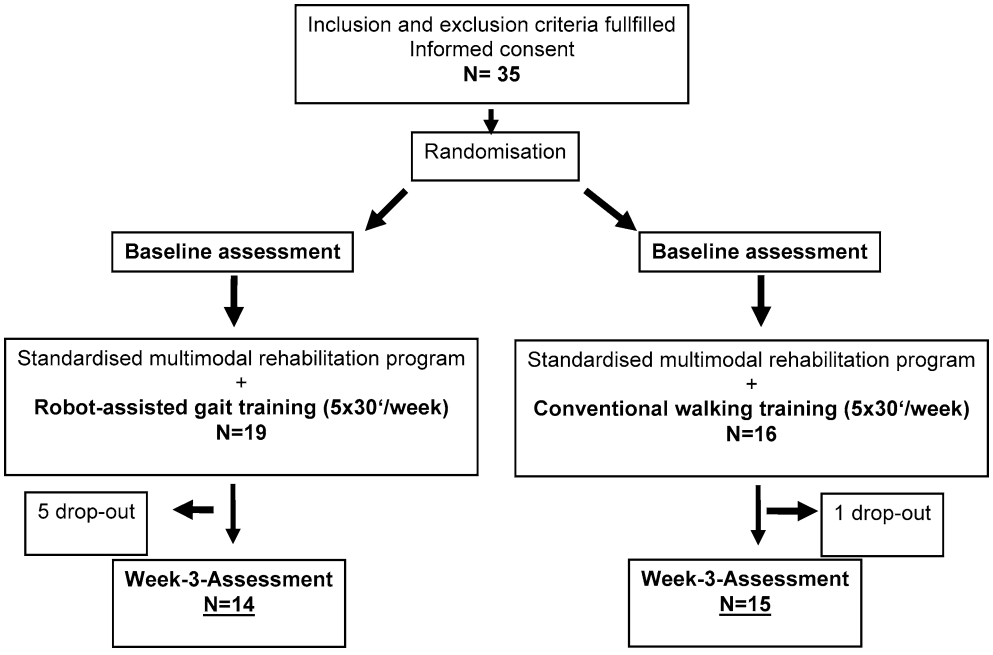

Figure 1 Flowchart of study.

Table 2 Between-group differences of change during treatment (week 3, effect sizes)

	Prepost change (95% CI)			
Outcome measures	RAGT	CWT	Effect size between-group difference (95% CI)	*P*
20-m-walking velocity, m/s (median, IQR)	0.11 (0.02–0.28)	0.07 (0.00–0.14)	0.700 (−0.089 to 1.489)	0.22
6-min-walking distance, m (median, IQR)	22 (2–38)	16 (−17–40)	0.401 (−0.370 to 1.172)	0.55
Stride length, cm (median, IQR)	4 (−1 to +8)	0 (−4 to +3)	0.360 (−0.409 to 1.130)	0.21
Strength knee-extensor right, kp (mean, SD)	3.5 (4.0)	−0.5 (3.0)	1.105 (0.278–1.932)	**0.04**
Strength knee-extensor left, kp(mean, SD)	3.3 (3.6)	0.6 (4.4)	0.650 (−0.135 to 1.436)	0.19

Table 3 Primary and secondary outcome measures at baseline and after three weeks treatment

	RAGT			CWT		
Outcome measures	Baseline	Week	*P*	Baseline	Week	*P*
20 m-walking velocity, m/s (median, IQR)	0.21 (0.09–0.27)	0.27 (0.15–0.49)	**0.003**	0.24 (0.17–0.28)	0.31 (0.19–0.42)	**0.026**
6-min-walking distance, m (median, IQR)	74 (34–97)	81 (44–137)	**0.006**	87 (62–101)	83 (64–145)	0.211
Stride length, cm (median, IQR)	37 (29–47)	39 (28–52)	0.133	38 (28–49)	38 (31–44)	0.917
Strength knee-extensor right kp (mean, SD)	15.9 (7.5)	19.4 (7.5)	**0.006**	13.5 (7.5)	13.0 (6.0)	0.522
Strength knee-extensor left kp (mean, SD)	13.6 (6.3)	16.9 (6.4)	**0.004**	13.6 (9.4)	14.2 (8.7)	0.589

Follow-up at 6 months was performed in 23 patients (10 RAGT, 13 CWT): at this time outcome values had returned to baseline in both groups (results not listed in Tables 2 and 3).

Discussion

This is the first trial evaluating RAGT in MS patients. Our results suggest that RAGT is feasible

and may be an effective therapeutic option in MS patients with severe walking disabilities improving significantly walking distance, velocity and knee-extensor strength. Due to several limitations of the study, discussed at the end of this section, however, these results should be interpreted with caution.

There are several studies showing a benefit of physical therapy on walking functions and disabilities [6,7,17,18]. In a randomized crossover study, Wiles *et al.* [7] could show that physical therapy (45 min twice weekly over 8 weeks) resulted in a highly significant improvement of mobility (Rivermead mobility index). Disability in these MS patients ($n = 40$) was lower compared with our patient group (EDSS range 4.0–6.5). The same is true for MS patients included in the randomized pilot trial published by van den Berg *et al.* [11] investigating the effect of an aerobic treadmill training: compared with the patient group effective walking distance was longer and walking velocity was higher (2-min walking distance 71.0 and 95.5 m, 10-m time 17.8 and 14.0s, EDSS not indicated). In this MS patient group with lower walking impairments ($n = 19$), van den Berg *et al.* [11] found a significant increase of walking velocity in the treadmill training group ($P < 0.05$). In our patients with a higher level of walking disabilities body weight supported treadmill training would be much more difficult because of the need of more assistance of limb movements during walking training.

A higher benefit of RAGT was found in the pre-post analysis, compared with CWT. One reason for this difference may be that individually adjusted body weight support and assisted walking movements may lessen central fatigability in MS patients [19], allowing a longer effective treatment time, higher intensity and higher speed in RAGT as compared to CWT. Other possible explanations are the lower anxiety (risk of fall) during RAGT, the lower demanding task (excluding stance instability) and the higher impact and intensity of eccentric quadriceps training during RAGT as compared to a more concentric and low activation of upper leg muscles (due to knee recurvation compensating weakness or extensor spasticity) during over ground CWT. The correlating findings of a significant strengthening of quadriceps muscles in RAGT group would be consistent with these assumptions. By measuring body weight and bio-impedance analysis, Husemann *et al.* [14] found some evidence suggesting a significant increase of muscle mass in stroke patients during Lokomat training as compared to CWT.

The return of assessment scores to baseline values at follow-up six month later is in accordance with the results of other studies, indicating a gradual decline of benefit over the following three to six months after physical therapy [6,7,11,17] and inpatient rehabilitation [20].

The finding of a significant improvement of disability, not limited to mobility, can be explained by the multimodal inpatient rehabilitation program during the study period, and is consistent with other studies [20]. In our study, EBI, however, was not a primary outcome measure and assessment was not blinded.

In two patients in the RAGT group treatment was stopped because of skin irritation at the belt fixation sites at the proximal lower leg. Both patients recovered completely without permanent harm. In the study of Husemann *et al.* [14], 2 out of 16 patients of the Lokomat group experienced minor skin sores, another patient a distortion of the ankle joint. Thus, even though risk of serious complications seems to be low in RAGT, one should be aware that some patients may not tolerate this treatment for mechanical reasons.

There was no indication that drop-outs showed a systematically different outcome. An intention to treat analysis with forward substitution of missing values using pretreatment test did not change the results.

There are several limitations of our study, especially the small sample size and the consequent low statistical power. Multiple significance tests have been performed and hence the significant P values in this study should be interpreted cautiously. Power calculation with walking velocity as the primary outcome, and mean changes and variance of change as found in this study revealed that 106 patients would be needed in each group for demonstrating a significant moderate effect (effect size 0.4). Another limitation is the high equipment investment, which precludes its use in countries with lower economic power.

In summary, it can been concluded that bias in this randomized controlled trial was minimal and that Lokomat treatment might actually be an effective treatment option for this subgroup of MS patients with severe walking disabilities. This is an important finding, as controlled data on the impact of physical therapy in MS patients with higher walking disabilities are almost completely lacking. Our findings are in accordance with other studies, which showed a benefit of physical therapy in MS by improving mobility and gait. Due to several limitations, however, our results should be regarded as preliminary, and further studies with a larger number of patients are needed. In addition, other important questions (optimal treatment intensity, impact in less disabled MS patients, cost–benefit analysis) should be addressed.

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Declaration of conflicts of interest

There are no conflicts of interest to be declared. Especially there was no financial support or influence on planning, performing, data analysis or publication of this trial by the manufacturer of the Lokomat (Hocoma).

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