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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