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Robot-assisted end-effector-based gait training in chronic stroke patients: A multicentric uncontrolled observational retrospective clinical study

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Abstract.

BACKGROUND: Until now studies report inconclusive results as regards the effectiveness of exclusive use of robot-assisted training and clinical indications in stroke patients.

OBJECTIVE: To evaluate if the only robot-assisted end-effector-based gait training can be feasible in chronic stroke subjects in terms of gait recovery.

METHODS: Five rehabilitation centers participated and one hundred chronic post-stroke patients were recruited. Patients underwent a robot-assisted end-effector-based gait training as only rehabilitation treatment.

6 Minute Walking Test, 10 Meter Walk Test, Timed Up and Go test, Modified Ashworth Scale, Motricity Index, Functional Ambulation Classification (FAC) and Walking Handicap Scale were used as outcome clinical measure. Patients were divided into two groups: those assessed as FAC < 3 (Group 1) and as FAC $\geq$ 3 (Group 2).

RESULTS: Statistically significant changes were observed in each clinical outcome measure. Significant changes were observed in in Group 1 and in Group 2. Significant percentages of patients achieved MCID in 6MWT in Group 2 and TUG in Group 1.

CONCLUSIONS: Chronic stroke patients exposed to only robot-assisted end-effector-based gait training showed significant improvements in global motor performances, gait endurance, balance and coordination, lower limbs strength and even spasticity.

Keywords: Rehabilitation, robotics, gait, stroke

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1. Introduction

Stroke is one of the common neurological disease: 16.9 million people suffer a stroke each year, representing a global incidence of 258/100,000/year, with differences between industrialized and poor countries and gender: in men the incidence is 1.5 times higher than in women. The number of stroke survivors doubled between 1990 and 2010, reaching now 33 million people and achieving 77 million by 2030, according to epidemiological projections (Béjot, Daubail, & Giroud, 2016; Kolominsky-rabas, Weber, Gefeller, Neundoerfer, & Heuschmann, 2001).

Stroke is a leading cause of long-term disability (Lloyd-Jones et al., 2010) and it often causes a partial damage of the cortical tissue which generates disturbed motor programs because of the involvement of sensory and motor areas, causing a permanent disability in the upper and/or lower limbs (Balami & Buchan, 2012).

The mobility is defines as the ability to move easily and without restrictions, and its recovery is essential for stroke survivors in order to return to an active and healthy lifestyle (Kendall & Gothe, 2016) and to obtain improvement in terms of health-related QoL (Rand, Eng, Tang, Hung, & Jeng, 2010). Gait disorders represent the main effects of stroke: more than 75% of individuals lose their ability to walk after stroke (Knecht, Hesse, & Oster, 2011; Thrift et al., 2014) and the most important determinants of mobility in stroke patients are gait endurance, gait speed and balance (Huh et al., 2015; van de Port, Kwakkel, & Lindeman, 2008; Rosa, Marques, Demain, & Metcalf, 2014; Vahlberg, Cederholm, Lindmark, Zetterberg, & Hellstrom, 2013).

Most of survivors require intensive rehabilitation and physiotherapy treatments in order to reduce disability effects and to recover most of the lost functionalities. Restoration of gait following stroke is a major task in neurorehabilitation (Langhorne, Bernhardt, & Kwakkel, 2011; Chollet & Albucher, 2012; Bohannon, Andrews, & Glenney, 2013), and different methods and technologies have been explored over the years (Park et al., 2015; Taqi, Vora, Callison, Lin, & Wolfe, 2012). Most of rehabilitation strategies are only partially able to solve mobility limitations: at discharge from rehabilitation unit, 44.85% of patients have to use a wheelchair, 8.70% can walk outside, and only 4.58% of patients are independent in stair climbing (Paolucci et al., 2008; (Moreland et al., 2009).

A critical need exists for specific rehabilitation approaches capable of improving mobility in post-stroke patients (Awad, Reisman, Pohlig, & Binder-Macleod, 2016). Innovative technological devices may play a crucial role on providing solutions to such challenge. There is strong evidence for rehabilitation favoring intensive high repetitive task-oriented and task-specific training post-stroke rehabilitation (Langhorne et al., 2011; Veerbeek et al., 2014; Bang & Shin, 2016) and robot-assisted training represents an effective opportunity for this aim.

There is evidence that stroke patients who receive robot-assisted gait training combined with standard physiotherapy obtain positive effects in terms of independent walking than patients who receive only standard gait training (Mehrholz & Pohl, 2012; Sale, Franceschini, Waldner, & Hesse, 2012) otherwise studies report inconclusive results as regards the effectiveness of exclusive use of robotic training and possible indications in stroke patients (Pollock et al., 2014; Chang & Kim, 2013; Hornby et al., 2008; Hesse, Schattat, Mehrholz, & Werner, 2013; Ochi, Wada, Saeki, & Hachisuka, 2015; Kelley, Childress, Boake, & Noser, 2013; Swinnen et al., 2015; Taveggia, Borboni, Mule, Villafane, & Negrini, 2016). In addition outcomes of robotic training show a wide variability due to the different devices, duration and frequency of treatment (Mehrholz & Pohl, 2012).

Recent studies have proposed the combined use of the robotic gait training and technologies such as functional electrical stimulation (FES) (Bae et al., 2014; Peurala, Tarkka, Pitkanen, & Sivenius, 2005; Tong, Ng, & Li, 2006), transcranial direct current stimulation (tDCS) (Danzl, Chelette, Lee, Lykins, & Sawaki, 2013; Picelli et al., 2015) and botulinum toxin type A (Picelli et al., 2016) but there is not yet a clear evidence on which patients can achieve gait improvement undergoing only robotic training and which protocol is appropriate to different gait disabilities.

A recent systematic review has highlighted that people in the first three months after the stroke and those who are not able to walk seem to mostly benefit this type of intervention (Hesse et al., 2013). Two types of robotic gait's devices are developed: end-effector and exoskeleton devices. Several randomized controlled trials have been published regarding the usage of these devices in stroke patients (Schwartz & Meiner, 2015), but no difference was found between the two types of robotic gait machines (Mehrholz & Pohl, 2012).

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We strongly believe that the effects of rehabilitation treatments based on the two different families of robotic devices for gait rehabilitation have to be investigated in detail in order to increase the clinical knowledge, to optimize their use and to define guidelines for standardized rehabilitation therapeutic protocols.

Unfortunately till now only few studies have investigated the effects of end-effector robot-assisted gait training on stroke patients (Mehrholz & Pohl, 2012).

The objective of this study are: 1) to evaluate if the only treatment based on an end-effector robotic device is feasible, in terms of gait improvement in chronic stroke subjects, 2) to analyse which factors (i.e., muscle strength, spasticity, balance, gait speed and endurance) may contribute to improve the gait function following a gait robot-assisted treatment and 3) to identify specific advises for an appropriate use of robot-assisted end-effector -based gait rehabilitation.

2. Methods

Five rehabilitation centers participated in the study. One hundred chronic post-stroke patients (mean age: 59.94 ± 15.39) were recruited, whose baseline characteristics are reported in Table 1.

Inclusion criteria: first-ever ischemic/hemorrhagic stroke; ≥3 months post-stroke; age ≥18 years. Exclusion criteria: severe cognitive/communicative disorders that hamper collaboration; unstable cardiovascular system conditions (i.e. labile compensated cardiac insufficiency, angina pectoris), deep vein thrombosis, severe neurological/orthopedic diseases which affect lower limb mobility; severe joint misalignment (Hesse, Tomelleri, Bardeleben, Werner, & Waldner, 2012) and other motor/sensory/cognitive impairments negatively affecting robot-assisted training; treatment of lower limb spasticity (i.e. botulinum toxin) in the 3 months prior to the start of the study and/or during its execution.

Table 1
Baseline characteristics of patients (values expressed as mean value ± standard deviation)

Age	59.94 ± 15.39
Number of sessions	17.46 ± 4.26
FAC	3.65 ± 1.26
WHS	3.83 ± 1.32
MI	57.04 ± 20.13
MAS	4.28 ± 3.11
TUG (s)	25.27 ± 16.57
10MWT (m/s)	1.33 ± 1.73
6MWT (m)	200.90 ± 104.65

This study was performed according to the principles outlined in the Declaration of Helsinki. Robot-assisted gait training duration ranged from ten to twenty sessions, three or five days a week (from January to December 2014). No other rehabilitation conventional treatment was added. The G-EO System (Reha Technology AG; Olten, Switzerland), an end-effector robotic device with fully programmable foot plates for gait and stairs climbing training was used in this study.

It consists of a harness which ensures the patient standing on two foot plates, and through a sledges system the movement is transmitted to the feet. An intelligent control is also able to react and adapt to each patient's ability and gait capability (Hesse, Waldner, & Tomelleri, 2010).

2. Clinical outcome measures

Motor and gait functions were measured before and after the training using the following outcome measures, already selected in a recent study as essential measures for the study of the results of the robot-assisted gait training (Franceschini, Colombo, Posteraro, & Sale, 2015; Geroin et al., 2013): 6MWT (Fulk & Echternach, 2008) as measure of gait endurance, 10MWT (Bowden, Balasubramanian, Behrman, & Kautz, 2009) as measure of speed, TUG (van Hedel, Wirz, & Dietz, 2005) as measure of balance and gait, MAS (Blackburn, van Vliet, & Mockett, 2002) for spasticity assessment, MI (Demeurisse, Demol, & Robaye, 1980) for the muscular coordination and strength. Gait performance was measured using the FAC (Mehrholz, Wagner, Rutte, Meissner, & Pohl, 2007) and participation was evaluated by using the WHS (Perry, Garrett, Gronley, & Mulroy, 1995), assessing indoor and outdoor disability.

4. Data analysis

Clinical outcome measures recorded a before (T0) and after (T1) treatment were compared: variables on ordinal scales were compared using the Wilcoxon signed-rank test, those on continuous scale using a Student *t*-test. The SigmaStat statistical package (version 3.5, Systat Software Inc., San Jose, CA, USA) was used.

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In order to investigate possible effects following the robot-assisted gait training based on the severity of gait impairment, patients were divided in two subgroups based on FAC value: Group 1, including patients assessed as FAC < 3, and Group 2 including those as FAC ≥ 3.

A further analysis based on the total number of sessions and weekly frequency was also performed as well.

Treatment gains on the different clinical outcomes were assessed on the entire patients population and on both groups.

The number of patients in the entire population and both subgroups able to reach the MCID on TUG (8 seconds) (Hiengkaew, Jitaree, & Chaiyawat, 2012), 10MWT (0.10 m/s) (Tilson et al., 2010) and 6MWT (20 meters) (Perera, Mody, Woodman, & Studenski, 2006) was computed as well. Statistical significance was set at $p < 0.05$.

5. Results

Statistically significant changes after treatment were observed in all clinical outcome measures (Table 2).

Significant changes were observed in the MI, TUG and FAC in the Group 1 and in all clinical outcomes, with the exception of the 10MWT, in the Group 2 (Table 3).

The comparison of the results based on the number of sessions shows that when 10 sessions are delivered significant improvements are achieved only in some measures (TUG, 6MWT and 10MWT) in the Group 2. In order to observe improvements in all measures, with the exception of the 10MWT, it is necessary to deliver 20 sessions (Table 4).

The comparison of results based on the frequency of treatment shows that the when three (or more) weekly sessions are delivered functional results are observed (Table 5).

Table 2
Pre- and post-treatment values of clinical outcome measures

	T0	T1
FAC	3.65 ± 1.26	$3.94 \pm 1.12^{**}$
WHS	3.83 ± 1.32	$4.09 \pm 1.29^{**}$
MI	57.04 ± 20.13	$61.51 \pm 20.14^{**}$
MAS	4.28 ± 3.11	$3.57 \pm 2.91^{**}$
TUG (s)	25.27 ± 16.57	$21.26 \pm 12.06^{**}$
10MWT (m/s)	1.33 ± 1.73	1.31 ± 1.60
6MWT (m)	198.37 ± 106.42	$222.15 \pm 100.83^{**}$

*, $p < 0.05$; **, $p < 0.001$.

Table 3
Changes in the clinical outcomes measures in the two groups

	Group 1 ($n = 17$)	Group 2 ($n = 83$)
FAC	0.44^{*}	0.25^{**}
WHS	0.83	0.25^{**}
MI	6.95^{**}	3.45^{**}
MAS	0.50	0.66^{**}
TUG (s)	11.02^{**}	4.22^{**}
10MWT (m/s)	0.23	0.02
6MWT (m)	22.85	44.51^{**}

*, $p < 0.05$; **, $p < 0.001$.

The number of patients in the Group 1 and Group 2 reported in Tables 4 and 5 is slightly lower than that reported in Table 3 due to a lower number of recorded values as clinical outcome measures when the overall number of sessions and the frequency of treatment are considered as analysis factors.

Table 6 shows the percentage of stroke patients who achieved clinically significant changes in the general population and subgroups. 50.0% of patients in the Group 1 reached the MCID on the TUG and the 61.4% of patients in the Group 2 reached the MCID on the 6MWT.

6. Discussion

Technological devices, especially robotic systems, applied to gait rehabilitation are revolutionizing clinical practice.

Most of these robots which are based on advances in neuroscience can contribute to a better understanding of the complex phenomenon of plasticity, but their application and effective use still represent open issues as the identification of gait parameters more responsive to robot-assisted training and specific indications for rehabilitation treatment tailored on each patient characteristics and recovery stage have to be identified yet. Moreover robotic systems for rehabilitation treatment may contribute to optimize healthcare resources as a single therapist is able to deal with more patients at the same time during the training sessions.

The state-of-the-art shows that the best results have often been observed when the robotic therapy is added to the conventional treatment as an augmentation rather than as replacement of the physiotherapist (Hesse & Werner, 2009). However results are often inconclusive and there is no clear evidence that the robotic gait training is superior to the conventional physiotherapy in patients with chronic stroke when delivered as the only treatment (Chang & Kim, 2013).

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Table 4
Changes in the clinical outcome measures in the two groups based on number of treatments sessions

	Group 1 ($n = 16$)		Group 2 ($n = 77$)	
	10 sessions ($n = 2$)	20 sessions ($n = 14$)	10 sessions ($n = 20$)	20 sessions ($n = 57$)
FAC	0.00	0.50	0.05	0.22**
WHS	0.50	0.29	0.11	0.34**
MI	0.50	8.64*	0.58	5.28*
MAS	1.50	0.31	0.18	1.04**
TUG (s)	17.50	9.61**	4.89*	3.01*
10MWT (m/s)	0.12	0.27	0.07*	0.01
6MWT (m)	19.00	9.75	21.21**	26.62**

*, $p < 0.05$; **, $p < 0.001$.

Table 5
Changes in the clinical outcome measures in the two groups based on the frequency (f) of weekly sessions

	Group 1 ($n = 16$)		Group 2 ($n = 70$)	
	f<3 ($n = 3$)	f≥3 ($n = 13$)	f<3 ($n = 20$)	f≥3 ($n = 50$)
FAC	0.00	0.53	0.00	0.23**
WHS	0.33	0.31	0.25	0.34**
MI	0.00	9.31*	2.50	5.52**
MAS	1.00	0.30	1.67	1.02
TUG (s)	17.7**	9.32*	3.21	3.06*
10MWT (m/s)	0.10*	0.33*	0.05	0.01*
6MWT (m)	15.50	13.50	2.50	28.14**

*, $p < 0.05$; **, $p < 0.001$.

Table 6
Percentage of patients reaching MCID. Values expressed as %

	TUG (8 s)	10MWT (0.10 m/s)	6MWT (20 m)
Group 1 ($n = 17$)	50.00	0.00	0.00
Group 2 ($n = 83$)	18.52	17.14	61.43
Group 1, 10 sessions ($n = 2$)	100.00	0.00	0.00
Group 1, 20 sessions ($n = 14$)	36.36	0.00	0.00
Group 2, 10 sessions ($n = 20$)	26.32	10.53	41.10
Group 2, 20 sessions ($n = 50$)	10.42	0.00	42.50

Though the systematic revision by Swinne et al. (2015) including studies on small populations highlights inconclusive results on BBS, Tinetti and TUG, other studies show encouraging results. Bae et al. (2014) compared robotic training vs robot plus FES on dorsiflexors muscles in a small population of chronic post stroke patients and showed an effectiveness on TUG and BBS in both groups. Ucar, Paker, and Bugdayci, (2014) showed the effectiveness of the robotic treatment: significant improvement on TUG and 10MWT were observed also after few sessions (i.e., ten). The robotic approach is roughly as effective as the conventional rehabilitation guided by the physiotherapist while requiring much less physical effort (Werner, Von Frankenberg, Treig, Konrad, & Hesse, 2002).

Till now only few studies have investigated the effects of the robotic end-effector device used in this study, though rather diffused in our country (Hesse et al., 2010; Picelli et al., 2016).

Our study aims to investigate the applicability of such end-effector device on chronic stroke survivors in terms of gait recovery and to identify possible specific advises for an appropriate use. Hesse et al. (2010) showed comparable activation patterns in the lower limbs muscles on six hemiparetic subjects during real and simulated walking on the floor, and a more timely pattern of the shank muscles during the simulated stair climbing on the robotic device. Moreover, Stoller et al. (2014) demonstred that robot-assisted end-effector-based training may provide improvements in terms of cardiopulmonary responses.

To the best of our knowledge this study presents the results on the largest population of stroke patients recruited so far who underwent a robot-assisted end-effector-based gait training, without any other additional rehabilitation treatment.

Although this is a retrospective study, the analysis of the outcomes on a large patients population provides relevant preliminary results, especially for moderately impaired chronic stroke patients.

Our findings demonstrate that chronic stroke patients exposed to only end-effector robotic gait show significant improvements in the global performances (FAC and WHS), endurance (i.e., 6MWT), balance and coordination (TUG), lower limbs strength (MI) and even spasticity (MAS). The statistically significant changes found in the FAC and

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WHS scores correspond to important improvement in the patient's autonomy.

In this study we analysed the outcomes on the basis of different disability severities. Patients were divided into two groups: those who need assistance during walking (Group 1, FAC < 3) and those who are independent or require only supervision (Group 2, FAC ≥ 3). Such classification is not reported in other similar studies.

The results in the Group 1, characterized by a low number of patients, seem to show significant improvements on MI and TUG. These clinical tests examine the strength and the balance necessary to the recovery of the upright posture and the ability to move as confirmed by some studies (Cho et al., 2015; Pennycott, Wyss, Vallery, Klamroth-Marganska, & Riener, 2012; Swinnen et al., 2015).

These findings suggest that in these patients an extension of the treatment duration at least of 20 sessions may contribute to achieve an improvement of the gait speed and endurance as suggested in literature in a recent study (Schwartz & Meiner, 2015).

The results in patients having a higher degree of gait autonomy (i.e., Group 2, FAC ≥ 3) on the contrary show significant changes in all outcomes with the exception of the 10MWT. Therefore it seems that a gait training based on an end-effector robotic device is effective on improving strength, balance, endurance but not in the gait speed.

These data are related to the results of a recent study (Chisari et al., 2015), which also showed that no increase in lower limb strength was observed but a significant increase of firing rate of vastus medialis was found. This study suggests an effect of robotic training on motoneuronal firing rate that thus contribute to improve motor control in the gait. Results on duration of treatment and frequency show interesting findings: stroke patients more severely impaired improve when at least 20 treatment sessions are delivered; probably if the treatment duration was extended additional improvements would be observed, as hypothesized in another study (Mazzoleni et al., 2013).

Results observed in patients with moderate impairment (i.e., FAC ≥3) also confirm this hypothesis: when exposed to 20 rehabilitation sessions and 3 (or more) sessions per week show an improvement in the FAC and WHS. Delivery of 10 sessions provides improvement in the endurance and TUG.

To analyse perceivable changes for the patient the number of subjects who achieved a change equal to or greater than the MCID for relevant clinical measures (i.e., 6MWT, TUG, 10MWT) was computed. In the overall population 44.16% of the recruited subjects achieved a functionally significant improvement in the 6MWT. Such finding confirms that the end-effector robotic gait training produce positive effects on the gait endurance. 50.0% of patients severely impaired achieved the MCID in the TUG and 61.4% of those moderately impaired achieved the MCID in the 6MWT. This latter finding in Group 2 is already observed after 10 treatment sessions: it probably implies that this is the first result which is obtained with this type of training in this subgroup of stroke patients.

These results show that the end-effector robotic gait training is effective even a year or more after the acute event, though no other additional rehabilitation therapy is delivered.

The subjects recruited in our study are chronic post-stroke patients characterized by a wide spectrum of age (i.e., 18–83 years old), corresponding to the population usually admitted to neuro-rehabilitation centers.

While some studies conclude that responders are patients who are not able to walk (Mehrholz & Pohl, 2012), our results seem demonstrate that especially patients moderately impaired may benefit the robotic gait rehabilitation treatment compared to severely impaired patients.

In our opinion during the chronic phase patients needs have to be clearly identified and a tailored rehabilitation programme has to be prepared accordingly. In order to achieve such objective we need to investigate which motor abilities the robotic gait training is able to effectively modify and if can replace conventional treatment or if it can considered as an adjunctive rehabilitation therapy. The results of this study may clarify which objectives can be pursued when an end-effector robot-assisted gait training is delivered to chronic post-stroke patients.

These results show for the first time that significant improvements in global performance measures (FAC and WHS), gait speed (10MWT), gait endurance (6MWT), muscular strength (MI) and spasticity (MAS) have been observed in chronic post-stroke patients undergoing only end-effector robotic gait training. In particular those severely impaired (i.e., FAC<3) significantly improved in TUG values.

In the recruited population a significant percentage of subjects were able to reach the MCID in 6MWT and TUG: such findings imply that significant changes on gait performances can be still observed

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even one year (or more) after the acute event and after short robot-assisted gait training.

As regards the duration of robot-assisted gait rehabilitation treatment, even if most clinical studies are based on treatments including 20 sessions or more, in our multicenter study some patients were exposed to 10 treatment sessions: improvement on the gait function was observed as well.

However the extension of the number of sessions seems to be supported by the findings of our study where higher improvements were observed after 20 sessions than 10 sessions and after a frequency of three times per week (or more). This has also been speculated in other studies that have shown the efficacy of the robotic treatment in real use conditions (Mazzoleni et al., 2013). Such observation contributes to the open issue on the possible correlation between prolonged treatment and improvement of speed and endurance (Franceschini et al., 2013)·

7. Study limitations

The main limitation of the study is the retrospective nature of the study design, which involves additional limitations. A direct comparison with stroke patients treated by conventional rehabilitation treatment was not possible, indeed it was not the aim of this study.

The unbalanced distribution of patients, especially in the Group 1 (i.e., severely impaired patients) as regards the duration of the training and the frequency of weekly sessions (i.e., most patients performed more than three sessions per week) limits any conclusion on the effects of treatment duration and frequency.

Finally the lack of a follow-up evaluation represents an additional limitation as regards the evaluation of possible retention of results observed at the end of the robot-assisted gait training and, as a consequence, the real effectiveness of such training for the patient motor recovery.

8. Conclusions

Gait abnormalities following neurological disorders are often severely disabling and negatively affect at a large extent the patients QoL. Therefore, regaining of walking is considered one of the primary objectives of the rehabilitation process.

Conventional gait training of stroke patients is technically difficult due to their motor weakness and balance disturbances requiring much physical effort for the physiotherapist. In order to achieve good results on gait recovery often two (or more) physiotherapists working on the same patient are needed.

The financial difficulties that healthcare systems has to manage, and that are leading to a reduction of human resources in rehabilitation centres, may compromise the effectiveness of rehabilitation treatments in these patients..

To overcome the problems related to conventional physical therapy, in the last decades a growing number of robotic devices for rehabilitation purposes have been developed: rehabilitation treatments based on such robots have been proven to play an important role for improving the ability to walk.

Our study presents the highest number of chronic post-stroke patients involved in a non-experimental environment so far who underwent an end-effector robotic gait rehabilitation treatment without any other additional conventional rehabilitation therapy. The results show that an intensive training in chronic stroke patients is feasible.

Our results show significant improvements in the different gait abilities, highlight the effectiveness of the robot-assisted end-effector-based gait training based on chronic stroke patients and contribute to identify the most appropriate gait training protocols for chronic post-stroke patients.

Until now no clear evidence for identifying an optimal rehabilitation protocol based on robot-assisted gait training was available: i) treatment duration, ii) amount of training and iii) and selection of patients clinical characteristics represent important factors to be defined.

However longer treatment duration and higher intensity (Ucar et al., 2014) of sessions seem to provide beneficial effects on the final ambulation outcomes of chronic stroke patients.

Conflict of interest

The authors declare that there is no conflict of interest with respect to the research, authorship, and/or publication of this article.

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