

Central neuroplasticity and lower limbs functional outcome following repetitive locomotor training in stroke patients

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Received 01 December 2013

Accepted 15 January 2014

Egyptian Rheumatology & Rehabilitation
2014, 41:85–91

Objective

To evaluate the efficacy of electromechanical gait training (EGT) versus treadmill training with partial body weight support (TTPBWS) on lower limb motor performance (MP) and on motor evoked potential (MEP) in patients with chronic stroke.

Patients and Methods

Fifty patients (age 43–75 years) with hemiparetic stroke (7–72 months' duration) were allocated randomly to two groups. Patients of group I ($n = 25$) received EGT and those of group II ($n = 25$) received TTPBWS (20 min/day, 6 days/week for 8 weeks). Main outcome measurements: Fugel-Meyer lower extremity (FMLE) MP test and MEP were assessed in all patients before rehabilitation (A-begin), at the end of rehabilitation (A-end), and 3 months later (A-3m). By transcranial magnetic stimulation, MEP threshold, MEP amplitude (MEPamp), and cortical latencies to the rectus femoris, tibialis anterior, and gastrocnemius (GC) muscles were assessed.

Results

Better improvement in FMLE was observed in group I compared with group II. In group I, FMLE scores improved significantly at A-3m compared with A-end. A significant reduction in GC cortical latencies and increase in GC MEPamp on the second and third follow-up were observed in group I compared with group II. Although all MEP parameters of the three lower limb muscles tested improved throughout the follow-up periods on intragroup compression, they did not reach statistically significant levels. More patients in group I (unlike group II) with unobtainable MEP at A-begin had obtainable MEP at A-end and A-3m from rectus femoris and GC muscles. The change in MEPamp was the most frequent MEP variable that correlated with the change in FMLE scores (in either group).

Conclusion

Better improvement in MP was observed following EGT at A-3m. Therefore, one EGT rather than TTPBWS may be recommended to improve lower extremity MP in chronic ambulatory stroke patients.

Keywords:

locomotor training, motor evoked potential, neuroplasticity, treadmill with partial body weight support

Egypt Rheumatol Rehabil 41:85–91

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1110-161X

Introduction

Classic models of stroke recovery indicate that motor function improvements plateau between 3 and 6 months [1]. The central nervous system (CNS) has plastic neural networks amenable to reorganization; [2] thus, motor learning-based rehabilitation therapies that target the use of hemiparetic limbs may improve motor control and induce neural plasticity. Basic repetitive motor learning strategies can alter underlying neural mechanisms to improve the function of the lower limb and may be effective in recovery of walking ability and restoration of independent gait in hemiparetic stroke patients. Treadmill training with partial body weight support (TTPBWS) is a task-oriented approach that stimulates repetitive and rhythmic stepping aimed at proper gait restoration in patients with chronic hemiparesis [3]. The major disadvantage of TTPBWS is the effort required by two therapists to assist gait of the patients. As this therapy is limited

by fatigue of the therapists and patients, the session time may not be fully used or the patient may repeat a suboptimal gait [4]. Therefore, an electromechanical gait trainer (EGT) that relieves the strenuous effort of the therapists and provides control of the trunk in a phase-dependent manner may be more effective in this respect, [3] but this hypothesis should be verified as it has not been proven [5]. In a previous study [5] comparing the efficacy of EGT with that of TTPBWS on lower limb functional outcome in unambulatory patients with subacute stroke, no significant differences in the outcome were found between the two methods, and it was concluded that EGT was at least as effective as TTPBWS, while requiring less input from the therapist. Therefore, it was suggested that further studies are warranted. Therapeutic effects of gait rehabilitation through task-specific repetitive training have been evaluated using functional scores (i.e. function ambulatory category) or by analysis of gait events

(i.e. cadence, stride length, velocity) [4]. However, its neurophysiologic effects cannot be measured by these evaluation methods. Besides, there is little evidence that brain plasticity underlies locomotor recovery after stroke in humans [6]. Transcranial magnetic stimulation (TMS) with resultant motor evoked potentials (MEP) can reflect the state of neuronal excitability, conduction velocity, and axon number through threshold intensity, MEP latency, and MEP amplitude (MEPamp) [7]. It is assumed that MEP recorded from key gait muscles in patients with chronic hemiparesis can reflect the neurophysiologic effects of gait rehabilitation. The aims of this study were as follows: (a) to investigate the effect of EGT versus TTPBWS on lower limb motor performance outcome in patients with chronic hemiparesis because of stroke and (b) to explore MEP changes accompanying lower limb motor performance improvement following the training protocols applied. This may show central changes (or neuroplasticity) that may be associated with lower limb functional improvement.

Patients and Methods

Patients

Fifty patients who had a first ever-unilateral chronic supratentorial ischemic cerebrovascular stroke were included in this study. Inclusion criteria were as follows: (a) age above 40 and up to 75 years; (b) ambulatory, but with difficult ambulation (either independently or required the assistance of a walker or a cane) to include patients who had some ability to voluntarily activate the rectus femoris (RF), tibialis anterior (TA), and/or gastrocnemius (GC); thus, most patients might have obtainable MEP from the lower limb muscles, and to lessen the effort made by the therapists during TTPBWS (a confounding factor); (c) disease duration 6 and up to 72 months; (d) score 2 according to the Modified Ashworth Spasticity Scale in the hip flexors, quadriceps, hamstring, TA, and calf muscles [8]; and (e) patients who received previous physical rehabilitation only in the form of therapeutic exercises and parallel bar gait training for 3–6 months before participation in the study.

Exclusion criteria were as follows: (a) unsatisfactory general condition; (b) cardiopulmonary diseases compromising walking ability; (c) clinical signs of heart failure (according to New York Heart Association); (d) lower extremity vascular insufficiency; (e) other neurological or orthopedic diseases precluding walking ability (e.g. peripheral neuropathy, joint stiffness, arthroplasty, painful joints, or musculoskeletal problems at the lower limb); (f) insufficient communication; (g) defective cognitive function [assessed by Mini Mental

State examination (total score = 30)]; (h) those with previous focal spasticity management; (i) previous experience with TTPBWS or EGT; and (j) presence of contraindications for TMS (e.g. seizure, metallic implant in the head or neck, pacemaker). All patients passed a cardiovascular screening test for exercise capacity that allowed them to participate in gait training before participation in the study. A preliminary treadmill exercise test was carried out. Patients who could walk for at least 6 min (at a minimum of 0.1 m/s) without signs of cardiopulmonary distress, myocardial ischemia, or treadmill exercise intolerance were enrolled. All patients provided their written informed consent for participation in the study, which was approved by the local ethics committee. Then, patients were assigned randomly to one of two groups (each of 25 patients) by a computer-generated randomization code. There were 14 men and 11 women in group 1 and 13 men and 12 women in group 2. The right side was involved in 14 patients of group 1 and 13 patients of group 2. The left side was involved in 11 patients of group 1 and in 12 patients of group 2. Group I received net 20 min of repetitive locomotor therapy on EGT of Hesse [9]. Group II participated in a rehabilitation program of net 20 min TTPBWS. Both programs were scheduled as one session/day, 6 days a week for 8 successive weeks. All patients in the two groups were fitted with rubber sport shoes (without ankle foot orthosis) during gait training. Training procedures: the EGT of Hesse consisted of two footplates whose driven movements simulated stance and swing phases in a symmetric manner with a ratio of 60–40%, respectively. The step length was adjusted at 48 cm; the cadence was adjusted individually, according to the patient's abilities, to a comfortable training speed ranging from 0.3 to 0.5 m/s (to allow for proper gait correction and to avoid considerable effort by patients), with an optional break after 10 min. Speed was increased progressively as the patient's abilities progressed. The vertical and horizontal movements of the center of mass were controlled by the gear system through two ropes connected by a modified parachute harness. The initial weight support started with 30% body weight, which was reduced progressively as the patient became capable of carrying the remaining load on the paretic limb throughout stance. Initially, one therapist assisted the affected knee control, and then with improvement, patients progressed independently [9]. In TTPBWS, patients walked on a motor-driven treadmill while suspended by a modified parachute harness to an overhead suspension system that allowed free movement of the lower and upper limbs. The initial weight support started with 30% body weight and was reduced progressively to ensure bearing weight on the affected limb during the single-support phase. Treadmill speed was adjusted below overground walking speed

(as determined by a 10-m self-selected comfortable walking speed) for a comfortable cadence and stride length in each patient that allowed gait correction. The mean treadmill speed was 0.4 m/s (range: 0.2–0.6 m/s). Patients were assisted manually by two therapists to correct gait deviation and encourage a symmetrical gait pattern. One therapist facilitated swing of the paretic limb, determined initial heel contact, and secured it during the stance phase. The other therapist stabilized the trunk, facilitated weight shift on stance limb, hip extension, and pelvic rotation according to individual requirements.

Outcome measures

All assessment methods were performed at baseline (immediately before the rehabilitation program) that is beginning of the study (A-begin), immediately at the end of the 8-week rehabilitation period (A-end), and at 3 months after the end of rehabilitation (A-3m) in both groups; the rater was blinded to patients' grouping. Two independent raters were involved: one performed Fugl-Meyer lower extremity (FMLE) motor performance assessment [10] and the other performed the neurophysiological assessment. Assessment before and after the rehabilitation program included the following:

- (1) Motor performance of the lower limb using the FMLE score (17 items and each item is scored on a 0–2 scale, yielding a total sum score of 34 points). It is a reliable quantitative measure that assesses motor impairments and recovery from hemiplegic stroke. Its motor domain includes items measurement of volitional movements (flexor synergy, extensor synergy, movement combining synergies, and movement out of synergy), coordination/speed, and reflex action around the hip, knee, and ankle [10].
- (2) Neurophysiological evaluation using percutaneous TMS of the corresponding cortical motor lower limb area. MEP parameters were recorded from the paretic RF, TA, and medial head of GC muscles using surface recording disc electrodes (1 cm diameter) connected to a conventional electrophysiological apparatus (Neuropack 2; Nihon Kohden, Tokyo, Japan). The filter was set to 3 Hz to 3 KHz. Gain was varied according to response amplitude (100–200 mV). Time base was set at 10 ms/division. Magnetic stimulation was performed using a Magstim 200 single pulse stimulator (Magstim company, Wales, UK), equipped with a high-power 90 mm circular coil that generates 2 T maximum field intensity. The testing protocol was carried out according to the International Federation of

Clinical Neurophysiology criteria for magnetic stimulation of the brain [11]. Reproducibility of recordings in each assessment was ensured using a latex cap marked with predetermined cortical areas of the target muscles for the tested patient. Resting threshold intensity (expressed as percent of the maximum machine output), MEP maximum peak to peak amplitude (in mV), and the shortest cortical latency (CL) to onset (in ms) were the recorded MEP parameters. Three trials were conducted and the highest MEPamp was included in the data analysis. MEP was considered unobtainable if 10 successive discharges failed to elicit a response from the target muscle at the maximum output (100%) intensity. Patients were assessed while in a relaxed supine position for RF and TA testing and prone for testing of GC muscle. To control for rehabilitation effects, the percent changes in the FMLE scores and in the MEP parameters at A-end and at A-3m were calculated for each patient, rather than the absolute difference between prerehabilitation and postrehabilitation values, and were used for comparisons between the two groups according to the following formulae:

$$\text{Percent change 1} = \frac{[(\text{A-end}) \text{ value} - (\text{A-begin}) \text{ value}]}{(\text{A-begin}) \text{ value}} \times 100,$$

$$\text{Percent change 2} = \frac{[(\text{A-3m}) \text{ value} - (\text{A-end}) \text{ value}]}{(\text{A-end}) \text{ value}} \times 100,$$

Statistical analysis

Data were entered and analyzed using the statistical package SPSS version 17 (USA). Data were summarized using descriptive statistics: mean \pm SD. Skewness of the measured variables was assessed to determine the normality of distribution at A-begin. Statistical differences between groups at A-begin assessment were tested using a nonparametric Mann-Whitney test. Repeated-measures analysis of variance test was used for the comparison of outcomes across all follow-up assessments. Correlations were performed to test for relations between variables in each group using Spearman's test. A *P* value equal to 0.05 was considered statistically significant.

Results

Both groups had homogeneous clinical data at the onset of the study. At A-begin, the studied groups were comparable without any difference in age, height, body weight, and the duration of stroke (Table 1). Also, there was no significant difference between the two groups

in the FMLE motor performance scores or the MEP variables at the onset of the study (Table 2). There were no dropouts throughout the study. None of the patients

Table 1 Patients' characteristics in the two groups studied

	Group I (n = 25)	Group II (n = 25)	P
Electromechanical gait trainer range (mean ± SD)		Treadmill with PBWS range (mean ± SD)	
Age (years)	43–75 (58.3 ± 8.6)	46–70 (59.7 ± 7.4)	0.56
Height (cm)	152–179 (166.4 ± 12)	154–180 (169.1 ± 6.7)	0.46
Weight (kg)	62–86 (75.7 ± 7.1)	60–87 (76.4 ± 6.7)	0.55
Disease duration (m)	7–72 (30.3 ± 21.8)	8–72 (28.4 ± 19.8)	0.47

PBWS, partial body weight support.

Table 2 Comparison between EGT group and TTPBWS group in the baseline FMLE and MEP variables

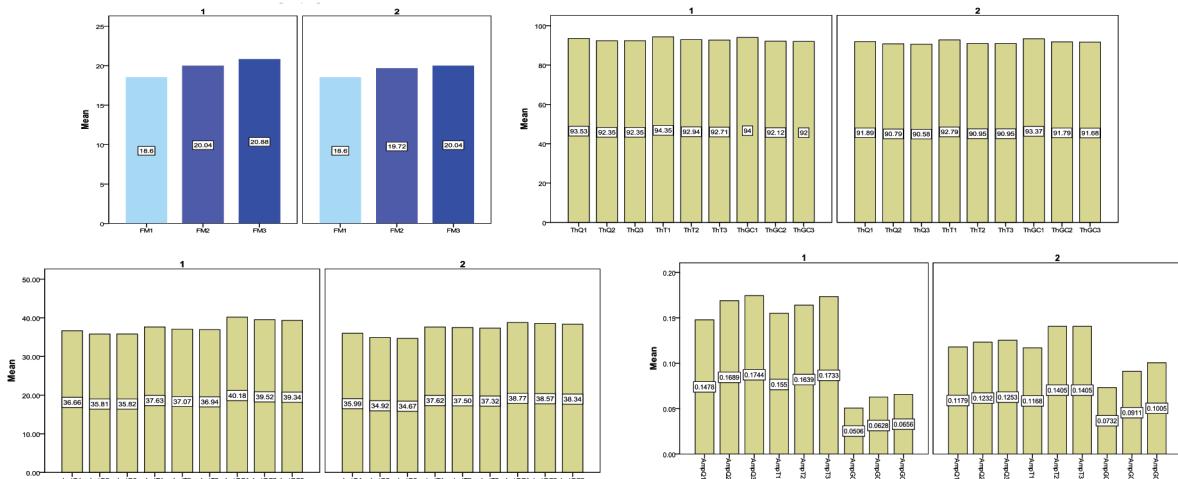
	Mean ± SD		P
	Group I Electromechanical gait trainer group	Group II Treadmill with PBWS group	
FMLE scores	18.6 ± 3.2 (n = 25)	18.6 ± 3.4 (n = 25)	1.0
RF threshold (%)	93.5 ± 5.9 (n = 17)	91.8 ± 7.0 (n = 19)	0.46
RF latency (ms)	36.6 ± 2.8	35.9 ± 2.8	0.48
RF amplitude (mV)	0.14 ± 0.04	0.11 ± 0.06	0.09
TA threshold (%)	95.1 ± 5.9 (n = 21)	92.7 ± 6.4 (n = 19)	0.23
TA latency (ms)	38.1 ± 3.0	37.6 ± 3.0	0.55
TA amplitude (mV)	0.14 ± 0.05	0.11 ± 0.05	0.16
GC threshold (%)	95.0 ± 6.1 (n = 21)	93.3 ± 5.7 (n = 19)	0.39
GC latency (ms)	40.8 ± 3.1	38.7 ± 2.7	0.06
GC amplitude (mV)	0.04 ± 0.02	0.07 ± 0.02	0.06

The table represents electrophysiological data obtained only from those with obtainable MEP variables at the beginning of the study (A-begin); EGT, electromechanical gait training; FMLE, Fugl-Meyer lower extremity motor performance scale; GC, gastrocnemius muscle; MEP, motor evoked potential; RF, rectus femoris; TA, tibialis anterior; TTPBWS, treadmill training with partial body weight support; P ≤ 0.05 is significant.

reported dyspnea or fatigue during or after training. All patients (in both groups) completed 48 sessions of the rehabilitation program over a period of 8 weeks and the time spent in therapies was comparable between the two groups (20 min/session). Although group comparison showed a progressive improvement in the FMLE motor performance scores at A-end and A-3m, better improvement in FMLE was observed in group I compared with group II (Fig. 1). Moreover, in group I, FMLE scores improved significantly at A-3m compared with A-end (P = 0.02). Meanwhile, improvement in FMLE scores did not reach the level of statistical significance at any follow-up assessment in group II. The number and percentage of patients with unobtainable MEP in both groups before and following rehabilitation are shown in Table 3. It was observed that more patients in group I (unlike group II) with unobtainable MEP at A-begin had obtainable MEP at A-end and A-3m from the RF and GC muscles (Table 3).

For neurophysiological parameters, on intergroup comparison, a significant reduction in GC CL and increase in GC MEPamp on the second and third follow-ups were observed in group I compared with group II (P = 0.02, 0.01, 0.01, and 0.04, respectively) and no other significant differences were observed. Although the MEP threshold of the three tested lower limb muscles decreased, MEP CL reduced, and MEPamp increased throughout the follow-up periods in both groups, no statistically significant differences were observed on intragroup comparison. In group I, Spearman's correlation test showed that the percent change one of FMLE scores correlated positively with the percent change one of TA MEPamp and the percent change two of RF MEPamp ($r = 0.574$,

Figure 1



(a) FMLE, (b) MEP threshold, (c) MEP cortical latency, and (d) MEP amplitude at A-begin, A-end, and A-3 months in the two groups studied. FMLE, Fugel-Meyer lower extremity; MEP, motor evoked potential.

Table 3 Number of patients with unobtainable MEP in both groups before and after rehabilitation

			n (%)		
Group I Electromechanical gait trainer group (n = 25)			Group II Treadmill with PBWS group (n = 25)		
A-begin	A-end	A 3-months	A-begin	A-end	A 3-months
RF	8 (32)	3 (12)	3 (12)	6 (24)	4 (16)
TA	4 (16)	4 (16)	4 (16)	6 (24)	5 (20)
GC	4 (16)	0 (0)	0 (0)	6 (24)	5 (20)

GC, gastrocnemius muscles; MEP, motor evoked potential; PBWS, partial body weight support; RF, rectus femoris; TA, tibialis anterior.

$P = 0.006$, and $r = 0.477$, $P = 0.025$, respectively). The percent change two of FMLE scores correlated negatively only with the percent change two of CL to GC muscle ($r = -0.601$, $P = 0.002$), whereas in group II, the percent change one of RF MEPamp showed a significant positive correlation with the percent change one ($r = 0.456$, $P = 0.05$) and percent change two ($r = 0.518$, $P = 0.023$) of FMLE scores. Also, percent change two of GC MEPamp correlated positively with percent change one of FMLE scores ($r = 0.527$, $P = 0.017$).

Discussion

The two groups studied were comparable in walking abilities, age, height, sex, and duration of stroke. Also, FMLE motor performance scores and MEP variables did not show any significant difference between the two groups at the first assessment (A-begin). Furthermore, all patients had received previous physical rehabilitation only in the form of therapeutic exercises and parallel bar gait training for 3–6 months before participation in the study. Homogeneity of the two studied groups at A-begin, besides uniformity (duration and number of sessions) of the training conditions, suggests that the observed differences in functional and neurophysiologic parameters between the two groups following the rehabilitation programs are most likely related to the effects of the program and ensure that preadmission physical therapy sessions did not influence the outcome measures. In the present study, FMLE scores improved more than 10% in both groups at the end of the 8-week rehabilitation programs (at A-end), which may represent a clinically meaningful improvement [10]. Furthermore, this improvement progressed over the next 3 months after the end of the rehabilitation program (i.e. until A-3m) in both groups. However, this improvement was better in group I than in group II at A-3m. This may suggest that EGT could have induced more central changes than TTPBWS. Treadmill training, as an active repetitive task-oriented practice of complex gait cycles instead

of single-limb gait-preparatory maneuvers, [3,12] provides kinesthetic activation of sensory inputs, locomotor pattern generators, and central neuronal circuits in chronic hemiparetic stroke patients [13]. Besides, EGT facilitates motor relearning and improves functional locomotor recovery in those patients through enforcement of complex stepping movements, and simulation of stance and swing phases in a highly physiological symmetrical manner that could be important in reminding patients how to perform gait movements properly and more independently. Moreover, it provides stabilization of the trunk and decreases requirement of participation of the physical therapists [4]. Practicing the entire task of gait in the functional context of walking on EGT or treadmill is more efficient than practicing components of walking in isolation, as concluded previously by Hesse *et al.* [3] The finding that motor performance was better in group I than in group II at A-3m may indicate that EGT has more significant impact at the neurophysiological level in chronic stroke patients compared with TTPBWS. Werner *et al.* [5] found that subacute nonambulatory stroke survivors trained on EGT had reached a significantly higher gait ability level at the end of the study than those trained for similar periods on TTPBWS. This is also in agreement with the study of Hesse *et al.* [14], which showed larger kinesiological electromyographic activation of the biceps femoris muscle in nonambulatory stroke patients trained on the gait trainer than those trained on TTPBWS. Forrester *et al.* [15] reported that treadmill training increased the MEPamp recorded from the vastusmedialis in a few patients with chronic stroke. Their findings do not contradict the findings of this study. Changes in regional brain activation evidenced by a functional MRI study suggested that task-repetitive treadmill exercise training restores locomotor capacity and functional gait abilities in chronic hemiparetic stroke patients through increased activation of corticosubcortical networks [6]. In stroke patients, there is axonal injury of the descending motor pathway, whether stroke involves cortical or subcortical levels in which anterograde axonal injury is suggested [16]. Therefore, it is assumed that training has to increase the number of fibers that project to the target muscles. Training-induced plasticity and cortical reorganization plays an important role in improvement in corticospinal tracts conductivity, perhaps through recruitment of the spared fibers or previously silent contralateral uncrossed corticospinal fibers [4], leading to increased MEPamp and decreased CL [17]. Also, gait training, through long-term training of different parts together, may lead to changes in synaptic efficiency or formation of new synaptic connections between neurons, [18] a factor that has probably contributed

toward the improvement in the recorded MEP variables. MEPs variables were capable of monitoring postrehabilitation neurophysiological improvements. MEP changes are much more likely to be the result of neuroplasticity rather than the muscular effects of training, as they were observed after 3 months of the end of gait training in the present study [19]. Locomotor training-induced cortical changes are use dependent; therefore, continued improvement in the FMLE score and MEP parameters at A-3m seems to be related to increased abilities of the studied patients to activate the RF, GC, and TA muscles when walking during daily activities. However, the absence of an outcome measure on activity level of the studied patients between treatment end (A-end) and the 3-month follow-up is considered a limitation of this study. In some patients, there were unobtainable prerehabilitation MEP responses in one or more of the tested muscles in both groups. MEP became obtainable after rehabilitation in some of them (larger percent was observed in group I). This suggests that the rehabilitation program applied had influenced cortical excitability. Besides, the MEP threshold, reflecting the excitability of central neurons and their local density, had improved in both groups in the three studied muscles following rehabilitation. These indicate that the programs used might have induced activation of central pattern generators [20] and potentiation of the motor cortex, which in turn modified the excitability of specific motor neurons through enhanced integration of somatosensory information into locomotion by repetitive movements [21]. In light of the findings of this study, one may suggest that EGT or TTPBWS should be attempted in patients with chronic stroke even when the prerehabilitation MEP responses may be unobtainable. This is because training appeared to improve cortical excitability in some patients with chronic stroke and because the CNS continues to be plastic. Therefore, improvements may be expected in any patient under the appropriate training irrespective to his initial evaluation. Significant correlations have been found between the percent changes in FMLE scores and the percent changes in some MEP variables in both groups. Improvements in MEP variables are consistent with the learning hypothesis and neuroplasticity, where task-specific activity results in changes in the CNS that correlate with improvements in motor performance [18]. The percent change in MEPamp was the most frequent MEP variable that correlated with percent changes in FMLE scores. As MEPamp reflects the degree of integrity of corticospinal tracts and hence the degree of recruitment of the relevant muscles, these correlations reflect the relationship between the ability to produce isolated voluntary muscle activation and

the integrity of the corticospinal pathways as assessed quantitatively by MEP.

All participants of this study were chronic stroke survivors; thus, the contribution of spontaneous recovery to the observed results is less likely. The possibility of a carryover or a sequence effect from one phase to the next, which has been considered a limiting factor in previous studies, was avoided by studying the effect of two rehabilitation programs on two comparable groups with an acceptable size in a single phase. Moreover, the relatively long duration of the rehabilitation programs (6 days/week for 8 weeks) was another advantage of the study design because it allowed a performance plateau to be reached and potentiated the intervention effects so that they could be maintained for 3 months after the end of the rehabilitation programs.

Conclusion

Eight weeks of EGT or TTPBWS improved lower limb function in chronic ambulatory stroke patients. However, EGT resulted in better lower limb functional improvement than TTPBWS at 3 months after the end of therapy. In addition, EGT can help to optimize the therapeutic approach in chronic stroke rehabilitation because of the requirement of fewer therapists. MEP changes suggest that the mechanism for functional improvement could be central neuroplasticity. This could be secondary to task-repetitive locomotor training.

Acknowledgements

Conflicts of interest

None declared.

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