The therapeutic application of functional electrical stimulation and transcranial magnetic stimulation in rehabilitation of the hand function in incomplete cervical spinal cord injury

Shereen Fawaz[a], Fatma Kamel[a], Ahmed El Yasaky[a], Heba El Shishtawy[a], Ahmed Genedy[d], Reda M. Awad[c], Lobna El Nabil[b]

Departments of [a]Physical Medicine, Rheumatology and Rehabilitation, [b]Neurology, Ain Shams University, [c]Department of Physical Medicine, Rheumatology and Rehabilitation, El Azhar University, [d]Department of Physical Medicine, Rheumatology and Rehabilitation, Armed Forces Military Academy, Cairo, Egypt

Correspondence to Shereen Fawaz, MD, MRCP, Lecturer in Physical Medicine and Rehabilitation, 2 El Maryland Buildings, Gesr El Suez, Flat 901, Ain Shams University, Cairo, 11757, Egypt. Tel: +20 100 124 2964; fax: 27767175;
e-mail: shereen_fawaz@yahoo.com

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Background
Functional electrical stimulation (FES) therapy has a potential to improve voluntary grasping and induce plastic changes among individuals with tetraplegia secondary to traumatic spinal cord injury (SCI). Also, evidence suggests that the use of high frequency repetitive transcranial magnetic stimulation (rTMS) to increase corticomotor excitability improves hand function in persons with cervical SCI.
Purpose
Our randomized controlled trial was carried out to compare the two rehabilitation programs, the first applied to FES and real rTMS whereas the second applied to FES and sham rTMS, with repect to hand function in chronic traumatic incomplete cervical SCI patients, and also with respect to changes in cortical excitability, and its relation to hand function before and after the rehabilitation programs.
Patients and methods
Our study included 22 patients with chronic traumatic incomplete SCI. Patients were randomly assigned into two groups, 11 patients each. Group I patients received FES for 12 weeks with an additional real rTMS therapy for the last two weeks, at 10 Hz frequency, subthreshold intensity for a total of 1500 pulse per session for 10 sessions. Whereas group II patients received FES for 12 weeks with an additional sham rTMS therapy for the last two weeks. All were followed by an intensive hand training program. Patients were assessed: using hand function tests (action research arm test, modified Sollerman hand function test, nine-hole pegboard scale, and finger tapping test) and corticomotor excitability tests (using amplitude of motor evoked potential).
Conclusion
Our study showed statistically significant improvements in hand function tests in group I, who received FES in addition to real rTMS therapy in comparison with group II, who received FES in addition to sham rTMS at 12-week assessment. This could support the evidence of the additional benefit of real rTMS therapy for 10 sessions/2 weeks in improving hand function and motor recovery following SCI.

Keywords:
functional electric stimulation, repetitive transcranial magnetic stimulation, hand rehabilitation, cervical spinal cord injury, spinal cord injury

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Introduction

Traumatic spinal cord injury (SCI) resultsin impairment of the motor or sensory function, or both (at and below level of injury), leading to tetraplegia and, subsequently, affecting the patient's quality of life [1].

The most common site of injury is the cervical spinal cord. Injuries in this area are often most devastating as the extent of the impairment and disability is greater than any other region in the body [2].

In cervical SCI, impaired arm and hand function impacts an individual's ability in self-care, work, and recreational activities. Many individuals with tetraplegia cite recovery of arm and hand function as the most important goal in rehabilitation. Hence, it becomes important to improve the hand functioning to give them confidence, thereby, independence to handle their own work [3,4].

Recently, the central nervous system has shown a great ability to adapt and change itself in response to any injury or damage via a process termed plasticity, which involves reorganization of brain centers, unmasking new synaptic connections, and changes at the neurotransmitter levels that affect its inhibitory or excitatory state [5].

Rehabilitation of tetraplegic patients largely depends on improving these plastic changes. Functional electric stimulation (FES) has long been shown to enhance these plastic changes [6]. Recently noninvasive brain stimulation has been used as a tool to modulate activity of cortical, subcortical, and corticospinal pathways to promote functional recovery [7,8].

The current study was carried out to compare the two rehabilitation programs, FES and real repetitive transcranial magnetic stimulation (rTMS) versus FES and sham rTMS, with respect to the hand function in chronic traumatic incomplete cervical SCI patients. The changes in cortical excitability between the two groups and its relation to the hand function before and after the rehabilitation programs were observed.

Patients and methods

A randomized controlled study of 22 patients was performed. Included patients had age range between 18 and 60 years. All were traumatic, chronic (>6 months), cervical incomplete spinal cord injury (iSCI) (at the level between C5 and C7) patients. All had functioning biceps and deltoid.

Exclusion criteria were history of head injury, history or family history of seizures, metal implants in the head (e.g. aneurysm clip), developed rash, allergy, or wounds at the location of stimulation electrodes placement; and presence of any other neurologic, orthopedic, or cognitive condition. They were recruited from Ain Shams University hospitals and Armed Forces Rehabilitation Center for over a 5-year duration.

All patients were subjected to the following clinical assessments: American spinal injury association (ASIA) scoring, FIM total tasks, Medical Research Council (MRC) scale, hand function tests: action research arm test (ARAT); modified Sollerman hand function test (mSHFT); nine-hole pegboard scale; and finger tapping tests. The electrophysiological assessment was done by measuring the motor evoked potentials (MEP) amplitude by TMS. The equipment used was MAGSTIM RAPID2 *P*/N 3576-23-09, Wales-UK. The pulses were applied to the motor cortical area of the upper limbs. Motor response evoked was recorded from the abductor pollicis brevis muscle using surface electrodes.

Patients were randomly assigned into two groups: the first group (group I) received FES followed by movement training for 12 weeks. Sessions were done three times a week. In addition to FES, patients received real rTMS for the last 2 weeks. The rTMS sessions were executed five times a week. The second group (group II) received FES followed by movement training for 12 weeks. Sessions were executed three times a week. In addition to FES, patients received Sham rTMS for the last 2 weeks. The rTMS sessions were also executed five times a week.

FES protocol was done using Cefar Physio4 (Scandinavian, Sweden) equipment, program of grasp and release, for 45 min followed by movement training for 30 min. The program stimulation parameters include a frequency of 35 Hz and a work period of 6 s.

The real rTMS protocol of group I was applied over the primary motor area (M1) to stimulate the abductor pollicis brevis. Stimulation parameters are at 10 Hz, applied for 5 s (work period), with interpulse interval of 25 s for 30 trains at an intensity of 90% resting motor threshold (MT); and total number of pulses as 1500 pulse per session, 5 days a week for 2 weeks, for 10 sessions.

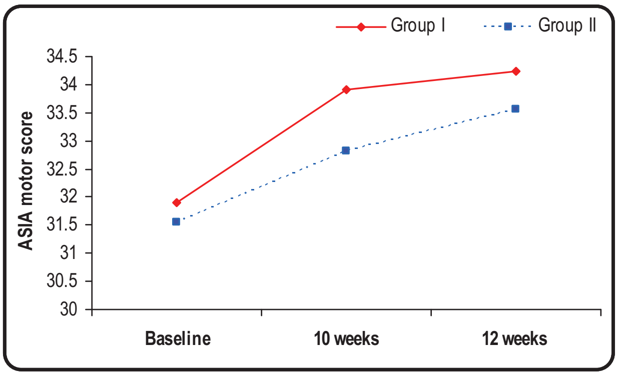
The sham rTMS protocol of group II was applied with the coil angled at 90 degrees from the scalp at a site away from the primary motor area (M1). Stimulation parameters are at 1 Hz, applied for 5 s (work period), with interpulse interval of 25 s for 30 trains at an intensity of 90% resting MT; and total number of pulses as 150 per session, 5 days a week for 2 weeks, for 10 sessions.

MT is defined as the stimulation intensity, wherein, it was possible to obtain responses greater than 50 μV peak-to-peak in amplitude either at rest or greater than baseline electromyography (EMG) during a voluntary contraction of 10–15% being the maximum. The relationship between increases in stimulation intensity and MEP amplitude was assessed using input–output curves. Beginning at the intensity corresponding to 80% of the thenar-active MT, five stimuli were delivered at each stimulator intensity with interstimulus interval of 4–6 s, in 20% increments of stimulator output, until it reached the maximum stimulator output. Assessments were done before therapy, at 10 and 12 weeks, and at the end of therapy.

Results

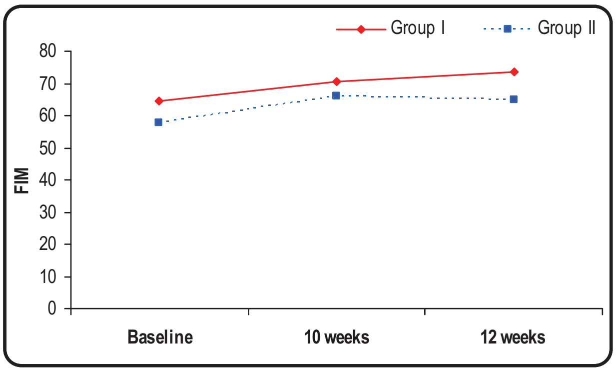
The results of both group I and II from baseline to 10 weeks are as follows: ARAT showed highly significant difference; mSHFT showed a significant increase; and

Figure 1



Follow-up chart of American spinal injury association (ASIA) motor score between group I and II at baseline, 10 weeks, and 12 weeks.

Figure 2



Follow-up chart of functional independence measure (FIM) score between group I and II at baseline, 10 weeks, and 12 weeks.

pegboard scale (both the put-on and removal time) showed a significant decrease in time.

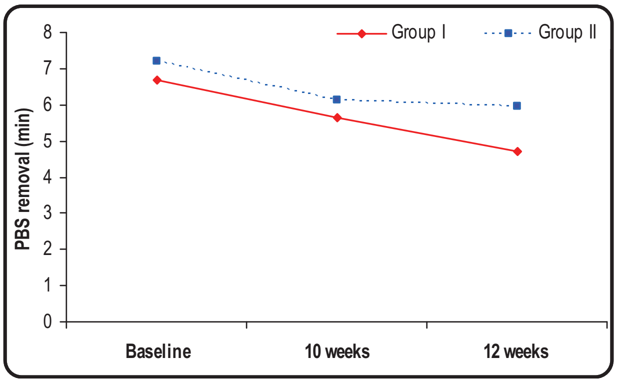
The results of both group I and II from baseline to 10 weeks (the intervention was basically FES) showed nonsignificant changes in the MRC scale of the thenars, long flexors, and extensor muscles.

The results of both group I and II from 10 to 12 weeks showed nonsignificant changes in the MRC scale of the thenars, long flexors, and extensor muscles.

Our study showed, 10–12-weeks assessments of group I, highly significant increases in mSHFT and finger tapping test. ARAT and MEP showed significant increases, whereas pegboard scale showed significant decreases. Results of group II, 10–12 weeks, showed improvements in these parameters but did not reach significant values.

Comparison of the clinical data of group I and II at baseline and 10 weeks' assessments showed nonsignificant differences.

Figure 3



Follow-up chart of pegboard scale (removal time) between group I and II at baseline, 10 weeks, and 12 weeks.

Comparison of clinical data of group I and group II at 12 weeks showed that there was a statistically highly significant increase in finger tapping test. There was a statistically significant increase in ARAT and mSHFT, whereas the pegboard scale showed a statistically significant decrease with respect to both the put-on and removal times of the pegs in group I versus group II.

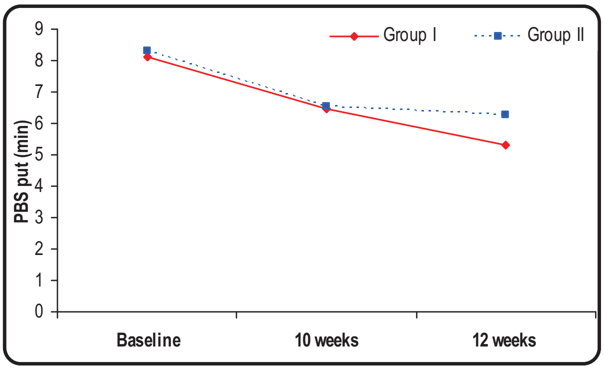
Group I, baseline to 12-week assessment, showed significant increases in the MRC scale of the thenars, long flexors, and extensor muscle groups. Other clinical and electrophysiological data of group I, baseline to 12 weeks' assessments, showed highly significant increases with respect to ARAT and mSHFT. There was also highly significant decrease in pegboard scale with respect to both the put-on and removal times of the pegs. There were significant increases in the FIM, Finger tapping test, MEP, and surface EMG of the long flexor muscles.

Group II, baseline to 12-weeks assessment, showed nonsignificant changes in the MRC scale of the thenars, long flexors, and extensor muscle groups. Whereas there were statistically significant increases in the FIM, ARAT, and mSHFT. The pegboard scale showed a significant decrease in both put-on and removal times (Figs 1–8).

Discussion

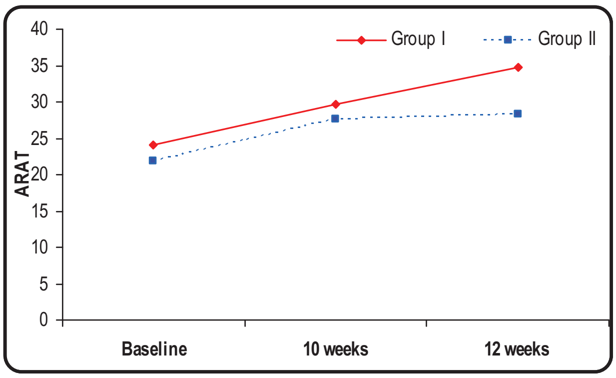
Assessment of functional independence measure (FIM) score, baseline to 10 weeks, in both group I and II showed improvements but did not reach significant values (P>0.05). These results were similar to that of the study of Popovic *et al.* [9]. However, Popovic *et al.* [10] published results that showed significant increases. This controversy might

Figure 4



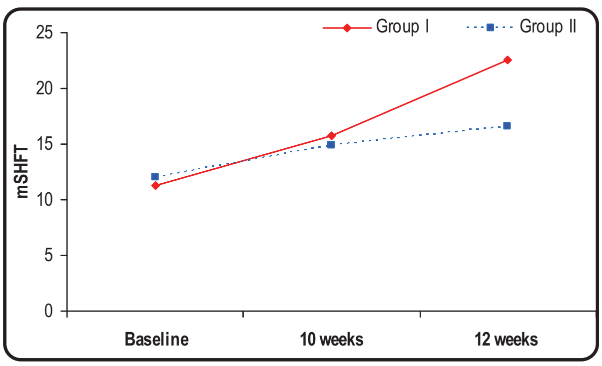
Follow-up chart of pegboard scale (put-on time) between group I and II at baseline, 10 weeks, and 12 weeks.

Figure 5



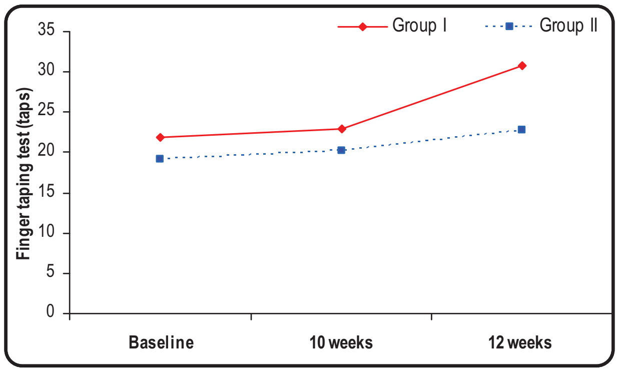
Follow-up chart of action research arm test between group I II at baseline, 10 weeks, and 12 weeks.

Figure 6



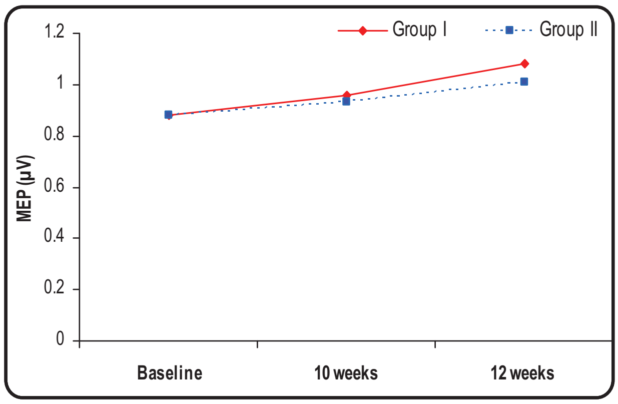
Follow-up chart of modified Sollerman hand function test between group I and II at baseline, 10 weeks, and 12 weeks.

Figure 7



Follow-up chart of finger tapping test between group I and II at baseline, 10 weeks, and 12 weeks.

Figure 8



Follow-up chart of motor evoked potentials between group I and II at baseline, 10 weeks, and 12 weeks.

be due to the difference in the method of assessment, as they assessed only the FIM motor tasks subscores. Whereas our study assessed the total FIM score. The duration of the injury of their patients was also up to 4 months only (subacute cases). Those cases might have a higher incidence of spontaneous resolution of the motor units and tracts in the spinal cord. On the contrary, our study included only chronic patients, 6 months past the injury date.

With respect to the hand function tests in our study, baseline to 10 weeks' assessment of ARAT score showed highly significant improvements ($P<0.001$). Whereas the pegboard scale showed significant improvements with decreases in the mean times taken to remove or put-on the pegs ($P<0.05$). The mSHFT score showed significant increases ($P<0.05$). This was in accordance with the results of Miller [2]. These results supported the evidence that FES had both peripheral and central effects; peripherally it improved the flexibility and range of motion of the affected limbs. It also had a training effect that improved fitness and strength of the remaining motor units, resulting in voluntary efforts becoming more effective, and reduced spasticity in the affected muscles. Also active stretching applied by FES, helped to increase the flexibility of the affected muscles[11]. FES could also be effective in strengthening the corticospinal circuitry. Several studies have demonstrated that voluntary motor training are caused by cortical reorganization [12,13]. Thus, the combination of FES with voluntary training has proven to produce changes in excitability of the motor cortex [13,14]. Popovic *et al.* [9] reported improvements in most of the hand functions following FES, despite including patients with both complete and incomplete SCI. They also used different assessment methods.

Assessment results of hand function tests of group I between 10 and 12 weeks in our study showed highly significant increase in mSHFT and finger tapping test, with a significant increase in ARAT. Whereas, pegboard scale showed significant improvements in the form of a decrease in the mean times of removal or put-on of pegs. These results were similar to that of Belci *et al.* [15], who showed a decrease in the mean times to complete a nine-hole peg test by ~10%. These results are also similar to Gomes-Osman and Field-Fote [16], who indicated significant improvements in the nine-hole pegboard scale. These results supported the concept that high frequency rTMS could increase more the rate of movement rather than the magnitude [16].

In contrast to our results Kuppswamy *et al.* [17], reported only modest improvement in ARAT results post-rTMS, but did not reach significant values. Whereas the pegboard scale showed no significant decrease. This could be attributed to a difference in the protocol applied in their study; rTMS was applied at 5 Hz only, with a total of 900 pulses, for five sessions only, and was not followed by a manual training program. Whereas, our protocol was at 10 Hz, with a total of 1500 pulse followed by a manual training program. Also, the age of their patients were higher than ours.

Moreover, measuring electric perception threshold showed highly significant improvements in 10–12 week assessments. These results were in accordance with Belci *et al.* [15], who showed a decrease in the treatment and follow-up period of average 15%. These results supported the concept that rTMS therapy could increase the activity of the sensory-motor areas, in general, not only the primary motor area. However, our results differed from that of Kuppswamy *et al.* [17], who showed improvements but did not reach significant values.

In our study, MEP showed a significant increase in the amplitude of the MEP, with a mean of 0.96±0.15 and a mean of 1.08±0.12 between pretreatment and post-treatment values. These results were in accordance with Belci *et al.* [15], who applied a protocol of 10 Hz using 720 pulses in doublets per session for 5 days and showed significant reduction in cortical silent period, which is a reflection of intracortical inhibition, more than 30%. These results supported the concept that high frequency rTMS could increase corticospinal tract excitability and, hence, improve the rate of movement [16].

While our results differed from those of Kuppswamy *et al.* [17] and Gomes-Osman and Field-Fote [16], who showed increase in MEPs but did not reach significant values. This could be secondary to a difference in the protocols applied. Gomes-Osman and Field-Fote [16] used 10 Hz frequency for a total of 800 pulses for three sessions, only for 1 week.

Results of the assessments of group II at 10–12 weeks showed improvements, but did not reach significant value (P>0.05) in all the clinical and electrophysiological data measured indicating that the therapeutic effect of FES needs more prolonged time than the TMS to achieve an evident functional improvement.

Since comparison of the clinical and electrophysiological data between the group I versus group II at baseline and 10 weeks showed nonsignificant differences, any changes in the functional parameters of group I at 12 weeks would be attributed to the effect of rTMS if there was no similar changes in group II.

Comparing both groups at 12 weeks, our study showed statistically highly significant increase with respect to finger tapping test in group I more than group II. This goes in accordance with other studies, which suggested that noninvasive brain stimulation might influence the rate of learning rather than its magnitude [16,18,19].

Our study also showed a statistically significant increase in FIM, ARAT, and mSHFT in group I more than group II, whereas the pegboard scale showed a statistically significant decrease with respect to both the put-on and removal times of the pegs more in group I.

Comparing the results of both groups, baseline to 12-week assessments, the MRC scale in group I showed significant increases in the tested muscle groups (thenars, long flexors, and extensors) in group I (P< 0.05), whereas group II showed nonsignificant increases (P>0.05). These results together with our previous results in the MRC scale go in accordance with several studies, which assessed the sensitivities of the MRC scale in detecting the changes in muscle strength following SCIs, and reported that the MRC scale was not sensitive enough to minor changes in muscle strength [20,21]. This probably explained why changes in muscle strength at baseline to 10 weeks and 10–12 weeks' assessments showed no significant values, as they were within the small to moderate ranges. However, baseline to 12 weeks, using FES with the added benefit of real rTMS in group I, showed marked changes in muscle strength and thus, the MRC scale showed significant increases. These findings proved the added value of real rTMS therapy to the FES protocol.Baseline to 12 weeks' assessments in group I showed highly significant improvements in the hand function tests (ARAT and mSHFT) ($P<0.001$), whereas group II showed only significant improvements ($P<0.05$). These differences could be secondary to the added benefits of using real rTMS in group I patients. Also FIM score, finger tapping test, MEP, and surface EMG activity on maximum volition for the long flexor muscles showed significant increases, whereas group II showed nonsignificant increases. These results could support the previous studies in which noninvasive brain stimulation could increase the rate of movement [16,18,19] and cortical excitability [15,22].

In summary, our results confirmed the positive influence of real rTMS added to FES on patients with incomplete SCI when compared with FES and sham rTMS. Real rTMS therapy added to FES led to greater improvement in the hand functions of the patients with incomplete SCI.

Long-term follow-up postrehabilitation would be needed and research on a large number of patients would be required for further studies. Altogether, studying the effects of rTMS therapy on the ability to ambulate, control of sphincters, and muscle tone would be helpful to evaluate the long-term usefulness of this approach.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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