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Effects of High-Frequency Repetitive Transcranial Magnetic Stimulation on Motor and Gait Improvement in Incomplete Spinal Cord Injury Patients

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Abstract

Objective. Incomplete spinal cord injury (SCI) patients have the potential to regain some ambulatory function, and optimal reorganization of remaining circuits can contribute to this recovery. We hypothesized that repetitive transcranial magnetic stimulation (rTMS) may promote active recovery of motor function during gait rehabilitation. *Methods*. A total of 17 incomplete SCI patients were randomized to receive active rTMS or sham stimulation coupled with rehabilitation therapy; 3 patients who began in the sham group crossed over to the active rTMS group after a washout period of more than 3 weeks. Active rTMS consisted of 15 daily sessions over the leg motor area (at 20 Hz). We compared lower-extremity motor score (LEMS), 10-m walking test for walking speed, timed up and go, Walking Index for SCI Scale, Modified Ashworth Scale, and Spinal Cord Injury Spasticity Evaluation Tool at baseline, after the last session, and 2 weeks later in the active rTMS and sham stimulation groups. *Results*. A significant improvement was observed after the last rTMS session in the active group for LEMS, walking speed, and spasticity. Improvement in walking speed was maintained during the follow-up period. Sham stimulation did not induce any improvement in LEMS, gait assessment, and spasticity after the last session and neither during follow-up. *Conclusion*. In incomplete SCI, 15 daily sessions of high-frequency rTMS can improve motor score, walking speed, and spasticity in the lower limbs. The study provides evidence for the therapeutic potential of rTMS in the lower extremities in SCI rehabilitation.

Keywords

incomplete SCI, functional improvement, transcranial magnetic stimulation, rehabilitation

Introduction

The spinal networks involved in locomotion require input from supraspinal structures for adequate control of gait in humans.[1] Only those with motor-incomplete spinal cord injury (SCI) demonstrate improvement in their ability to walk overground following gait training, suggesting that supraspinal centers play a critically important role in the recovery of overground locomotor function.[2-4] Walking function is highly related to motor-evoked potential (MEP) recovery in the tibialis anterior muscle (TA) in SCI patients.[5] Thomas and Gorassini[6] reported that the degree of locomotor recovery after intensive locomotor training correlated positively with the percentage increase of MEP in the TA or vastus lateralis muscle. With functional magnetic resonance imaging, Winchester et al[2] found an increase in activity of the leg motor area after improving gait in persons with SCI.

Spasticity is classically defined as a motor disorder[7] that contributes to impairment of voluntary movements in SCI.[8] Improvement in spasticity might induce some improvement in motor strength in the lower extremity.[9]

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive and painless procedure to modulate cortical

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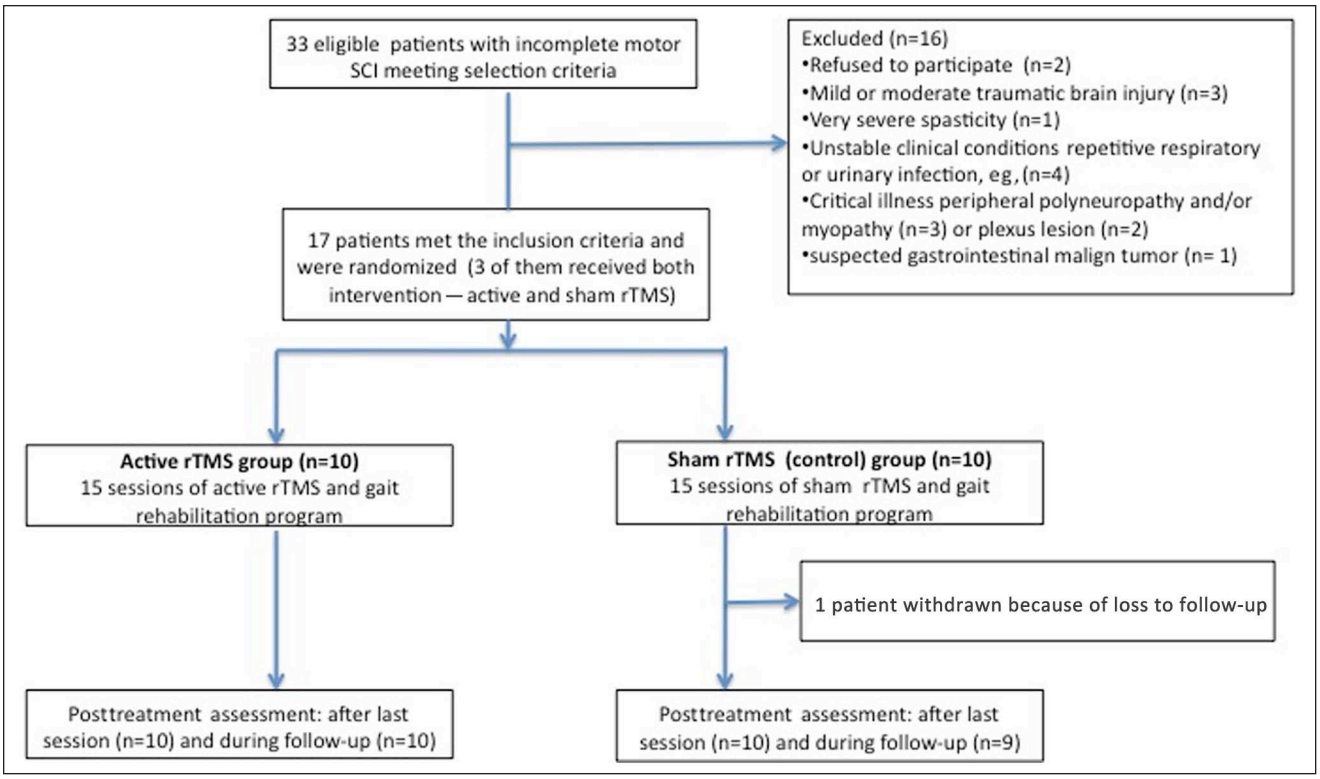

Figure 1. Flow diagram of patient categorizations. Abbreviations: SCI, spinal cord injury; rTMS, repetitive transcranial magnetic stimulation.

excitability of motor areas and induce changes over the descending corticospinal output.[10-12] This modulation may be useful to promote active recovery of motor function and to obtain functional benefit from gait rehabilitation. Through the use of repetitive high-frequency rTMS, improvement has been reported in motor and sensory functions measured by the American Spinal Cord Injury Association (ASIA) Impairment Scale (AIS) and time to complete a peg-board task in 4 chronic incomplete cervical SCI patients.[10]

Here we hypothesized that high-frequency rTMS coupled with gait training can improve motor recovery in the lower extremities and locomotion in incomplete SCI patients to a greater degree than sham stimulation.

Methods

The study was a randomized, double-blind, sham-controlled trial. We recruited 17 patients with SCI (see details in the following) to be randomly distributed in 2 study groups: an active rTMS group and a sham group. Three patients who began in the sham group were crossed over to the active rTMS group after a washout period of more than 3 weeks. Therefore, 10 individuals were studied in each group. All patients underwent 15 consecutive daily sessions (3 weeks) of active or sham rTMS. Patients and investigators were blinded to the treatment arm except for HK, who applied rTMS.

Patients

Inclusion criteria were the following: (1) incomplete SCI AIS-D,[13] with possible gait capacity; (2) cervical or thoracic SCI; (3) time lapse since SCI between 3 and 12 months; (4) no changes in medical treatment at least 1 week before and during the study; (5) no limitation of passive range of movement in joints; and (6) written informed consent for the study, which was approved by the institutional review board of Institut Guttmann. All patients were naive to rTMS and unaware of the purpose of the study.

A total of 33 individuals were identified as potential participants for this study, and 17 gave informed consent and participated in the study (Figure 1). All patients received standard care for SCI rehabilitation at our institution. The program comprises 5 hours of therapy 5 days per week, including training in activities of daily living, occupational therapy for the upper extremities for patients with cervical SCI, fitness training, sports, hydrotherapy, and gait training.

Patients received daily gait training therapy (5 d/wk) during the 3 weeks of rTMS session and for 2 more weeks during follow-up. Each training session lasted 1 hour and consisted of overground gait training assisted by a therapist

using orthesis and technical aids as needed, in accordance with the functional level of each patient. The session of overground gait training was performed immediately (within less than 30 minutes) after active or sham rTMS sessions for all patients.

Clinical and Functional Assessment

Primary outcome measurements included the following: (1) lower-extremity motor score (LEMS), obtained from the standardized AIS clinical exam[14]; (2) 10-m walking test (=time in seconds to walk 10 m) for walking speed[15] (patients were asked to walk at their fastest but most comfortable speed); (3) timed up and go (TUG) test[16]; and (4) Walking Index for SCI Scale (WISCI-II; to quantify walking ability).[17]

Secondary outcome measures included the following: (1) Modified Ashworth Scale (MAS) evaluated at both knees for spasticity assessment[18] and (2) the Spinal Cord Injury Spasticity Evaluation Tool (SCI-SET).[19]

rTMS Protocol

Patients received 15 rTMS sessions, 5 d/wk for 3 weeks, in the morning between 9:00 and noon. We used a MagStim Super Rapid magnetic stimulator (MagStim Company, Whitland, Wales, UK) equipped with a commercially available double-cone coil (each wing measuring 110 mm in diameter), which was held over the vertex. All active and sham rTMS sessions were conducted at rest, with the patient lying supine.

For active (real) rTMS, we applied 2-s long bursts at 20 Hz (40 pulses/burst) with intertrain intervals of 28 s, for a total of 1800 pulses over 20 minutes. These rTMS parameters were selected for this study because when we used it in patients with incomplete SCI for spasticity, some of our patients reported better gait function (data not reported in the article).[20] Also, according to previous publications, the magnitude and duration of the after-rTMS effects seem to depend on the total number of stimuli, with longer periods of rTMS inducing a more consistent and persistent change in corticospinal excitability.[11,21,22]

Electromyographic recordings (EMGs) were obtained with pairs of Ag-AgCl surface EMG electrodes placed over the first dorsal interosseous, abductor pollicis brevis, and biceps brachii muscles. We also recorded motor threshold at rest (RMT) in TA on both sides. The intensity of repetitive TMS was set at 90% RMT of the upper-extremity muscles.

For motor threshold determination, the double-cone coil was held lateral to the vertex over the optimal scalp position overlying the contralateral hemisphere to the less-affected side from SCI, from which single-pulse TMS evoked responses of maximum amplitude in muscles in the upper extremity. The EMG signal was amplified (×50) with filters set as 10 to 2000 Hz. RMT was defined as the lowest intensity that elicited MEPs of >50 μV peak-to-peak amplitude in at least 5 of 10 consecutive stimulations.

For sham stimulation, the double-cone coil was held over the vertex but was disconnected from the main stimulator unit. Instead, a second coil (8-shaped) was connected with the MagStim stimulator and discharged under the patient's pillow. Thus, no current was induced in the brain, and although the patients did not experience a tapping sensation on the scalp, they were exposed to a similar clicking noise. When explicitly asked at the end of the trial, 8 of the 10 patients in the sham stimulation group thought that they had received active stimulation; 2 patients were not sure whether it was active or sham stimulation.

Experimental Design

The experimental protocol included the following steps:

1. Clinical and functional assessment at baseline
2. After the first rTMS session, spasticity reevaluation by MAS
3. Daily rTMS sessions for 14 additional days
4. Clinical and functional assessment after completion of the 15th rTMS session
5. Follow-up of functional outcomes (gait) 2 weeks after the last session of rTMS and spasticity reevaluation by SCI-SET.

Data Analysis

MAS was calculated for both knees and the results averaged. Data are presented as mean ± standard deviation. Change scores were calculated by subtracting baseline data from the last session of rTMS data and from follow-up period data.

Because the distribution of the data was not normal according to the Kolmogorov-Smirnov test, the Friedman test was used for multiple repeated-measures comparisons and the Wilcoxon t for post hoc comparisons. The Mann Whitney U test and χ^2 test were used to compare data between different groups of patients. The significance level was set as $P < .01$, with Bonferroni correction for multiple comparisons.

Spearman ρ was used to study correlations between the absolute value of MAS or of SCI-SET and LEMS or gait function and between the change scores in LEMS, SCI-SET, and gait functions. The significance level was set as $P < .05$.

Results

Demographic and clinical characteristics of the patients included in the study are summarized in Table 1. Both groups were homogeneous for age, gender, time lapse since injury, etiology, AIS scale, and LEMS for active and sham

Table 1. Clinical and Demographic Characteristics of Patients.

rTMS	Sex	Age, y	Neurological Lesion Level	AIS	Time Since SCI, mo	Etiology	Pharmacological Treatment
Active	M	29	T12	D	8	Trauma	Baclofen, gabapentin
Active[a]	M	19	T1	D	6	Tumor	Baclofen, fluoxetina
Active	M	47	C6	D	8	Trauma	Baclofen
Active	M	21	C5	D	9	Trauma	Baclofen
Active	F	51	T7	D	12	Tumor	Clonazepam
Active	M	60	T7	D	3	Infection	Baclofen
Active[a]	M	19	T5	D	12	Myelitis	Baclofen, fluoxetina
Active[a]	M	24	C6	D	5	Trauma	Baclofen
Active	F	40	C4	D	8	Trauma	Baclofen, venlafaxina, tizanidina
Active	M	21	T2	D	12	Trauma	Baclofen
Sham[a]	M	18	T1	D	4	Tumor	Baclofen, fluoxetina
Sham	M	50	C4	D	5	Trauma	Gabapentin, clonazepam, venlafaxina
Sham[a]	M	18	T5	D	9	Myelitis	Baclofen, fluoxetina
Sham	M	56	C6	D	10	Trauma	Baclofen
Sham	M	34	T7	D	11	Infection	Baclofen
Sham	M	37	T3	D	12	Trauma	Sirdalud, baclofen
Sham[a]	M	24	C6	D	3	Trauma	Baclofen
Sham	F	41	T2	D	5	Infection	Diazepam, gabapentin, mirtazapina
Sham	M	54	T3	D	3	Infection	Lorazepam
Sham	F	33	C5	D	6	Tumor	—

Abbreviations: rTMS, repetitive transcranial magnetic stimulation; M, male; F, female; C, cervical; T, thoracic; AIS, American Spinal Cord Injury Association (ASIA) Impairment Scale.
[a]Three patients who received sham stimulation first and then received active stimulation after at least a 3-week washout period.

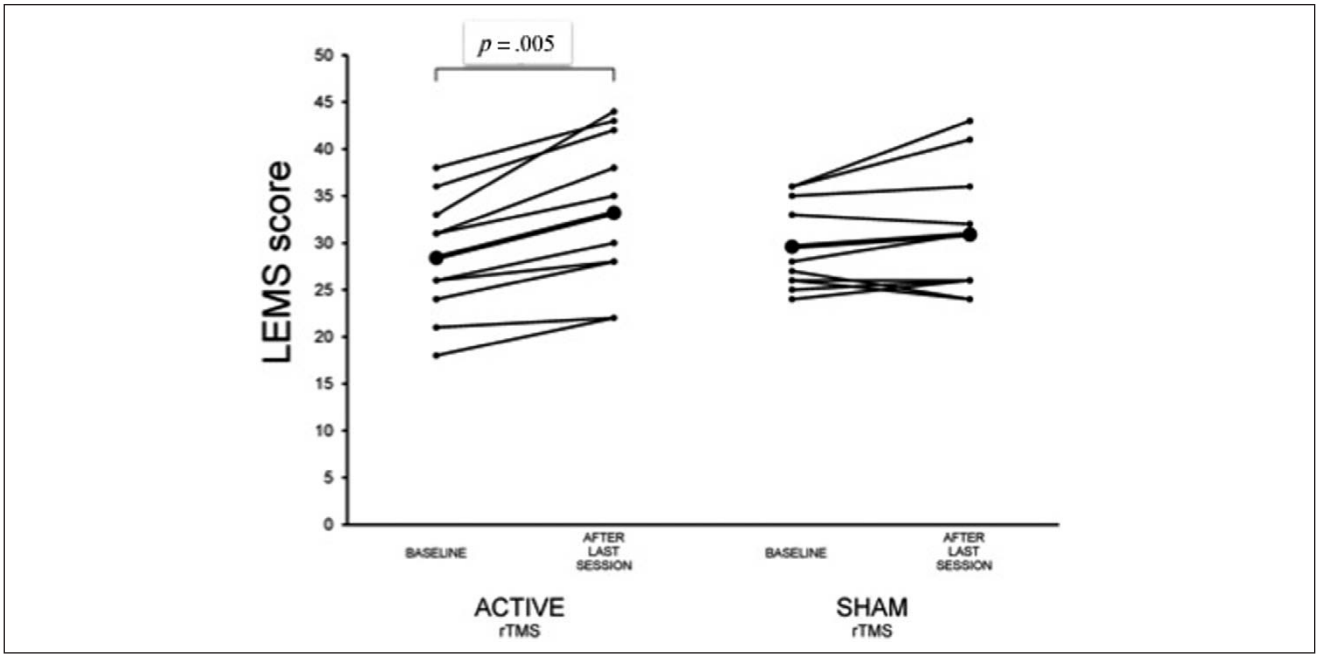

Figure 2. Total motor score in the lower extremities at baseline and after the last rTMS session for each studied patients (small black circle) and the average of the each group (big black circle). Abbreviations: LEMS, lower-extremity motor score; rTMS, repetitive transcranial magnetic stimulation.

Table 2. Change Scores for Spasticity and Functional and Clinical Assessment After First and Last Session of rTMS and During the 2-Week Follow-up Period in Active and Sham rTMS.[a]

	First Session			Last Session			Follow-up		
	Active	Sham	*P*	Active	Sham	*P*	Active	Sham	*P*
LEMS	—	—		4.80 (2.78)	1.30 (3.09)	.006	NA	NA	
Walking speed	—	—		0.16 (0.20)	0.08 (0.21)	.20	0.25 (0.24)	0.14 (0.24)	.14
TUG	—	—		−26.0 (20.17)	−16.0 (19.01)	.40	−35.1 (26.76)	−17.2 (26.82)	.43
WISCI-II	—	—		1.6 (2.41)	2.0 (2.56)	.93	1.5 (2.32)	3.0 (2.47)	.54
MAS	−0.68(0.35)	0.18 (0.2)	<.0001	−0.70 (0.55)	0.28 (0.66)	.001	NA	NA	
SCI-SET	—	—		0.36 (0.32)	0.04 (0.42)	.02	0.44 (0.57)	0.13 (0.35)	.04

Abbreviations: rTMS, repetitive transcranial magnetic stimulation; LEMS, lower-extremity motor score; TUG, timed up and go; WISCI-II, walking index for SCI; SCI, spinal cord injury; MAS, Modified Ashworth Scale; SCI-SET, spasticity evaluation tool; NA, not available.
[a]Change scores were expressed as mean (standard deviation) for each group. *P* value: comparison is between active versus sham rTMS groups.

groups (Table 1 and Figure 2). The mean age of patients in the active rTMS group was 32.9 ± 15.4 years and 36.5 ± 13.9 years in the sham rTMS group. The mean time lapse since injury was 8.3 ± 3.1 months in the active rTMS group and 6.8 ± 3.4 months in the sham rTMS group.

At baseline, MEPs could be obtained in the TA in only 5 patients, 3 assigned to the active rTMS group (with an RMT of 60%, 48%, and 80%) and 2 assigned to the sham rTMS group (with an RMT of 48% and 86%). In all other patients, we were unable to elicit MEPs in the TA even at 100% TMS intensity. The motor threshold in the TA did not change after 15 days of rTMS sessions in both groups. The mean rTMS intensity used for active rTMS was 39.8% ± 5.8% of maximum stimulator output.

Adverse Effects

All patients tolerated the study without complications, and no adverse effects were reported, with the exception of 6 patients who complained of a slight twitching of facial muscles during the first session of active stimulation.

Between-Group Comparisons

Absolute mean values at baseline for LEMS, walking speed, TUG, and WISCI-II were similar in both sham and active rTMS groups (Mann-Whitney *U* test, $P > .2$ for all comparisons). At baseline, patients included in the sham group had a significantly lower MAS score than those included in the active rTMS group (Mann-Whitney *U,* $P = .04$). There were no between-group differences in SCI-SET (Mann-Whitney *U,* $P = .39$). There were no differences between the active and sham rTMS groups at the end of the last session of rTMS and during follow-up in LEMS and gait scales, MAS, and SCI-SET (Mann-Whitney *U* test, $P > .1$ for each comparison).

Change scores revealed significant improvement in LEMS and in spasticity measured by MAS after 3 weeks of active rTMS in comparison to sham rTMS (Table 2). Improvement in gait parameters was larger in the active rTMS group than in the sham group, but the change scores reached no significant level, neither after the last session of rTMS nor during the follow-up period (Table 2).

Within-Group Comparisons

Primary outcome measurements. Total lower-extremity muscle strength (ie, LEMS) improved significantly (Table 3, Figure 2) after the last session in the active rTMS group (Wilcoxon *t,* $P = .005$) but not in the sham group (Wilcoxon *t,* $P = .25$).In the 3 patients who received both stimulations, LEMS improved 18.6% with active rTMS and 3% with sham rTMS.

In patients who received active rTMS, walking speed showed significant improvement after the last session, and the effect was maintained during follow-up ($P < .01$ for all comparisons; Table 3, Figure 3). No significant changes were observed in the TUG and WISCI-II (Table 3, Figure 3).

Secondary outcome measurements. There was significant reduction of spasticity according to MAS after the first and last sessions in the active rTMS group (Wilcoxon *t,* $P = .0001$ for both comparisons; Table 3) but not in the sham rTMS group. SCI-SET did not change significantly after the last session or during the follow-up period in both groups (Table 3).

Correlation Analysis

The change scores of LEMS were significantly correlated with the change scores of walking speed in the active rTMS group ($\rho = 0.708$; $P = .02$) but not in the sham rTMS group ($P = .06$). There was no correlation between absolute value of gait scales and MAS and SCI-SET. The change scores of gait scales were not correlated with the change scores of SCI-SET at any time of evaluation in both groups (Spearman ρ, $P > .1$ for each comparison).

Table 3. Primary and Secondary Outcome Measurements.[a]

	rTMS	Baseline	First Session	Last Session	Follow-up
Primary outcome measures					
LEMS	Active	28.4 (6.8)	NA	33.2 (8.8)[b]	NA
	Sham	29.6 (4.8)	NA	30.9 (7.0)	
Walking speed	Active	0.24 (0.32)	NA	0.40 (0.44)[b]	0.48 (0.53)[b]
	Sham	0.26 (0.20)	NA	0.34 (0.26)	0.39 (0.31)
TUG	Active	84.6 (76.19	NA	62.1 (57.9)	54.11 (46.0)
	Sham	74.0(55.84)	NA	49.0 (40.1)	43.4 (41.1)
WISCI-II	Active	9.50 (5.7)	NA	11.1 (4.4)	11.0 (4.4)
	Sham	10.6 (5.2)	NA	12.1 (4.6)	13.1 (4.3)
Secondary outcome measures					
MAS	Active	2.30 (0.8)	1.62 (0.77)[b]	1.60 (0.9)[b]	NA
	Sham	1.30 (0.7)	1.58 (0.76)	1.78 (0.7)	NA
SCI-SET	Active	−067 (0.4)	NA	−0.31 (0.5)	−0.23 (0.5)
	Sham	−0.47 (0.9)	NA	−0.43 (0.8)	−0.34 (0.7)

Abbreviations: LEMS, lower-extremity motor score; TUG, timed up and go; WISCI-II, walking index for SCI; SCI, spinal cord injury; MAS, Modified Ashworth Scale; SCI-SET, spasticity evaluation tool; rTMS, repetitive transcranial magnetic stimulation; NA, not available.

[a]The data show mean (standard deviation, Wilcoxon test) of LEMS, walking speed, TUG test, WISCI-II, MAS, and SCI-SET at baseline, after first and last sessions of rTMS, and during follow-up.

[b]$P < .01$ in comparison to baseline.

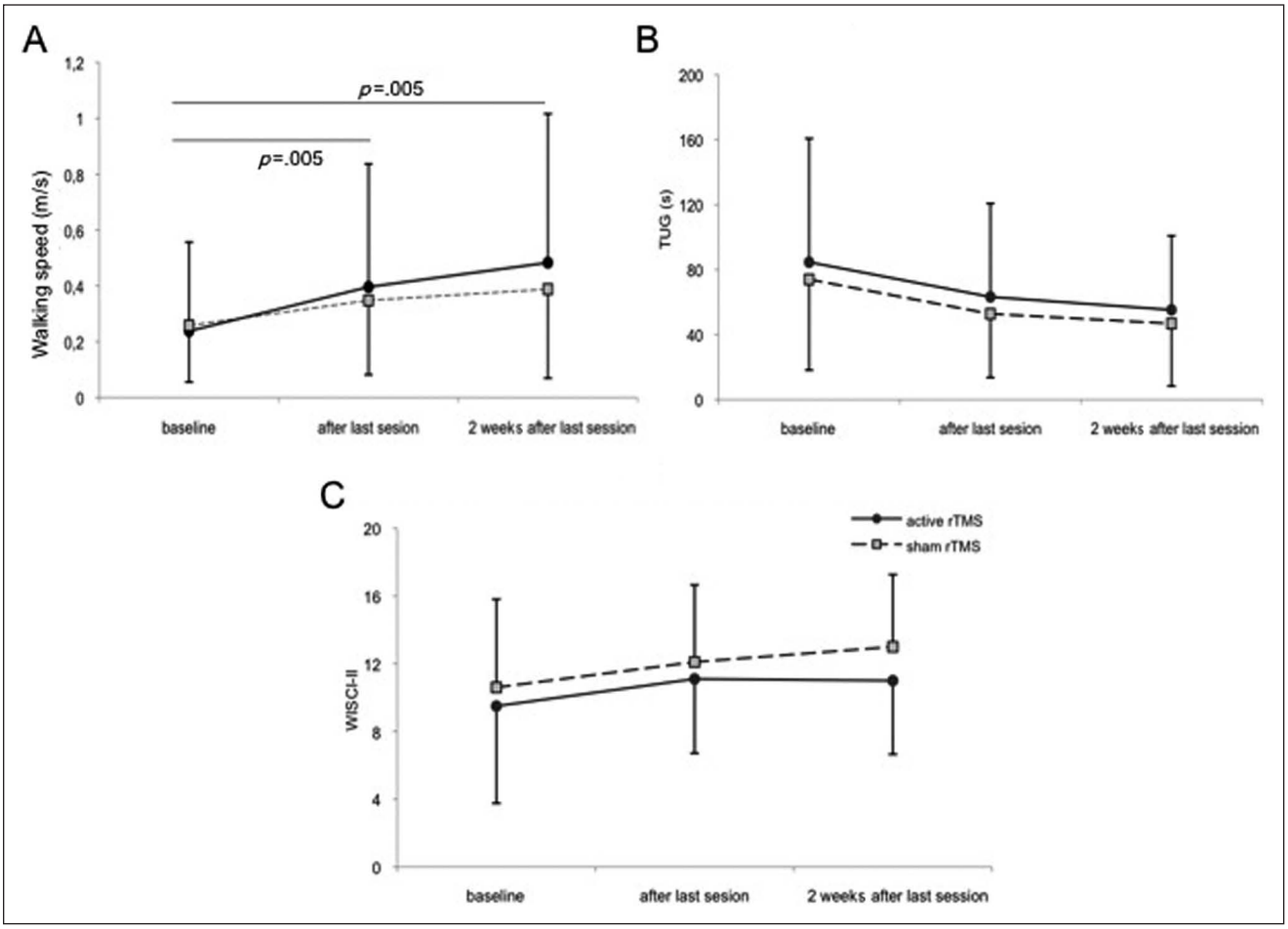

Figure 3. Gait scales at baseline, after the last rTMS session and during follow-up period (2 weeks after the last session). Abbreviations: TUG, timed up and go; WISCI-II, walking index for SCI; SCI, spinal cord injury; rTMS, repetitive transcranial magnetic stimulation.

Discussion

The main findings of our study are a significant improvement in LEMS, walking speed, and spasticity after high-frequency rTMS in motor-incomplete SCI patients. The main effects of 15 daily sessions of stimulation on LEMS and walking speed were found in the active rTMS group after the treatment, and it lasted for at least 2 weeks during the follow-up period. In contrast, patients receiving sham stimulation did not show any improvement in clinical and functional assessment after treatment or during follow-up.

Our results demonstrate that high-frequency rTMS combined with rehabilitation therapy can be more effective in the management of motor impairment and spasticity in lower limbs following incomplete SCI than rehabilitation therapy coupled with placebo. In the literature, Belci et al[10] reported improvement in general motor score (upper and lower extremities) and in upper-extremity function in 4 patients with incomplete chronic cervical SCI after applying high-frequency rTMS over the vertex for 5 days. High-frequency rTMS at subthreshold intensity can lead to an increase in regional glucose metabolism immediately after the end of the stimulation, suggesting the possibility of an rTMS-induced increase in overall neuronal activity in the stimulated motor area (M1).[23] The magnitude and duration of the after effects seem to depend on the intensity and the total number of stimuli, with longer periods of rTMS inducing a more consistent and persistent change in corticospinal excitability.[11,21,22] The facilitation of corticospinal excitability induced by high-frequency rTMS could be long lasting.[20,24,25] According to the other study, rTMS also could reduce corticospinal inhibition, which consequently could induce motor improvement in SCI.[10] It is possible that motor score improvement and amelioration of spasticity with rTMS in SCI can be induced through enhancement of descending corticospinal projections and/or reduction in corticospinal inhibition.[20] Enhancement of descending corticospinal projections may induce amelioration of spasticity through some effect on propriospinal interneurons, as has been hypothesized before.[20,24] Further studies are needed to understand the effect of rTMS on the improvement of spasticity.

Our results showed also that there was improvement in walking speed in the active rTMS group, which was correlated with the improvement in LEMS. Supraspinal centers are activated during locomotion, especially to provide equilibrium and visuomotor control and to coordinate leg responses.[26] In patients with SCI, MEP amplitudes in the TA seem to allow for prediction of recovery of function mediated by the corticospinal tracts.[5,6] Furthermore, walking function is highly related to MEP recovery in the TA in these patients.[5] It is striking that the length of time since injury onset in SCI may have affected the efficacy of synaptic plasticity within the spinal cord, within supraspinal centers, or between those centers.[26,27] It is possible that some improvement in gait function can be induced through the facilitation of corticospinal excitability,[20,24,25] with reduction in corticospinal inhibition[10] and with motor score improvement in the lower limbs. In this study, LEMS with active rTMS improved 4.8 out of 50 in 3 weeks, which was correlated with walking speed. This did not occur with sham rTMS, in which LEMS improvement was 1.3 out of 50. Prior studies had shown that the higher the LEMS, the more likely a patient was to recover the ability to walk without physical assistance.[28,29] Greater motor control for walking in terms of walking speed and strength was found as the LEMS approached and exceeded 40 of a possible 50 points.[30] In this study, the mean time since SCI was 4.5 weeks, and reevaluation was done in 12 weeks.[30] However, in our patients, the mean time since SCI was 6.8 months, and reevaluation was done in 3 weeks.

Timing of stimulation during performance of a psychological task is crucial to producing a TMS-related effect.[31,32] Production of facilitatory effects appears to be time dependent. In studies reporting facilitation, TMS is often applied immediately before a block of trials[31] or, within each trial, immediately before a response is to be made.[32] In our patients, rTMS was applied less than 30 minutes before onset of training therapy.

Improvement in LEMS and some gait parameters with rTMS was maintained during the follow-up period. Previous studies have demonstrated that cumulative plastic changes can be produced by rTMS in healthy participants[33] as well as in those with SCI,[20] multiple sclerosis,[24] and stroke.[25] Another mechanism might be that repeated episodes of long-term potentiation (LTP) lead to remodeling with an increase in active synapses.[34,35] LTP is a long-lasting enhancement in signal transmission between 2 neurons that results from stimulating them synchronously.[36] One of several phenomena underlying synaptic plasticity is the ability of chemical synapses to change in strength. LTP is widely considered to be one of the major cellular mechanisms that underlie learning and memory.[36]

The limitations of our study are as follows: (1) the stimulation intensity applied during active rTMS was relatively low for leg muscles (90% RMT in the lowest muscle threshold of the upper extremity because of absent MEP in the lower extremity in most patients or very high RMT in the 3 other patients); (2) the time lapse since SCI was less than 12 months, which limits the possibility of spontaneous or training-induced recovery to that time; however, according to the literature, greater gains in gait function in SCI occur when training is begun earlier (<6 months postinjury),[37] and in this study, only 2 patients from the active rTMS had less than 6 months of evolution, in contrast to 5 patients from the sham group; (3) our patients had variable causes of SCI, and it is unknown whether or not the natural progression of improvement in the first 6 months differs based on SCI

etiology; (4) another possible weakness of our study is that improvement in gait parameters may occur when the participant becomes familiar with a given test; to rule out learning the test, inclusion of multiple baseline tests would have been preferable; and (5) MAS used for spasticity evaluation has poor reliability in SCI.[15]

In conclusion, our results indicate that rTMS combined with gait training is beneficial for motor recovery in the lower limbs, walking speed, and reduction of spasticity in SCI patients. Based on the small effect size for the LEMS and walking speed, a larger trial may need approximately 75 to 100 subjects in each arm to determine efficacy with a moderate effect size for the experimental intervention. At a more conceptual level, our findings show potential advantages of combining rehabilitation strategies with noninvasive brain stimulation techniques to optimize outcome. These beneficial effects were achieved with minimal side effects and with good tolerability. Challenges that remain include exploring the optimal dose and timing of stimulation, developing better strategies for rehabilitation therapy, determining the most responsive characteristics of SCI patients, and examining how to extend the duration of motor and functional improvement to the long term in a larger sample population after SCI.

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Declaration of Conflicting Interests

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