Research article

The effect of repetitive transcranial magnetic stimulation on refractory neuropathic pain in spinal cord injury

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Objective: To investigate the analgesic effect of repetitive transcranial magnetic stimulation (rTMS) on intractable neuropathic pain in patients with spinal cord injury (SCI).

Design: A single center, prospective, randomized, double-blinded, controlled study.

Setting: SCI rehabilitation unit of university rehabilitation center.

Participants: Seventeen patients with SCI and chronic neuropathic pain who met the inclusion criteria recruited between April 2010 and January 2012.

Interventions: Ten daily treatment sessions of real or sham rTMS (30 trains of 10-Hz stimuli for a duration of 5 seconds; a total of 1500 pulses at intensity equal to 110% of the resting motor threshold) was applied over vertex using a figure-of-8-shaped coil.

Outcome measures: Pain was assessed with visual analog scale (VAS) at baseline and 10 days, 6 weeks and 6 months after the treatment. Patients' satisfactions obtained using a 5-point Likert scale at 6 months.

Results: Both real and sham rTMS provided a significant reduction in the VAS scores (real rTMS group, $P = 0.004$; sham rTMS group, $P = 0.020$). *Post hoc* analysis revealed the significant difference was at 10 days and 6 weeks compared to baseline in the real rTMS group and only at 10 days compared to baseline in the sham rTMS group. Comparison of VAS scores and patient satisfaction did not show any significant difference at each assessment point ($P > 0.05$).

Conclusion: Our results demonstrated analgesic effect of rTMS on intractable neuropathic pain in SCI was not superior to placebo. However, middle-term (over 6 weeks) pain relief by rTMS is encouraging and suggests the need for future studies with a larger sample size.

Keywords: Pain, Spinal cord injury, Repetitive transcranial magnetic stimulation

Introduction

Neuropathic pain is one of the most challenging complications after spinal cord injury (SCI) and can have a significant impact on daily living. Pharmacological and interventional therapies are generally tried but have mostly limited success.^{1,2} Brain stimulation techniques have been used to control chronic neuropathic pain by directly altering brain activity in various conditions such as post-stroke pain and trigeminal neuralgia.³ Repetitive transcranial magnetic stimulation (rTMS) as one of a non-invasive brain stimulation technique has been suggested to be more beneficial in the treatment of neuropathic pain of central origin.⁴ Therefore,

a series of magnetic stimulation of the motor cortex seems to be a treatment option for neuropathic pain in SCI. However, previous studies on this topic presented controversial results. Defrin *et al.*⁵ reported improvement in pain with rTMS, which was similar to sham. Whereas Kang *et al.*⁶ reported no reduction in pain. We conducted a randomized controlled trial to investigate the analgesic effect of rTMS on neuropathic pain, which could not be treated with conventional therapies and assess long-term results in patients with SCI.

Methods

Seventeen patients who were recruited from the inpatient SCI Rehabilitation Unit of our rehabilitation center between April 2010 and January 2012 participated in

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the study. Inclusion criteria for the study were (i) chronic paraplegia for more than a year, (ii) chronic neuropathic pain below the lesion level, with a minimum duration of 12 months, (iii) pain not attributable to any other cause such as rheumatologic disorders or diabetes, and (iv) pain that is resistant to pharmacological (anticonvulsants, antidepressants, narcotics) and interventional treatments. Patients having epileptic attacks, metal implants in the head and neck, cardiac pacemaker, and psychiatric illness were excluded. All participants provided written informed consent, and the study was approved by the Local Ethics Committee of Gülhane Military Medical Academy.

This study was designed as a prospective, randomized, double-blinded, clinical trial. We compared real and sham rTMS. The patients were randomized to receive one treatment session of either real or sham rTMS a day for 10 days. A computer-generated randomization schedule was used. In the real rTMS sessions, 30 trains of 10-Hz stimuli for a duration of 5 seconds at an inter-train interval of 25 seconds, a total of 1500 pulses, was applied. Total duration of a rTMS session was 15 minutes at intensity equal to 110% of the resting motor threshold.⁷ A figure-of-8-shaped coil (each loop 70 mm in outer diameter) connected to a Magstim Rapid2 Magnetic Stimulator (Magstim, Whitland, Dyfed, UK) was used for stimulation of the motor cortex. The patients received the rTMS, while sitting in a comfortable chair or their wheelchair. The intersection of the coil was placed tangentially to the scalp with the handle pointing backward over the vertex. The vertex is the projection of motor cortex area corresponding to the lower extremities in which part of the body all the patients felt the pain. Resting motor threshold was determined with 1% TMS machine = output increment as the minimal stimulus intensity required to produce motor evoked potentials of >50 μ V in 5 out of 10 consecutive trials in the flexor pollicis brevis muscle. A muscle in the hand was chosen, because the neural tracts to lower extremities were not intact in a patient with paraplegia. The

average of the left and right side resting motor threshold was used to determine stimulation intensity. In the sham group, the same protocol was used but the coil was angled away from the head. The patients and the researcher evaluating the patients were blinded to type of rTMS. The patients in the sham group were offered a real rTMS treatment sessions after follow-up period.

Pain was assessed with 10-cm visual analog scale (VAS) at baseline, 10 days (immediately after the 10th treatment session), 6 weeks after the treatment sessions, and 6 months after the treatment sessions. “0” and “10” on the VAS was set as “no pain at all” and “worst pain imaginable”, respectively. Patients’ satisfactions with the treatment obtained using a five-point Likert scale from strongly dissatisfied through strongly satisfied at 6 months.

Data analysis was performed by using SPSS for Windows, version 13.0 (SPSS Inc., Chicago, IL, USA). Data were shown as mean $\pm$ standard deviation or medians and interquartile range, where applicable. Mann–Whitney *U* test was applied for comparisons between the groups. Repeated measures comparisons within the groups were evaluated by Friedman test. *Post hoc* analysis with Wilcoxon signed rank tests was conducted with a Bonferroni correction. A *P* value less than 0.05 was considered statistically significant.

Results

Seventeen patients with SCI were recruited for this study. Patients were grouped into the real ($n = 9$) and sham ($n = 8$) rTMS groups. One patient in the sham group who was obliged to quit the treatment after first session for personal reasons withdrew from the study. Sixteen patients completed the study and analyzed (mean age, 38.6 ± 6.5). Both groups showed similar baseline characteristics (Table 1). SCI levels and pain sites⁸ of the patients demonstrated in Table 2.

Repeated measures comparisons within the groups by Friedman test revealed an overall significant difference in the VAS scores for both groups (real rTMS group, $P = 0.004$; sham rTMS group, $P = 0.020$) (Fig. 1). *Post*

Table 1 Patients characteristics

	Real rTMS group ($n = 9$)	Sham rTMS group ($n = 7$)
Age (years)	40.0 ± 5.1	36.94 ± 8.0
Sex (male/female)	9/0	7/0
Mean time after SCI (months)	142.9 ± 92.8	123.4 ± 101.5
Duration of pain (months)	32.3 ± 25.9	35.4 ± 17.9
Type of SCI (complete/incomplete)	5/4	5/2
Baseline pain intensity*	7.0 (7.0–8.0)	7.0 (7.0–7.0)

rTMS, repetitive transcranial magnetic stimulation; SCI, spinal cord injury.

*Median (interquartile range).

Table 2 SCI levels and pain sites of the patients

Patients	Group	SCI Level	ASIA Classification grade	Pain sites*
1	Real	T10	D	Both upper legs/lower legs
2	Real	T11	B	Both upper legs/lower legs
3	Real	T4	A	Both buttocks/both legs
4	Real	T12	D	Both upper legs/lower legs
5	Real	T11	A	Both lower legs
6	Real	T12	A	Both upper legs/lower legs
7	Real	T12	C	Left upper leg/genitals
8	Real	T11	B	Both upper legs/lower legs
9	Real	T4	A	Both upper legs/lower legs
10	Sham	L1	B	Both upper legs/lower legs
11	Sham	T10	A	Both buttocks/both legs
12	Sham	T12	A	Genitals/both upper legs/lower legs
13	Sham	T12	B	Low upper leg/low lower leg
14	Sham	T12	A	Both lower legs
15	Sham	T6	C	Both upper legs/lower legs
16	Sham	T11	A	Both upper legs/genitals

ASIA, American Spinal Injury Association.

*Pain sites are described according to the International Spinal Cord Injury Pain Basic Data Set.⁸

Figure 1 Changes in the VAS scores over time. There was a significant reduction in the VAS scores for both groups (real rTMS group, $P = 0.004$; sham rTMS group, $P = 0.020$). (**Post hoc* analysis showed the reduction was significant at 10 days and 6 weeks compared to baseline in the real rTMS group [1A] and was significant only at 10 days compared to baseline in the sham rTMS group [1B]). rTMS, repetitive transcranial magnetic stimulation; VAS, visual analogue scale.

Table 3 Comparison of study outcome data* between the real and sham rTMS groups

	Real rTMS group	Sham rTMS group	P values
VAS			
Baseline	7.0 (7.0–8.0)	7.0 (7.0–7.0)	>0.05
10 days	5.0 (3.5–7.5)	6.0 (4.0–7.0)	>0.05
6 weeks	5.0 (3.5–7.5)	7.0 (6.0–7.0)	>0.05
6 months	7.0 (6.5–8.0)	7.0 (6.0–7.0)	>0.05
Patients satisfaction	3.0 (1.0–5.0)	1.0 (1.0–2.0)	>0.05

rTMS, repetitive transcranial magnetic stimulation; VAS, visual analog scale.

*Median (interquartile range).

hoc analysis showed that there was a significant reduction in the VAS scores at 10 days and 6 weeks compared to baseline in the real rTMS group. In the sham rTMS group, a significant reduction was seen only at 10 days compared to baseline. There was no significant difference between the groups in terms of VAS scores at

all assessment points and patients' satisfactions ($P > 0.05$) (Table 3).

Discussion

Both real and sham rTMS demonstrated analgesic effects on refractory neuropathic pain in patients with

SCI. Pain relief was seen over a month after the treatment sessions in the real rTMS group. The sham rTMS group presented a pain relief immediately after the treatment sessions. However, comparison of the groups did not show any significant difference at each assessment point. There was also no pain relief provided by the real or sham rTMS at 6-month follow-up.

Our results are consistent with the study of Defrin *et al.*⁵ who compared a series of rTMS in central pain of spinal origin to sham stimulation and found similar significant reduction in pain scores by the real and sham rTMS immediately after 10 treatment sessions. In the follow-up visits after 2–6 weeks after the treatment, real and sham rTMS groups reported 30 and 10% reduction in chronic pain, respectively. In this study, 5 Hz of high frequency rTMS was applied to vertex represented to lower extremities motor cortex area, which was similar to our study protocol. In the study of Kang *et al.*,⁶ hand motor cortex area was targeted for rTMS to induce analgesic effect on chronic central pain in patients with SCI. Both real and sham rTMS did not provide a significant reduction in average pain after a 5-day treatment.

Analgesic mechanism of motor cortex stimulation is speculated to depends on altering activity and induce plastic changes in the motor cortex area and its projection to sites of brain involved in pain processing such as thalamic nuclei, anterior cingulate cortex and brainstem periaqueductal gray matter.⁹ Imaging studies showed the modulation of activity in this brain region.^{10,11} A recent meta-analysis suggests rTMS applied to the motor cortex provide short-term pain reduction in various chronic neuropathic pain states. The results for medium-term (≤ 6 weeks) and long-term pain relief are controversial.³ Our results are in agreement with this meta-analysis and did not demonstrate a beneficial long-term effect of rTMS on chronic pain in patients with SCI.

The main limitation of this study is the small sample size. A type II error may be responsible for the results of the study that did not demonstrate the superiority of rTMS compared to sham. Future studies in larger population are needed to reduce this risk. Lack of navigation for rTMS¹² may be regarded as another limitation of the study. Localization of the motor cortex corresponding to lower extremities by motor evoked potential responses is impossible in patients with paraplegia. Therefore, vertex was used as a skull landmark to predict target area. Navigated rTMS might have enabled

a more accurate application and might be more effective. The type of sham we used could also be a limitation for the study. Even though there have been numerous previous rTMS studies employed the coil angled away as sham control, it is speculated that it could not provide a sufficient reliable and valid sham control. Recently developed sham coils that control for all of the sensory aspects of stimulation are advised for rTMS researches.³ Finally, we did not investigate whether the patients had a comorbid depression which could be a confounder in our study.

In conclusion, our results demonstrated analgesic effect of rTMS on intractable neuropathic pain in SCI was not superior to sham. However, middle-term pain relief provided by rTMS is encouraging and suggests the need for future studies with a larger sample size which may reveal clinically relevant difference.

References

- Cardenas DD, Felix ER. Pain after spinal cord injury: a review of classification, treatment approaches, and treatment assessment. *PM R* 2009;1(12):1077–90.
- Cardenas DD, Jensen MP. Treatments for chronic pain in persons with spinal cord injury: a survey study. *J Spinal Cord Med* 2006; 29(2):109–17.
- O'Connell NE, Wand BM, Marston L, Spencer S, Desouza LH. Non-invasive brain stimulation techniques for chronic pain. A report of a Cochrane systematic review and meta-analysis. *Eur J Phys Rehabil Med* 2011;47(2):309–16.
- Leung A, Donohue M, Xu R, Lee R, Lefaucheur JP, Khedr EM, *et al.* rTMS for suppressing neuropathic pain: a meta-analysis. *J Pain* 2009;10(12):1205–16.
- Defrin R, Grunhaus L, Zamir D, Zeilig G. The effect of a series of repetitive transcranial magnetic stimulations of the motor cortex on central pain after spinal cord injury. *Arch Phys Med Rehabil* 2007;88(12):1574–80.
- Kang BS, Shin HI, Bang MS. Effect of repetitive transcranial magnetic stimulation over the hand motor cortical area on central pain after spinal cord injury. *Arch Phys Med Rehabil* 2009;90(10): 1766–71.
- Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol* 2009;120(12):2008–39.
- Widerström-Noga E, Biering-Sørensen F, Bryce T, Cardenas DD, Finnerup NB, Jensen MP, *et al.* The international spinal cord injury pain basic data set. *Spinal Cord* 2008;46(12):818–23.
- Garcia-Larrea L, Peyron R. Motor cortex stimulation for neuropathic pain: from phenomenology to mechanisms. *Neuroimage* 2007;37(Suppl 1):71–9.
- Garcia-Larrea L, Peyron R, Mertens P, Gregoire MC, Lavenne F, Le Bars D, *et al.* Electrical stimulation of motor cortex for pain control: a combined PET-scan and electrophysiological study. *Pain* 1999;83(2):259–73.
- Peyron R, Faillenot I, Mertens P, Laurent B, Garcia-Larrea L. Motor cortex stimulation in neuropathic pain. Correlations between analgesic effect and hemodynamic changes in the brain. A PET study. *Neuroimage* 2007;34(1):310–21.
- Ruohonen J, Karhu J. Navigated transcranial magnetic stimulation. *Clin Neurophysiol* 2010;40(1):7–17.