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CASE REPORT

Hand Function Improvement with Low-Frequency Repetitive Transcranial Magnetic Stimulation of the Unaffected Hemisphere in a Severe Case of Stroke

ABSTRACT

Boggio PS, Alonso-Alonso M, Mansur CG, Rigonatti SP, Schlaug G, Pascual-Leone A, Fregni F: Hand function improvement with low-frequency repetitive transcranial magnetic stimulation of the unaffected hemisphere in a severe case of stroke. Am J Phys Med Rehabil 2006;85:927–930.

Previous research has shown that low-frequency rTMS of the unaffected hemisphere can improve motor function in acute and chronic stroke patients. However, these studies only investigated patients with mild or moderate motor deficits. We report a case of a stroke patient with a severe motor impairment who underwent sham and active repetitive transcranial magnetic stimulation (rTMS) of the unaffected hemisphere and had significantly improved motor function after active, but not after sham, stimulation of the unaffected primary motor cortex. In an additional session of active rTMS, this patient maintained and further enhanced the initial motor improvement. This case report shows that inhibitory rTMS of the unaffected hemisphere can also be beneficial for stroke patients with severe motor deficits and suggests that this approach of noninvasive brain stimulation should be further investigated in this population of patients.

Key Words: Transcranial Magnetic Stimulation, Motor Function, Stroke, Transcallosal Inhibition

Stroke is a major public health concern in industrialized countries. Despite its high incidence and prevalence, there are few currently available therapies. Partial or total recovery can sometimes be achieved, but in a substantial number of patients, severe deficits in the motor and language function result in a great burden for patients, their families, and the healthcare system. In the last few years, several lines of evidence have coalesced around the finding that after a stroke, the brain undergoes plastic changes involving areas beyond the site of lesion in an attempt to recover function.[1,2] Recent evidence suggests, however, that the results of some of these changes may not be beneficial but, rather, maladaptive. In such a circumstance, they can hinder motor recovery.[1–4] Interhemispheric inhibitory interactions through callosal connections seem to be dysfunctional in chronic stroke patients.[3] In lesions involving the corticospinal tract, this may result in an excessive inhibitory drive from intact M1 over its damaged homologous counterpart, with negative consequences.[3] Two recent studies have demonstrated an improvement in hand motor function after decreasing excitability of M1 in the unaffected hemisphere, using low-frequency (1 Hz) repetitive transcranial magnetic stimulation (rTMS).[5,6] However, these investigations targeted a population of stroke patients with mild-to-moderate motor deficits. It is not yet clear whether severely impaired individuals could also benefit from this new therapeutic approach. Here, for the first time, we report positive effects of 1-Hz rTMS in a chronic stroke patient with total paralysis of the affected hand.

CASE REPORT

A 74-yr-old woman participated in a pilot study investigating the utility of rTMS for motor recovery. This patient had had a stroke in the right internal capsule 23 mos before enrollment in the study. She had no movements in her left hand and only proximal movements in her left shoulder. Furthermore, she had moderate spasticity (score of 2 in the modified Ashworth scale) in her left hand. This patient had had an intensive physical therapy program in the first year after the stroke, during which she had recovered some of the proximal but not distal movements.

On enrollment in the study, using a figure-eight coil and a Dantec MagPro Stimulator (Medtronic, Minneapolis, MN), her motor threshold (MT) was determined to be 60% (maximum stimulator output) in the right abductor pollicis brevis, and although small MEPs (smaller than 50uV) could be elicited in the left abductor pollicis brevis, the MT could not be determined using the maximum output (100%) in the affected hand. MT was defined as the stimulus intensity capable of evoking a motor-evoked response of 50 uV (peak to peak, using surface electromyography) in the resting abductor pollicis brevis muscle in at least 6 of 10 trials. The angle of movements such as finger flexion and extension; thumb flexion, extension, abduction, and adduction; and wrist flexion and extension were assessed before treatment. Importantly, because muscle synergy is frequently observed in stroke patients, the assessment was performed with the patient having her arm flexed at 90 degrees and rested and fixed at the armrest. No movements could be elicited (0 degrees) in any of these muscles of the left, affected hand before the treatment. Furthermore, we assessed short-term mood changes using a visual analog scale in which the patient had to rate her mood from 0 (very unhappy) to 10 (very happy) before and after treatment. She scored 8 before the stimulation.

Initially, as part of the double-blind pilot study, the patient received sham rTMS with a frequency of 1 Hz. The stimulation site was the "hot spot" for the stimulation of the muscle abductor pollicis brevis (as defined for the MT determination) in the unaffected hemisphere. The coil handle was positioned at 45 degrees from the parasagittal plane so that the induced current would be in the optimal position for the stimulation of the motor cortex strip; stimulation was applied with an intensity of 100% of MT in a continuous train of 20 mins, 1200 pulses. We used a specially designed sham figure-eight stimulation coil (commercially available from Medtronic, Inc.) that has the same appearance as the real rTMS coil. This sham rTMS contains a small copper-wire loop inside a plastic casing and produces a similar sound artifact and a mechanical tapping sensation on the subject's scalp. She had no improvement in motor function or change in the MT of the affected and unaffected hemispheres after this stimulation. After 2 mos, the patient returned and received real rTMS using identical parameters compared with the initial sham stimulation session. After this session, the patient was able to perform small movements with her thumb (5 degrees of abduction and adduction, and 5 degrees of finger flexion). There was no change in spasticity or mood. MT in the unaffected hand increased by 8% compared with baseline (Fig. 1).

After 4 mos, the patient returned for a new session of active rTMS using the same parameters of stimulation. The patient maintained the initial improvement obtained after the first real rTMS session and also had additional improvements:

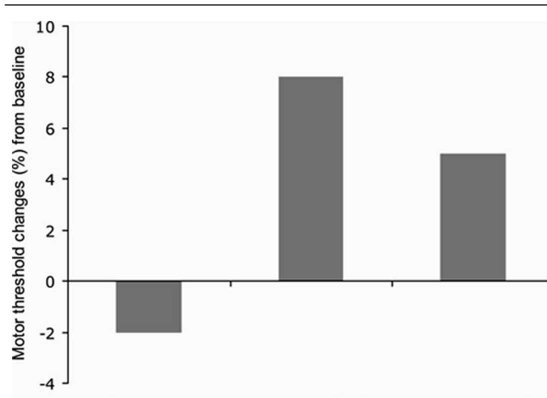

FIGURE 1 *Motor threshold changes (%) from baseline after sham repetitive transcranial magnetic stimulation and active repetitive transcranial magnetic stimulation (first and second session) in the stimulated, unaffected hemisphere. A positive change indicates motor threshold increase.*

thumb adduction, 10 degrees, thumb abduction, 5 degrees; finger flexion, 15 degrees; and finger extension, 5 degrees. After this second session of real rTMS, a further improvement was observed (thumb adduction, 20 degrees; thumb abduction, 15 degrees; finger flexion, 20 degrees; finger extension, 10 degrees). Similar to the first real rTMS session, there was no change in spasticity (as evaluated by the modified Ashworth scale) or mood (as indexed by visual analog scale), and there was a small increase in MT in the unaffected hemisphere (increase of 5%). No adverse effects were associated with this treatment.

DISCUSSION

We have shown that a chronic stroke patient with no movements in the affected hand was able to partially gain hand motor function after inhibitory 1-Hz rTMS was applied on the unaffected, contralesional M1. Importantly, there was no change in spasticity or mood from baseline through the follow-up period. At the time rTMS was delivered in our patient, she had already reached a chronic, stable phase (23 mos post-stroke), and thus it seems unlikely that the effects we observed could have been attributable to spontaneous recovery. According to observational studies, this is not expected beyond 5 mos after the onset of a stroke.[7] In addition, placebo effects can be reasonably ruled out in this particular case because no changes were found either immediately after or during the period of 2 mos after sham stimulation.

On the other hand, although no voluntary movements were present in this patient's affected hand at baseline, small MEPs could still be elicited at that level. A number of studies have demonstrated a positive correlation between preserved MEPs—a physiologic marker of corticospinal integrity—and motor outcome after a stroke.[8,9] Additionally, a link has been suggested between high interhemispheric inhibitory drive from contralesional M1 to damaged M1 and poor motor recovery.[3] To date, however, it is not known whether the presence of MEPs in severely impaired patients could serve as a predictor of response to 1-Hz rTMS over the contralesional M1. Based on our results with this patient, it is tempting to speculate that this might be the case. Excessive interhemispheric inhibition might preclude motor improvement despite residual substrate for recovery as revealed by MEPs. Thus, inhibition of contralesional M1 might be especially beneficial in these individuals. Further studies are needed to address this hypothesis in detail.

Our case is in line with two previous studies documenting beneficial effects of 1-Hz rTMS on contralesional M1 in patients with upper-limb motor deficits after stroke. Mansur et al.[5] reported an improvement in reaction times and motor performance (Purdue pegboard test) in a group of 10 patients after a single session of rTMS (1 Hz, 100% of the resting MT for 10 mins). Of these patients, five had mild impairment and three had moderate impairment. The remaining two patients, who were severely impaired, were excluded from the study because they were not able to perform the required task and did not receive the treatment. Takeuchi et al.[6] recently reported an improvement in hand function (pinch acceleration) after rTMS, using different parameters (1 Hz, 90% RMT, 25 mins). Interestingly, these authors also demonstrated a correlation between motor improvement after rTMS and the degree of interhemispheric inhibition. The group of patients included in this study had a degree of motor performance on the Fugl-Meyer scale ranging from 21 to 100%. No patients with total paralysis participated in either of these two studies.

Despite growing evidence that excessive interhemispheric inhibition is a maladaptive compensation in patients with chronic stroke,[3,5,6] some authors have suggested a different role for ipsilateral motor areas in the process of recovery. A beneficial effect of the unaffected hemisphere was suggested by reports of patients who had recovered well after a stroke, where a second cerebrovascular event on the undamaged hemisphere led to worsening of the paresis associated with the first stroke.[11] Some studies have explored the role of contralesional motor areas using single-pulse TMS or rTMS to directly disrupt activity during or before motor tasks in chronic stroke patients ("virtual lesions"); no relevant changes have been found in these studies. Disruption of ipsilateral M1, either with online TMS or offline 1-Hz rTMS, did not change simple reaction times or finger tapping in the paretic hand.[12,13] The study of Werhahn et al.[13] applied 1-Hz rTMS over the intact M1 only in patients with good recovery, although single-pulse TMS did not interfere with motor performance in either group (good or poor recovery). The study of Johansen-Berg et al.,[12] however, found decreased reaction times in the paretic hand with online single-pulse TMS applied on the ipsilateral premotor cortex but not M1. Moreover, the authors found greater disruption associated with more impairment, suggesting that recruitment of this ipsilateral region might play a functional role. Finally, evidence supporting the negative effect of the unaffected hemisphere is shown in a recent longitudinal study that found an inverse correlation between the activation of ipsilateral motor areas and recovery, with this activation pattern diminishing over time as a function of recovery.[10] The discrepancies found in these studies may be explained by the different tasks employed, the type of lesion, and the time course (i.e., online *vs.* offline TMS).

Finally, the duration of the positive motor effects in this patient is remarkable. In contrast, the study of Takeuchi et al.[6] demonstrated a short-lived effect that lasted less than 30 mins. There is evidence that several rTMS treatment sessions can lead to long-lasting effects for weeks after stimulation[14,15]; however, the relatively long-lasting effect was observed after the first session of real rTMS. Similar effects have been observed in patients with epilepsy,[16] and it has been hypothesized that a highly dysfunctional cortical activity can be more susceptible to the modulatory effects of rTMS.[16]

This case report has some limitations that should be considered. First, the arm relaxation might have changed after active rTMS and, thus, confounded our results. Because we did not assess it directly, we cannot rule out that relaxation was a potential confounder in this study. However, the long-lasting effects of this treatment make this hypothesis less likely. Second, because we used an intensity of stimulation that was 100% of the MT that induces muscle hand contractions, it is possible that the patient realized the difference between sham and active rTMS and that the effects were derived from this perception. We cannot rule out this potential placebo effect; however, after sham treatment, the patient reported that she believed she had received active treatment (she was naïve to rTMS), and, thus, a placebo effect might have occurred after sham rTMS if placebo played an important role in our study. Third, our hypothesis that the modulation of transcallosal inhibition was responsible for the beneficial effects on motor function should be viewed with caution, considering that we could not measure cortical excitability in the affected hemisphere because of the small size of MEPs in this hemisphere. However, in a recent paper, we showed that low-frequency rTMS of the unaffected hemisphere decreases cortical excitability in the unaffected hemisphere and increases it in the contralateral, affected hemisphere.[17] Further studies should evaluate brain activity in patients lacking MEPs in the paretic hand using other tools such as electroencephalography and neuroimaging.

In sum, we have reported, for the first time, positive effects of rTMS in a stroke patient with total paralysis of the upper limb. Our case suggests that subjects with severe motor deficits may find benefits from this therapeutic approach. Therefore, our findings underscore the importance of further exploration of rTMS in patients with severe motor deficits using different parameters of stimulation and longer, systematic follow-up assessments. Stroke lesion characteristics that might be more susceptible to the beneficial effects of rTMS also should be investigated.

REFERENCES

1. Ward NS, Cohen LG: Mechanisms underlying recovery of motor function after stroke. *Arch Neurol* 2004;61:1844–8
2. Ward NS: Plasticity and the functional reorganization of the human brain. *Int J Psychophysiol* 2005;58:158–61
3. Murase N, Duque J, Mazzocchio R, Cohen LG: Influence of interhemispheric interactions on motor function in chronic stroke. *Ann Neurol* 2004;55:400–9
4. Pascual-Leone A, Amedi A, Fregni F, Merabet LB: The plastic human brain cortex. *Annu Rev Neurosci* 2005;28: 377–401
5. Mansur CG, Fregni F, Boggio PS, et al: A sham stimulation-controlled trial of rTMS of the unaffected hemisphere in stroke patients. *Neurology* 2005;64:1802–4
6. Takeuchi N, Chuma T, Matsuo Y, Watanabe I, Ikoma K: Repetitive transcranial magnetic stimulation of contralesional primary motor cortex improves hand function after stroke. *Stroke* 2005;36:2681–6
7. Jorgensen HS, Nakayama H, Raaschou HO, Vive-Larsen J, Stoier M, Olsen TS: Outcome and time course of recovery in stroke. Part II: time course of recovery. The Copenhagen Stroke Study. *Arch Phys Med Rehabil* 1995;76:406–12
8. Delvaux V, Alagona G, Gerard P, De Pasqua V, Pennisi G, de Noordhout AM: Post-stroke reorganization of hand motor area: a 1-year prospective follow-up with focal transcranial magnetic stimulation. *Clin Neurophysiol* 2003;114:1217–25
9. Escudero JV, Sancho J, Bautista D, Escudero M, Lopez-Trigo J: Prognostic value of motor evoked potential obtained by transcranial magnetic brain stimulation in motor function recovery in patients with acute ischemic stroke. *Stroke* 1998;29:1854–9
10. Ward NS, Brown MM, Thompson AJ, Frackowiak RS: Neural correlates of motor recovery after stroke: a longitudinal fMRI study. *Brain* 2003;126:2476–96.
11. Fisher CM: Concerning the mechanism of recovery in stroke hemiplegia. *Can J Neurol Sci* 1992;19:57–63
12. Johansen-Berg H, Rushworth MF, Bogdanovic MD, Kischka U, Wimalaratna S, Matthews PM: The role of ipsilateral premotor cortex in hand movement after stroke. *Proc Natl Acad Sci U S A* 2002;99:14518–23
13. Werhahn KJ, Conforto AB, Kadom N, Hallett M, Cohen LG: Contribution of the ipsilateral motor cortex to recovery after chronic stroke. *Ann Neurol* 2003;54:464–72
14. Fregni F, Santos CM, Myczkowski ML, et al: Repetitive transcranial magnetic stimulation is as effective as fluoxetine in the treatment of depression in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2004;75: 1171–4
15. Dannon PN, Dolberg OT, Schreiber S, Grunhaus L: Three and six-month outcome following courses of either ECT or rTMS in a population of severely depressed individuals–preliminary report. *Biol Psychiatry* 2002;51:687–90
16. Fregni F, Thome-Souza S, Bermpohl F, et al: Antiepileptic effects of repetitive transcranial magnetic stimulation in patients with cortical malformations: an EEG and clinical study. *Stereotact Funct Neurosurg* 2005;83:57–62.
17. Fregni F, Boggio PS, Valle AC, et al: A sham-controlled trial of 5-day course of rTMS of the unaffected hemisphere in stroke patients. *Stroke* 2006;37:2115–22