Therapeutic trial of repetitive transcranial magnetic stimulation after acute ischemic stroke

Eman M. Khedr, Mohamed A. Ahmed, Nehal Fathy and John C. Rothwell

Neurology 2005;65;466-468
DOI: 10.1212/01.wnl.0000173067.84247.36

Therapeutic trial of repetitive transcranial magnetic stimulation after acute ischemic stroke

Abstract: Repetitive transcranial magnetic stimulation (rTMS) or sham stimulation was given over the motor cortex daily for 10 days to two randomly assigned groups of 26 patients with acute ischemic stroke. Patients otherwise continued their normal treatment. Disability scales measured before rTMS, at the end of the last rTMS session, and 10 days later showed that real rTMS improved patients' scores more than sham.

NEUROLOGY 2005;65:466–468

Eman M. Khedr, MD; Mohamed A. Ahmed, MD; Nehal Fathy, MD; and John C. Rothwell, MD

Repetitive transcranial magnetic stimulation (rTMS) can have long-term after effects on the excitability of the cerebral cortex. Potential therapeutic uses have been explored in many conditions including depression and movement disorders with varying degrees of success.[1] However, there are few studies of patients after stroke. One report showed transient improvement of hand motor function after a single session of anodal transcranial direct current stimulation (TDCS) over motor cortex.[2] The current study was a preliminary investigation of the possible effects of repeated daily motor cortex rTMS on recovery of movement in patients with hemiplegia. We reasoned that it might improve motor performance in two ways: first, by increasing excitability of remaining pathways from the damaged hemisphere and second, by improving the response of patients to standard therapy.

Given its possible dual action, we applied rTMS at the same time every day for 10 days while patients continued to receive their normal therapy. To maximize patient recruitment and compliance, we studied patients during their initial hospital admission within the first 2 weeks of the stroke. Although functional recovery is not stable until several months after a stroke, early intervention might maximize the potential benefit. In addition, if rTMS has any significant effect on recovery at this stage, it would have the practical benefit of allowing patients to be discharged home earlier than expected.

From the Departments of Neurology (Drs. Khedr and Ahmed), Rheumatology and Rehabilitation (Dr. Fathy), Assiut University Hospital, Assiut, Egypt; and Sobell Research Department of Motor Neuroscience and Movement Disorders (Dr. Rothwell), National Hospital for Neurology and Neurosurgery, London, UK.

Dr. Rothwell was funded by the Medical Research Council, UK.

Disclosure: The authors report no conflicts of interest.

Received September 26, 2004. Accepted in final form March 21, 2005.

Address correspondence and reprint requests to Dr. Eman M. Khedr, Department of Neurology, Assiut University Hospital, Assiut, Egypt; e-mail: emankhedr99@yahoo.com

Methods. Fifty-two right-handed patients (36 men and 16 women) at the Assiut Stroke Unit were recruited between the fifth and tenth day post-stroke with informed consent and ethical approval from January 2002 to March 2003. Inclusion criteria were acute hemiplegia with single thromboembolic nonhemorrhagic infarction documented by CT in the distribution of middle cerebral artery. Exclusion criteria were head injury or neurologic disease other than stroke, unstable cardiac dysrhythmia, and previous administration of tranquilizer. Patients who were unable to give informed consent because of severe aphasia, anosognosia, or cognitive deficit were not included.

Scandinavian Stroke Scale (SSS), NIH Stroke Scale (NIHSS), Barthel Index scale (BI), resting motor threshold (RMT) of healthy side, and motor evoked potentials (MEPs) of healthy and hemiplegic sides were used to assess patients before and after treatment. All patients received standard physical and medical therapies (passive limb manipulation from the second day, increasing by the end of the first week to more active movements if patients improved function) plus anticoagulant low molecular weight heparin in the first week and then aspirin and notropic drugs.

RMT and the motor "hot spot" of the abductor digiti minimi (ADM) muscles were evaluated according to the recommendations of the International Federation of Clinical Neurophysiology[3] using surface EMG monitoring. TMS was delivered through a figure-of-eight coil (9-cm outer wing diameter, 1.5-T maximum output) attached to a Mag-Lite stimulator held tangentially to the scalp with the junction region approximately perpendicular to the line of the central sulcus. rTMS was applied over the ADM area of the stroke hemisphere using an intensity of 120% RMT of the nonstroke hemisphere. If MEPs were absent to stimulation of the stroke hemisphere, the motor ″hot spot″ was defined as being symmetric to the nonstroke hemisphere. If MEPs appeared during recovery, the optimal site for stimulation of the stroke hemisphere was reidentified.

rTMS (daily at noon) consisted of ten 10-second trains of 3-Hz stimulation with 50 seconds between each train. Sham rTMS with the same parameters was applied with the coil angled away from the head to reproduce the noise of the stimulation as well as some local sensation. Patients were randomly assigned to real or sham rTMS. Because the patients had never experienced rTMS, they did not know whether they were receiving real or sham rTMS. During rTMS, all patients wore earplugs.

Patients were followed up after the tenth session, and 10 days after the last session using the three clinical rating scales plus measures of MEPs evoked in muscles on the hemiplegic side. Evaluation was performed by a neurologist who was blind to the type of rTMS treatment that the patients had received.

Results. All patients completed the protocols, and there were no side effects of rTMS except occasional mild headache. Table 1 gives clinical details; patients' motor scores at each evaluation are plotted in the figure. Two-factor analyses of variance of each of the scales revealed a time × treatment interaction ($F_{1,1.3} = 16.1$, $p < 0.0001$ for SSS;

Editorial, see page 353

Table 1 *Clinical details of patients*

	Real rTMS	Sham rTMS
No. (M/F)	19/7	17/9
Side of stroke (R/L)	12/14	12/14
Age mean (SD), y	53.5 (9.5)	52.2 (8.4)
Time after stroke of first assessment mean (SD), d	7.1 (1.4)	7.3 (1.5)
Barthel Score mean (SD)	28 (11)	33 (13)
Scandinavian Stroke Scale mean (SD)	28 (7)	31 (7)
NIH Stroke Scale mean (SD)	12 (2)	12 (4)
No MEP at first assessment	12	9
Type of stroke* (cortical/subcortical/massive)	8/12/6	7/14/5

* Based on CT findings, a lesion was classified as cortical if it involved cortical structures; subcortical if it involved the corona radiata, thalamus, or internal capsule; and massive if it involved both cortical and subcortical structures (complete middle cerebral artery territory infarction).

MEP = motor evoked potential.

$F_{1,2} = 26.4$, $p < 0.0001$ for NIHSS; $F_{1,1.4} = 26.8$, $p < 0.0001$ for BI). This was because real rTMS produced a greater improvement than sham rTMS.

A stratified analysis (table 2) showed that real rTMS led to a higher percentage of independent patients (BI ≤75)[4] and a higher percentage of patients having only mild (SSS 50 to 58)[5] disability by the time of the third assessment. Eleven patients with massive infarcts (six real rTMS, five sham rTMS) had the worst improvement and were unaffected by rTMS.

Just less than half of the patients in each group had no response to single-pulse TMS over the affected hemisphere at presentation. A larger number of patients in the real rTMS group (from 14 to 21) recovered MEPs by the time of the last assessment, but this was not significantly different from the sham group (from 17 to 18). There was no correlation between clinical recovery and changes in MEP.

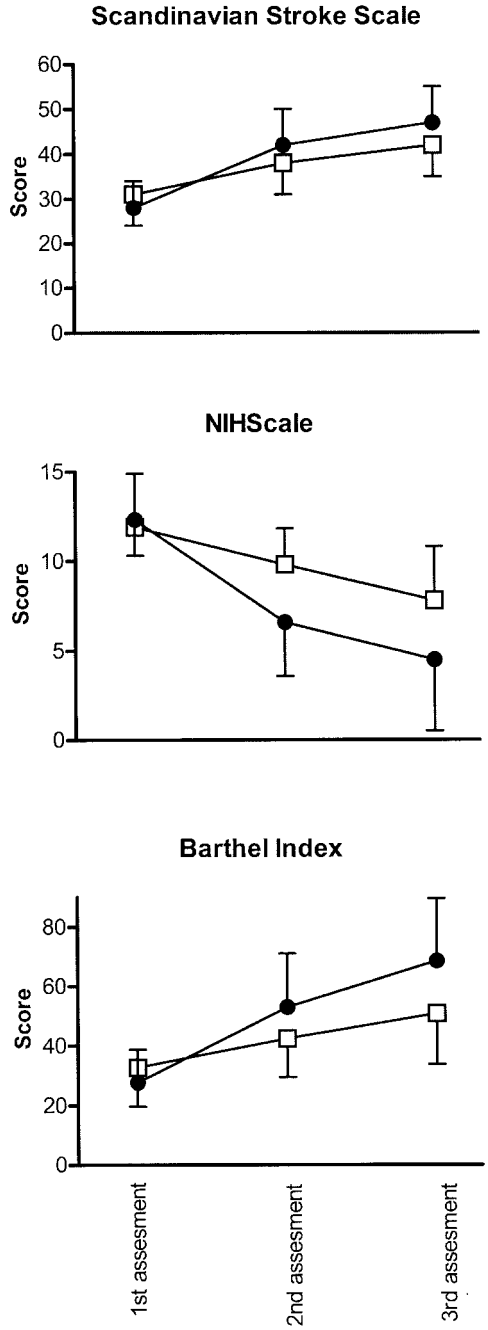

Figure. Changes in mean (± SD) clinical scores at the three assessment points for the two groups of patients. The first assessment was immediately before commencing repetitive transcranial magnetic stimulation (rTMS) treatment, the second assessment was immediately after the last (tenth) session of rTMS, and the third assessment was 10 days later. (A) Data from the Scandinavian Stroke Scale. (B) Data from the NIH Stroke Scale. (C) Data from the Barthel scores. Filled circles show data from real rTMS group; open squares show data from sham treatment group. Improvement was greater in the real rTMS group for all three scores.

Discussion. This study shows that 10 consecutive days of rTMS employed as an add-on intervention to normal physical and drug therapies improves immediate clinical outcome in early stroke patients. It is consistent with previous observations from animal models of stroke,[6] as well as in a single human patient, which have reported beneficial effects of motor cortex stimulation through electrodes implanted for long-term therapy.[7] The data extend the previous report of transient improvement in hand function after a single session of 10 minutes of TDCS.[2]

The parameters that we chose for rTMS were governed by three considerations. First, given the increased risk of seizures after stroke, we chose rTMS parameters that were well within current safety guidelines.[8] Second, to influence as much of the remaining intact tissue as possible, we employed a stimulus intensity of 120% RMT, which can spread as much as 2 to 3 cm from the coil in healthy subjects. Third, to increase excitability of remaining motor areas, we used a relatively high frequency of rTMS. Our concern for safety made us choose a frequency of 3 Hz. Despite the absence of side effects of rTMS in this series, EEG would be an important

Table 2 *The outcomes of patients receiving real and sham rTMS according to Barthel Index Scale and Scandinavian Stroke Scale*

	rTMS	Sham	p value (χ^2)
Barthel Index			
Good-excellent outcome >75	9 (34.6%)	2 (7.7%)	0.0175
Moderate-severe disability ≤75	17 (65.4%)	24 (92.3%)	
Scandinavian Stroke Scale			
Mild disability ≤50	13 (50%)	5 (19.2%)	0.019
Severe disability >50	13 (50%)	21 (80.8%)	

rTMS = repetitive transcranial magnetic stimulation.

monitor to include in future studies to warn of possible seizure onset.

Several factors could contribute to the improvement after rTMS. The fact that MEPs from the affected hemisphere tended to improve more in the real rTMS group suggests that part of the effect may have been related to increased excitability of the corticospinal system. However, all patients received their normal therapy; rTMS may have increased the motor system response to treatment because of an effect on mechanisms of cortical plasticity. Future studies with dual-pulse TMS methods could be used to examine changes in intracortical circuitry.[9] Alternatively, there may have been indirect effects of rTMS in reducing patients' depression, thereby increasing compliance with treatment. We did not score depression in this series, but this would be an important feature to include in future studies. Another possibility is that rTMS increased release of dopamine in the striatum,[10] and this could have contributed to our results. The short follow-up time means that we cannot comment on whether the benefit is sustained, but we hope to address this in future studies.

References

1. Epstein C, Rothwell JC. Therapeutic uses of r TMS.: Boniface S, Ziemann U, eds. Plasticity in the human nervous system: investigations with transcranial magnetic stimulation. Cambridge: Cambridge University Press , 2003:246–263.
2. Hummel F, Celnik P, Giraux P, et al. Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke. Brain 2005;128:490–499.
3. Rothwell JC, Hallett M, Berardelli A, Eisen A, Rossini PM, Paulus W. Magnetic stimulation: motor evoked potentials. Report of an IFCN committee. Electroencephalogr Clin Neurophysiol 1999;52:97–104.
4. Bendszus M, Urbach H, Ries F, Solymosi L. Outcome after local intra-arterial fibrinolysis compared with the natural course of patients with a dense middle cerebral artery on early CT. Neuroradiology 1998;40:54–58.
5. Hacke W, Kaste M, Fieschi C, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). JAMA 1995;274:1017–1025.
6. Plautz EJ, Barbay S, Frost SB, et al. Post-infarct cortical plasticity and behavioral recovery using concurrent cortical stimulation and rehabilitative training: a feasibility study in primates. Neurol Res 2003;25:801–810.
7. Brown JA, Lutsep H, Cramer SC, Weinand M. Motor cortex stimulation for enhancement of recovery after stroke: case report. Neurol Res 2003;25:815–818.
8. Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines form the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. Electroencephalogr Clin Neurophysiol 1998;108:1–16.
9. Chen R. Interactions between inhibitory and excitatory circuits in the human motor cortex. Exp Brain Res 2004;154:1–10.
10. Strafella AP, Paus T, Fraraccio M, Dagher A. Striatal dopamine release induced by repetitive transcranial magnetic stimulation of the human motor cortex. Brain 2003;126:2609–2615.

Therapeutic trial of repetitive transcranial magnetic stimulation after acute ischemic stroke

Eman M. Khedr, Mohamed A. Ahmed, Nehal Fathy and John C. Rothwell

Neurology 2005;65;466-468
DOI: 10.1212/01.wnl.0000173067.84247.36