Daily Repetitive Transcranial Magnetic Stimulation for Poststroke Upper Limb Paresis in the Subacute Period

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Background: We conducted a randomized, double-blind, sham-controlled study to assess the efficacy in motor recovery and safety of daily repetitive transcranial magnetic stimulation (rTMS) in subacute stroke patients. *Methods:* Forty-one patients were randomly assigned to a real or sham stimulation group. Each patient underwent regular rehabilitation accompanied by a series of 10 daily 5-Hz rTMS of the ipsilesional primary motor cortex (M1) or sham stimulation. The primary outcome was motor recovery evaluated by the Brunnstrom stages (BS). The secondary outcomes were improvement in the Fugl-Meyer Assessment (FMA), grip power, National Institutes of Health Stroke Scale (NIHSS), Functional Independence Measure (FIM), a quantitative measurement of finger tapping movement, and the incidence of adverse events. *Results:* Thirty-nine patients completed the study and were included in the analyses. The real rTMS group demonstrated additional improvement in the BS hand score at the last follow-up compared to the sham. The grip power, the NIHSS motor score, and the number of finger taps in the affected hand improved in the real stimulation group but not in the sham group. The BS upper limb scores, the FMA distal upper limb score, the NIHSS total score, and the FIM motor score showed improvement from baseline at the earlier time points after the real rTMS. There were no additional improvements in the other scores after the real rTMS compared to the sham. No serious adverse events were observed. *Conclusions:* Our results suggest that daily

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high-frequency rTMS of the ipsilesional M1 is tolerable and modestly facilitates motor recovery in the paralytic hand of subacute stroke patients. **Key Words:** Repetitive transcranial magnetic stimulation—motor cortex stimulation—rehabilitation—subacute stroke—stroke recovery—randomized controlled trial.

Introduction

Poststroke motor disturbance not only reduces the quality of life and activities of daily living of patients but also has a great social impact through lost productivity. With this in mind, efforts have been made to improve the functional outcomes of poststroke patients undergoing rehabilitation. One such approach is repetitive transcranial magnetic stimulation (rTMS), with the purpose of facilitating poststroke recovery of motor function. Two common approaches have been advocated. One of these is low-frequency rTMS (1 Hz or less) to the contralesional primary motor cortex (M1) area to decrease excessive excitability and thus decrease excessive interhemispheric inhibition to the ipsilesional side. The other approach involves high-frequency rTMS (greater than 1 Hz), or excitatory stimulation, to facilitate the decreased cortical excitability on the stroke-affected side.[1-4] In the past, there have been a variety of reports on the use of low-frequency rTMS to the contralesional M1,[2,4-8] and high-frequency rTMS to the ipsilesional M1[1-3,6-12] with the purpose of neurorehabilitation. About half of these studies have involved chronic stage infarction patients.[2,4,5,7,10-12] Although some studies have shown improvements in acute stroke patients both as a result of low-frequency contralesional stimulation and as a result of high-frequency ipsilesional stimulation,[3,6,8,9] a few randomized double-blind controlled trials have investigated the efficacy of high-frequency ipsilesional stimulation in subacute stroke patients.[8] As functional recovery after stroke is said to be most pronounced in the period within 3 months after onset,[13] we postulated that rather than rTMS at the chronic stage, the add-on effects of rTMS may be greater when it is applied at an earlier stage. To study the add-on effects of rTMS on ischemic and hemorrhagic subacute stroke patients, we undertook a randomized, double-blind, parallel study to test the hypothesis that 10 sessions of daily rTMS, combined with regular rehabilitation, improve the results of recovery of motor function in subacute stroke patients.

Methods

Patients

This was a randomized, double-blind, sham-controlled, parallel study conducted at 3 centers (a university hospital and 2 rehabilitation hospitals) in Japan from September, 2010, to December, 2012. We enrolled patients with the following conditions: (1) 20 years old and over, (2) motor disturbances in the upper limb caused by ischemic or hemorrhagic stroke (Brunnstrom stages [BS][14] arm ≤ 5 or BS hand ≤ 5), and (3) within 8 weeks of stroke onset. The following conditions excluded patients from participating in the present study: (1) total paralysis of the upper limb (BS arm = 1 and BS hand = 1); (2) contraindications to transcranial magnetic stimulation, such as the implantation of a cardiac pacemaker; (3) previous rTMS; (4) aphasia, dementia, psychological disorders, or suicidal wishes; (5) a history of epilepsy; and (6) pregnancy.

This randomized controlled study was conducted in accordance with the Declaration of Helsinki and Japanese ethical guidelines for clinical studies. The study protocol was thoroughly reviewed and approved by the institutional review boards and the ethics committees of all the participating institutions (approval number, 09278-2). The protocol was finalized on September 1, 2010, and this clinical trial was registered with the Japanese University Hospital Medical Information Network Clinical Trials Registry, number UMIN000007594. All patients provided written informed consent and approval before enrollment.

Randomization

The participants were recruited from 2 hospitals specializing in rehabilitation, where they received daily rehabilitation. Randomization was performed using a computer-generated permuted-block method by a third-party statistician upon confirmation of patient eligibility, prior to the start of the study. Patients were randomly assigned to 1 of 2 treatment groups (real rTMS plus regular rehabilitation therapy versus sham stimulation plus regular rehabilitation therapy) according to age (<65 and ≥ 65 years old), severity of symptoms (BS hand score ≤ 3 [severe] and ≥ 4 [mild]), and institution. The patients were identified by sequential numbers assigned at randomization. An assignment notice was sent only to investigators who conducted the rTMS intervention. The patients and assessors were blinded to group assignment until the study was completed.

Procedures

Stimulation sessions were undertaken daily for 10 consecutive days except for weekends, after which follow-up evaluations were undertaken over the next 2 weeks