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Case study

Long-term effect of repetitive transcranial magnetic stimulation on disability in patients with stroke

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ABSTRACT

High-frequency repetitive transcranial magnetic stimulation (rTMS) is widely used to improve motor function in stroke patients. However, the long-term effects of rTMS on disability and motor function are not clear. We investigated the effects of high-frequency rTMS administered within 1 month of stroke on disability and motor function 6 months after stroke onset. The study was conducted by an open-label longitudinal study, and were included 76 (38 rTMS and 38 control) subacute stroke patients. The rTMS group received 10 Hz stimulation over the primary motor cortex of the affected hemisphere for 10 days with a daily dose of 1000 pulses. The Korean version of the Modified Barthel Index (K-MBI), the Medical Research Council (MRC) scale for motor deficits in the affected arm, the Manual Function Test (MFT), and the Functional Ambulation Classification (FAC) were administered at baseline (within 1 month of stroke onset) and at 3 and 6 months after onset. The K-MBI, MRC scale, MFT, and FAC scores of both groups changed significantly over time ($p < 0.001$); however, the motor strength, hand function, FAC classification, and K-MBI scores of the rTMS and control groups did not differ. Our findings indicate that rTMS did not have a long-lasting effect (6 months after onset) on disability and motor function in patients with stroke.

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1. Introduction

Stroke is a major cause of long-term neurological disability worldwide. A significant number of patients do not achieve complete motor recovery despite intensive rehabilitation [1]. About 40% of patients require some assistance with their activities of daily living (ADL), and post-stroke disability is a strong predictor of poor quality of life [2,3]. Repetitive transcranial magnetic stimulation (rTMS) has been often used to increase functional recovery in patients with stroke.

rTMS can modify excitability at the cerebral cortex site stimulated as well as in remote structures along functional anatomical connections [4]. Thus, function may be expected to improve as the availability and excitability of corticospinal connections increase following stroke, which supports the rationale for its use in post-stroke rehabilitation [5]. rTMS treatment is based on the concept of disruption of the interhemispheric balance after stroke [6]. However, the therapeutic effectiveness of rTMS on motor func-

tion and disability is controversial [7,8]. A previous meta-analysis found that rTMS was not associated with a significant increase in the Barthel Index score or significant improvement in motor function [7]. Furthermore, although several studies have demonstrated an effect of high-frequency rTMS on stroke, the long-term effects on disability are not clear [9–12].

Thus, we investigated the effect of rTMS in stroke patients to determine whether application of high-frequency rTMS to the ipsilesional hemisphere facilitated motor recovery and reduced disability 6 months after treatment.

2. Methodology

2.1. Study designs and subjects

We recruited 76 subacute stroke patients who were hospitalized in our rehabilitation department between March 2014 and February 2015. All subjects had experienced a supratentorial cerebral infarction or supratentorial intracranial hemorrhage and (1) had experienced their first-ever unilateral stroke, (2) had received rTMS treatment within 14–28 days of stroke onset, and (3) were able to follow 1-step directions [13]. Exclusion criteria were (1) a

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history of inflammatory arthritis or inflammatory myopathy, and (2) peripheral nervous disease [13]. rTMS is not widely used in Korea and is not supported by the National Health Insurance Cooperation; thus, we conducted an open-label longitudinal study. The sample sizes in previous studies ranged from 28 to 60 patients [11,12,14]. We projected a 30% loss to follow-up; thus, we determined that, including control subjects, a sample size of 90 was necessary for our study. Fourteen patients dropped out of the study due to second attack within 6 months, withdrawal from the study, or loss to follow up (moved or transfer to another hospital or unknown causes).

Subjects who requested rTMS treatment in addition to conventional therapy were assigned to the rTMS group ($n = 38$), and those who received conventional treatment alone were included in the control group ($n = 38$). Patients in the rTMS group received 10 Hz rTMS over the ipsilesional primary motor cortex for 10 sessions in addition to conventional rehabilitation therapy. All subjects received physical therapy based on the neurodevelopmental treatment approach and occupational therapy according to the task-oriented approach [13,15]. The rehabilitation program started within 1 month of stroke onset for all subjects and continued for 6 months after onset. The treatment regime consisted of physical and occupational therapy 1–2 h per day, 5 days a week. Additionally, the subjects received speech therapy as needed. The interventions focused primarily on using and strengthening the affected limb, basic mat activity, symmetric weight bearing and transfer activities, and gait training, but they were not performed exclusively for a particular purpose [15].

Our study was approved by the Ethics Committee of the Catholic University of Korea. Written consent was obtained from all subjects according to the Declaration of Helsinki.

2.2. Clinical assessments

The clinical assessments were performed at baseline (within 1 month of stroke onset) and at 3 and 6 months after stroke onset. Functional disability was assessed using the Korean version of the Modified Barthel Index (K-MBI) as the primary outcome. The K-MBI has 10 subscales with scores ranging from 0 (completely dependent) to 100 (independent in basic activities of daily living) [16]. Motor impairment, the secondary outcome, was assessed using the Medial Research Council (MRC) scale, Manual Function Test (MFT), and Functional Ambulation Classification (FAC). Muscle strength in the affected arm (shoulder flexion and wrist extension) was measured on a scale of 0 (no contraction) to 5 (movement against a resistance equal to the maximum resistance overcome by the healthy side) using the MRC muscle scale [17]. The MFT is used to assess arm motion and manipulative activities in stroke patients [18]. The MFT scores were categorized into ordinal data: 0 (unable to grasp or release), 1 (clumsy grasp and release), 2 (able to grasp and release, but unable to perform in-hand manipulation), 3 (clumsy in-hand manipulation), 4 (able to perform the task with extended time or safety measures), and 5 (no difference before and after stroke). The FAC categorizes patients according to the basic motor skills necessary for functional ambulation, with scores ranging from 0 (unable to ambulate) to 5 (independent ambulation on uneven and level surfaces, stairs, and inclines) [19].

2.3. Repetitive transcranial magnetic stimulation interventions

All participants were seated comfortably in chairs wearing a swimming cap. A Synergy electromyography/evoked potentials system (Medelec, Kingswood, Bristol, UK) was used to record and monitor contralateral abductor pollicis brevis muscle (APB) activity [20,21]. Single-pulse TMS was applied over the ipsilesional primary motor cortex with a Magstim BiStim 2 stimulator (Magstim,

Spring Gardens, Wales, UK). The coil was held tangentially to the scalp with the handle pointing backward and laterally 45° from the midsagittal line. Using TMS, the optimum position ("hot spot") was defined as the site where TMS evoked motor potentials of maximum peak-to-peak amplitude in the contralesional APB muscle. The hot spot was marked on the swimming cap to ensure that the coil was held in the correct position throughout the experiment. The resting motor threshold (rMT) was defined as the lowest stimulus intensity able to evoke motor potentials of at least 50 μ V peak-to-peak amplitude in 5 of 10 consecutive trials [22,23]. The rTMS group received 10-Hz stimulation at 80% of each individual's rMT for 5 s at 55-s inter-train intervals. This procedure was repeated 20 times for a total of 1000 pulses of stimulation. rTMS was administered in 10 treatment sessions over 2 weeks. (1000 pulses per each session, 10 session in total) Head movement was visually monitored during the sessions.

2.4. Statistical analysis

Data are expressed as means and 95% confidence intervals (CIs). Group demographic and clinical characteristics were compared using independent *t*- or Mann–Whitney *U*-tests for continuous variables and chi-square tests for categorical variables. The functional assessment (K-MBI, MRC scale, MFT, and FAC) findings were compared between groups at baseline, 3, and 6 months using a linear mixed model analysis, which allowed us to include the data of patients with missing variables. A linear mixed model for a repeated-measures covariance pattern model with a first-order autoregressive covariance structure was used. Two fixed effects were included in the model: the between-subject rTMS treatment effect and the within-subject time effect (baseline, 3 months, and 6 months). Differences in function across time were assessed by *time* $\times$ *rTMS* treatment interactions. The mixed model analyses were adjusted for age, and the baseline functional assessment score was used as a covariate. *P*-values <0.05 were deemed to indicate statistical significance. All statistical tests were conducted using the Statistical Package for the Social Sciences for Windows (ver. 21.0; SPSS Inc., Chicago, IL, USA).

3. Results

The patient baseline demographic and clinical characteristics are shown in Table 1. We found no significant differences between groups with the exception of age ($p = 0.001$), MRC wrist extension grade ($p = 0.03$), and MFT score ($p = 0.001$). Thus, relatively young patients with upper arm paralysis chose to receive rTMS treatment. All patients in the rTMS group tolerated the treatment well without any adverse effects. The mean interval from stroke onset to rTMS treatment was 35.84 days (95% CI, 29.20–42.47).

Fig. 1 and Table 2 show changes in disability and motor impairment in the rTMS and control groups according to assessment time points. After adjusting for age and baseline functional assessment values (K-MBI, MRC scores for the affected arm, MFT, and FAC), the linear mixed model analysis revealed a significant reduction in disability and significant improvement in motor function over time in both groups ($p < 0.001$). However, we did not observe a significant positive *time* $\times$ *rTMS* treatment interaction. MRC scale scores for the affected arm and MFT scores for the control group both increased with time; rTMS treatment provided no additional improvement.

4. Discussion

Although a previous meta-analysis found that rTMS did not significantly improve the Barthel Index score or motor function [7],

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