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Brief Report

Can repetitive transcranial magnetic stimulation enhance motor outcomes in cerebral infarct patients?

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The effectiveness of repetitive transcranial magnetic stimulation on the post-stroke motor recovery is not apparent. To perform an accurate evaluation, we adjusted for critical factors that determine motor outcomes, including lesion location and the state of the corticospinal tract. We only included patients with cerebral infarct in the corona radiata and with corticospinal tract interruption, apparent on diffusion tensor tractography. We retrospectively enrolled 34 patients whose diffusion tensor tractography corticospinal tract was interrupted by a cerebral infarct. The corticospinal tract state of each patient was evaluated using diffusion tensor tractography. Of the 34 patients whose corticospinal tract was interrupted on diffusion tensor tractography, 12 patients underwent repetitive transcranial magnetic stimulation treatment at the early stage after cerebral infarct (repetitive transcranial magnetic stimulation group). In comparison, 22 patients did not receive repetitive transcranial magnetic stimulation treatment (non-repetitive transcranial magnetic stimulation group). High-frequency repetitive transcranial magnetic stimulation (10 Hz) was performed on the primary motor cortex of the affected hemisphere. At the six month evaluation after the onset of the infarct, motor function was measured in each patient. In both groups, compared to their states during the initial evaluation, significant improvement was found in all measurements of motor function. However, six months after onset, no significant differences between the two groups were found in these measurement scores. When a patient's CST is interrupted, high-frequency repetitive transcranial magnetic stimulation treatment at the early stage after cerebral infarct might have no additional therapeutic effect on motor outcome. Qualified randomized controlled trials are needed to support our findings further.

Keywords

Transcranial magnetic stimulation; motor function; prognosis; cerebral infarct; stroke; diffusion tensor tractography; corona radiata

1. Introduction

Stroke results in various neurological deficits, among which, the motor deficit is a significant disabling sequela for patients (Kim et al., 2005). Conventional physical therapy, such as take-oriented and neurodevelopmental techniques, is used to treat motor dysfunction after stroke (da Silva et al., 2019; Pin-Barre and Laurin, 2015). Recent studies have proposed the use of invasive and noninvasive neurostimulation to enhance motor outcome. These techniques influence cortical excitability in the brain (Choi et al., 2018; Fisicaro et al., 2019; Kang et al., 2016; Liu et al., 2019; van Lieshout et al., 2019). Accordingly, clinicians have combined conventional physical therapy with neurostimulation methods to treat motor deficits better.

Repetitive transcranial magnetic stimulation (rTMS) is a frequently used noninvasive neurostimulation tool that involves applying an electromagnetic coil to the patient's scalp to produce a magnetic field, which alters the excitability of cortex at the stimulation site and modifies transsynaptic excitability at distant sites. High-frequency ($>$ 3 Hz) rTMS is known to increase cortical excitability, while low-frequency rTMS ($\leq$ 1 Hz) decreases cortical excitability (Gu and Chang, 2017). The treatment is effective for depressive symptoms, cognitive deficit, and various types of pain (Choi and Chang, 2018; Choi et al., 2018; Gu and Chang, 2017; Kim et al., 2010). Concerto et al. (2015) reported that rTMS might have long-lasting antidepressant effects. Also, rTMS has been proposed as a disease-modifying strategy in post-stroke dementia and vascular cognitive impairment (Bordet et al., 2017).

Several studies have reported that neurostimulation enhances motor outcome after stroke; however, this is still the subject of debate (Chang et al., 2010; Hao et al., 2013; He et al., 2019; Simis et al., 2016). Many previous studies have limitations in that they did not adjust for critical factors that can affect the motor outcome, including the location of the stroke lesion and the state of motor function-related neural tracts. We put forward that the lack of adjustment for these critical factors might be the source of the discrepancies observed in previous studies. To accurately evaluate the effect of rTMS treatment on motor function in the early stage after stroke, we controlled for the location of the stroke lesion and the state of the corticospinal tract ICST). Therefore, we recruited only patients with corona radiata infarct. Also, we investigated the state of the CST using diffusion tensor tractography (DTT) and recruited only patients whose CSTs were interrupted by the infarct. We hypothesize that rTMS treatment could help enhance the recovery of motor function after corona radiata infarct.

2. Methods

2.1 Patients

Thirty-four consecutive patients who underwent stroke rehabilitation in our University Hospital were recruited. This study was retrospectively conducted without randomization or blinding, and approved by the Board of Ethics Committee of Yeungnam University Hospital (YUMC 2019-10-046). Patients (1) who recently experienced their first-ever stroke; (2) who were between the ages of 20 and 79 years; (3) who had severe weakness in the affected extremities (Medical Research Council scale of finger flexors and extensors, < 2) within 24 hours of infarct onset; (4) who had a corona radiata infarct underlying the unilateral weakness as determined by magnetic resonance imaging (MRI); (5) whose CST was interrupted on DTT; (6) in whom rTMS was initiated within 8-30 days of stroke onset; and (7) who had undergone $\geq$ 6 consecutive rTMS sessions were enrolled in the study. We did not apply rTMS treatment to patients who had a history of seizures or underwent craniotomy. We excluded patients who had severe medical complications (which can affect the prognosis of motor function) between the onset of the infarct and the six-month follow-up evaluation.

2.2 Diffusion tensor tractography

We conducted diffusion tensor imaging (DTI) using a Philips Gyroscan Intera 1.5-T (Hoffman-LaRoche, Ltd., Best, Netherlands). Totally, 60 contiguous slices (2.3 mm thickness of slice) were obtained with applying the 32 noncollinear diffusion-sensitizing gradients (matrix = 128 $\times$ 128, field of view = 221 mm $\times$ 221 mm, echo time = 76 mm, repetition time/echo-planar imaging factor = 10,726/67 ms, b = 1000 s/mm/mm, number of excitations = 1, and scanning time = 452 seconds). Image distortions caused by the Eddy-current effect were removed by affine multiscale 2D registration. For depicting CST, we applied the deterministic approach. The 3D fiber reconstruction algorithm from Philips PRIDE software was used for depicting CST. The direction of CST is determined following the major eigenvector of the diffusion tensor. On a 2D color map, we drew a seed region of interest (ROI) at the location in which the CST passed through the anterior lower-pons, and the other ROI was drawn at the CST location in the anterior upper-pons (threshold: fractional anisotropy (FA) more than 0.2; direction threshold less than 60°) (Fig. 1A and 1B) (Moon et al., 2019). Tracts that pass through the above two ROIs were determined to be the last tracts of interest (Fig. 1C). Of the 80 patients whose CST integrity was assessed, 34 patients' CSTs were interrupted. The average duration from infarct onset to the day that DTI was conducted in each patient was 12.6 $\pm$ 5.8 days.

2.3 Grouping of patients

Twelve of the 34 patients who had interrupted CST underwent rTMS treatment (rTMS group), while the remaining 22 patients did not (non-rTMS group). The patients in the non-rTMS group did not receive rTMS treatment, and none received sham stimulation.

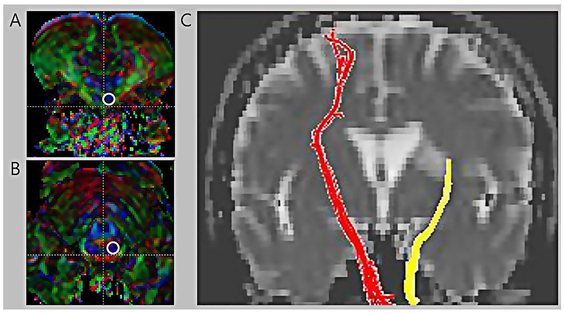

Figure 1. Placing regions of interest on lower (A) and upper pons (B). Interrupted Lt. corticospinal tract on diffusion tensor tractography (C).

2.4 Repetitive transcranial magnetic stimulation

Each patient in the rTMS group underwent consecutive rTMS treatment sessions (Monday through Saturday, six times per week; Table 1), conducted by one physiatrist. The rTMS was used to stimulate the area homologous to the site above the primary motor cortex (M1) in the unaffected side cortex related to the abductor pollicis brevis muscle. For determining the exact location for rTMS treatment, transcranial magnetic stimulation (TMS) was conducted using a 7-cm Magnetic Stimulator (figure of eight, air-cooled coil; Magstim Company Ltd, Whitland, UK). A cloth was placed on scalps of the patients, marked with spacing 1-cm apart, and Cz referenced to the intersection of midsagittal and interaural lines (Choi and Chang, 2018; Choi et al., 2018). During TMS treatment, the patients were seated in a reclined chair with earplugs in their ears.

We defined the resting motor threshold (MT) as the minimum stimulus needed to elicit a motor evoked potential (MEP) with $>$ 50 μV peak-to-peak amplitude in three out of five trials in the abductor pollicis brevis muscle of the unaffected side. If the MT was less than 80%, the stimulation intensity was set to plus 20% (Choi and Chang, 2018; Choi et al., 2018). However, if the MT was over 80%, the stimulation intensity was set to 100% of the stimulator output. MEPs were obtained by stimulating the unaffected hemisphere with TMS. Stimulation was conducted at each 1-cm interval site, with at least 10-second-intervals between stimuli. The site (referred to as site A) was determined where the motor potential with maximal peak-to-peak amplitude was evoked. The site for rTMS treatment was the location homologous to site A in the contralesional hemisphere.

In the rTMS group, treatment was applied over the site homologous to site A at 10 Hz (intensity: 90% of the MT; duration: 5 seconds; total trains: 20 trains; inter-train pause: 55 seconds; total pulses: 1,000 pulses). We placed the coil tangentially to patients' scalp at about 45° backward and laterally. The patients received rTMS treatment once a day consecutively from Monday through Saturday. All patients underwent conventional physical therapy for 6 days/week, primarily for enhancing motor function and movement pattern of the affected limbs, and postural control.

2.5 Clinical evaluation

The motor function was evaluated in all the included patients at infarct onset and six months after the onset of the infarct. To measure motor function, the Motricity Index (MI) at upper and lower limbs was investigated (maximum score = 100) (Demeurisse et al.,

Table 1. Demographic and clinical data for patients in the rTMS and non-rTMS groups

	All patients	rTMS group	non-rTMS group	*P*
Demographic data				
Number of patients, n	34	12	22	
Age, year	69 (59.3-72.8)	66 (47.8-71.3)	70 (60.5-73)	0.168
Days to DTT	10 (9-14)	12 (9-15.3)	10 (8.3-13.8)	0.557
Initial upper limb MI	0 (0-0)	0 (0-0)	0 (0-0)	0.683
Initial lower limb MI	0 (0-18)	0 (0-4.5)	0 (0-18)	0.79
MBC	1 (1-1)	1 (1-1)	1 (1-1)	1
FAC	0 (0-0)	0 (0-0)	0 (0-0)	1
6-month motor function				
Upper limb MI	48 (31.3-61)	54.5 (37.5-61)	45.5 (26.8-57.5)	0.261
Lower limb MI	53.5 (39.3-60)	56 (38-70)	53.5 (43-59.8)	0.557
MBC	2.5 (1-5)	3.5 (1.8-5)	2 (1-4)	0.466
FAC	3 (2-3)	3 (1.8-4)	3 (2-3)	0.245

Values are presented as median (interquartile range).

1980). We evaluated hand function with the modified Brunnstrom classification (MBC) (Brunnstrom, 1996; Fujii and Nakada, 2003), which is categorized as follows: 1: unable to voluntarily move fingers; 2: able to voluntarily move fingers; 3: can grasp the hand voluntarily but cannot open the hand; 4: able to grasp a card between the thumb and the medial side of the index finger and extend fingers slightly; 5: able to pick up and hold a glass and extend fingers; and 6: able to catch and throw a ball as well as button and unbutton a shirt.

We measured walking ability with the standardized functional ambulation category (FAC) (Cunha et al., 2002), which quantifies the degree of assistance needed during a 15-minute walk. The FAC has six categories: 0: cannot ambulate at all; 1: one person should continuously support one person during ambulation; 2: intermittent support from one person is required; 3: able to walk with verbal supervision only; 4: needs assistance is necessary on stairs and uneven ground; and 5: able to walk independently anywhere.

2.6 Statistical analysis

For Statistical analysis, SPSS version 23.0 was used. Motor functions at the onset, and six months after onset were made using the Wilcoxon signed-rank test. For the intergroup comparison, the Mann-Whitney test was applied to analyze differences in age, time from onset to DTT, and measurements for evaluating the motor function. Statistical significance was set at $P < 0.05$.

3. Results

The mean number of sessions for rTMS treatment in the rTMS group was 27.6 $\pm$ 10.8 sessions (range: 7 to 49 sessions, median: 26.5, interquartile range: 22-32.3). In the comparison between the rTMS and non-rTMS groups, no significant differences were observed in demographic data, including the distribution of age, initial MIs (upper and lower limbs), MBC, and FAC scores ($P >$ 0.05) (Table 1). In both groups, compared with initial evaluations, significant improvements were found in all the measurements of motor function (upper limb MI, lower limb MI, MBC, and FAC) at the 6-month evaluation ($P < 0.001$). However, these scores were not significantly different between the two groups ($P > 0.05$) (Table 1).

4. Discussion

We evaluated whether rTMS treatment at the early stage after stroke could enhance motor outcome. High-frequency stimulation (10 Hz) was administered over M1 of the affected hemisphere. For an accurate evaluation, we only included patients with corona radiata infarct and CST interruption apparent on DTT. However, motor outcomes of patients who received rTMS treatment and those who did not were not significantly different after six months, although motor function six months after stroke onset in both groups was significantly improved, compared to motor function at the onset.

In contrast to our results, several studies have reported the positive short- and long- term effectiveness of rTMS treatment on recovery of motor function after stroke (Chang et al., 2010; He et al., 2019; Nam et al., 2018; Noh et al., 2019; Ueda et al., 2019). Previous studies proposed that increased excitability of the affected hemisphere by rTMS treatment improves motor function by facilitating corticomotor excitability (Khedr et al., 2010; Kim et al., 2006; Wassermann, 1998). However, the number of previous studies is limited since they did not control for the location of the lesion and CST status. Additionally, a meta-analysis showed no evidence of an effect of rTMS on motor recovery after stroke (Hao et al., 2013; Pomeroy et al., 2006). It is possible that the patients included in this study were too severely affected to have benefited from rTMS treatment.

The CST is the most important motor function-related neural tract. Thus, the CST is the most critical factor for the motor outcome after stroke when patients have the same location of stroke lesion (Moon et al., 2019). Accordingly, we adjusted for CST status in our study. To evaluate CST status, we used DTT. This technique allows researchers and clinicians to assess various neural tracts (Moon et al., 2019). Several DTT studies have demonstrated the validity or accuracy of DTT for evaluating the state of the CST (Kwak et al., 2019; Lee and Chang, 2018; Moon et al., 2019). By using DTT, we accurately evaluated the state of the CST and recruited only patients with interrupted CST. We believe that we adequately controlled for factors that can affect the motor outcome.

Our work is the first to evaluate the effectiveness of high-frequency rTMS at M1 on motor recovery after stroke, following adjustments for both lesion location and CST state. We found that high-frequency stimulation (10 Hz) over M1 of the affected hemisphere at the early stage after onset might have no additional therapeutic effect on the recovery of motor function when the patient's CST is interrupted after corona radiata infarct.

In future work, qualified studies that compensate for the limitations of our research are warranted. In particular, we recruited only patients whose CST was interrupted because we aimed to apply rTMS treatment to patients with reduced motor function. In the chart review, a few patients with preserved CST received rTMS treatment. Thus, we could not evaluate the effectiveness of rTMS treatment on patients whose CST was preserved. Second, our research was retrospectively conducted. Third, a relatively small number of patients were recruited. Fourth, the number of sessions for each patient was different. Fourth, we did not adjust for the infarct volume of each patient. Fifth, we could not clearly explain the reason why rTMS treatment showed no additional therapeutic effect on motor outcome.

Abbreviations

DTI: diffusion tensor imaging; DTT: diffusion tensor tractography; FA: fractional anisotropy; FAC: functional ambulation category; MBC: modified Brunnstrom classification; MEP: motor evoked potential; MI: Motricity Index; MT: motor threshold; ROI: region of interest; rTMS: repetitive transcranial magnetic stimulation; TMS: transcranial magnetic stimulation.

Ethics approval and consent to participate

This research was retrospectively conducted without randomization or blinding, and approved by the Board of Ethics Committee of Yeungnam University Hospital (YUMC 2019-10-046).

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Conflict of Interest

The authors declare no conflict of interest.

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