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Clinical short communication

Comparative study of ipsilesional and contralesional repetitive transcranial magnetic stimulations for acute infarction

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ABSTRACT

Background and purpose: Repetitive transcranial magnetic stimulation (rTMS) is reported to improve chronic post-stoke hemiparesis. However, application of rTMS during the acute phase of post-stroke has not fully been investigated. We investigated the safety and the efficacy of intermittent theta-burst stimulation (iTBS) of the affected motor cortex and 1-Hz stimulation of the unaffected hemisphere during the acute phase in patients with hemiparesis due to capsular infarction.

Methods: Twenty one patients who met the study criteria were randomly assigned to receive, starting within 7 days after stroke onset and for a period of 10 days, iTBS of the affected motor cortex hand area (n = 8), 1-Hz stimulation of the unaffected motor cortex hand area (n = 7), or sham stimulation (n = 6). Upper limb motor function was evaluated before rTMS and 12 weeks after onset of the stroke. Evaluation was based on the Fugl-Meyer Assessment (FMA), Stroke Impairment Assessment Set (SIAS), Modified Ashworth Scale (MAS), grip strength, and motor evoked potential (MEP) amplitude in the first dorsal interosseous (FDI) muscle.

Results: Both iTBS applied to the affected motor cortex hand area and 1-Hz stimulation applied to the unaffected motor cortex hand area enhanced motor recovery. In comparison to sham stimulation, iTBS increased the SIAS finger-function test score, and 1-Hz stimulation decreased the MAS wrist and finger score.

Conclusions: Ipsilesional iTBS and contralesional 1-Hz stimulation applied during the acute phase of stroke have different effects: ipsilesional iTBS improves movement of the affected limb, whereas contralesional 1-Hz stimulation reduces spasticity of the affected limb.

1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive technique commonly used clinically to modulate neural excitability of the human brain. rTMS at high frequency (> 5 Hz) increases neural activity (long-term potentiation) [1], whereas rTMS at low frequency (1 Hz) reduces neural activity (long-term depression) [2]. rTMS is applied to patients mainly during the chronic phase of stroke for treatment of hemiparesis. High-frequency stimulation is applied to the affected hemisphere to enhance neural excitability there [3], and low-frequency stimulation is applied to the contralateral hemisphere to reduce the abnormally high degree of interhemispheric inhibition seen in patients during the chronic phase of stroke [4]. The efficacy of rTMS for chronic post-stroke hemiparesis is being established.

Therapeutic rTMS is rarely applied during the acute phase, especially within the first week after stroke onset; only a few reports of use of conventional rTMS during this phase exist [5,6]. A patterned rTMS protocol, known as the intermittent theta-burst stimulation (iTBS) protocol, consisting of delivery of a 2-s train of theta-burst stimulation (bursts of 3 stimuli at 50 Hz with an interburst interval of 200-ms) repeated every 10 s, has been developed, and this stimulation protocol has been shown to induce a longer-lasting increase in neural excitability than conventional rTMS [7]. Although iTBS has been applied in the treatment of hemiparesis during the chronic phase of stroke [8,9], it has not been applied therapeutically during the acute phase.

We conducted a study to investigate the safety and feasibility of application of iTBS during the acute phase of stroke and to compare the effects of iTBS over the affected motor cortex against those of conventional low-frequency stimulation over the contralateral motor cortex.

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2. Methods

2.1. Study design

The study was designed as a prospective, randomized, sham-controlled, single-institution trial. The study protocol was approved by the ethics committee of Yokohama Brain and Spine Center. The study protocol and associated risks were explained to all patients included in the study, and all provided informed consent for their participation. This study is registered in the UMIN-CTR (UMIN000018819).

2.2. Participants

Patients included in the study were identified at the time of emergency admission to Yokohama Brain and Spine Center for acute stroke between September 2014 and August 2016. The inclusion criteria were as follows: a clinical diagnosis of newly developed isolated unilateral capsular infarction confirmed by magnetic resonance imaging (MRI); the possibility of starting the study intervention (rTMS) within 7 days after stroke onset; age ≥ 20 years; Brunnstrom Stage I–III and a modified Ashworth Scale (MAS) score of 0–2 in the affected upper limb; no intravascular or other surgical intervention, no use of tissue plasminogen activator; no disturbance of consciousness; no apparent cognitive deficit; no serious general complication requiring intensive medical management; no use of drugs with seizure threshold lowering potential such as antidepressants; and no contraindication for rTMS, such an implantable cardiac pacemaker or a history of seizures. Twenty-one patients were enrolled during the recruitment period.

2.3. Intervention

Using the envelope method, the patients were assigned randomly to 1 of 3 study groups: an iTBS group (n = 8), a 1-Hz stimulation group (n = 7), and a sham stimulation group (n = 6), and stimulation, whether actual or sham stimulation, began within 7 days after stroke onset (Fig. 1). A high-speed stimulator with a figure-of-eight coil (diameter = 70 mm) (Magstim Rapid Square System, Magstim Inc., Whitland, UK) was used for rTMS. Guided by an MRI based optical navigation system (Brainsight, Rogue Research Inc., Montreal, Canada), the coil was placed against the scalp over the motor hand area of the primary motor cortex. Resting motor threshold (RMT) was set at the lowest intensity able to produce motor evoked potentials (MEPs) in the unaffected first dorsal interosseous (FDI) muscle.

In the iTBS group patients, iTBS (for a total of 600 pulses) was applied daily to the motor hand area of the primary motor cortex on the affected side at an intensity of 80% RMT for 10 days. In the 1-Hz stimulation group patients, low-frequency 1 Hz stimulation (for a total of 1200 pulses) was applied daily to the motor hand area of the primary motor cortex on the unaffected side at an intensity of 110% RMT for 10 days. In the sham stimulation group patients, iTBS (for a total of 600 pulses) was applied daily across a 10-cm-thick plastic board to the motor hand area of the primary motor cortex on the affected side at an intensity of 80% RMT for 10 days. After each daily rTMS session, all patients received the same conventional rehabilitation therapy (with PT and OT for 120 min a day), and this therapy was continued after the 10-day rTMS treatment period until 12 weeks after onset of the stroke. All patients were also given antiplatelet agents aspirin (200 mg/day) and clopidogrel (75 mg/day).

During study period, the patients were hospitalized even after acute phase of infarction to receive daily examinations by neurologists; if the patient developed symptoms suggestive of seizure such as a change in consciousness and involuntary movements, the patient was supposed to undergo electroencephalography and be treated immediately. Other side effects such as hearing problems were also checked by daily examinations.

2.4. Outcome measures

Upper limb functional outcome of motor recovery was evaluated on the basis of the Fugl-Meyer Assessment (FMA), Stroke Impairment Assessment Set (SIAS), Modified Ashworth Scale (MAS), grip strength, and MEP amplitude in the FDI muscle. Evaluation was done before rTMS (week 0) and 12 weeks after stroke onset. Changes in results of these evaluations after 12 weeks of actual or sham treatment were compared between the 3 treatment groups.

Upper extremity motor function was the focus of the study, so the 4 scales were applied as follows: The upper extremity motor set score of FMA (range, 0–66) was obtained [10]. The SIAS knee-mouth test score (range, 0–5) and the finger-function test score were obtained for assessment of proximal and distal upper limb function, respectively. For quantitative evaluation, the finger-function test scores 0, 1a, 1b, 1c, 2, 3, 4, and 5 were transformed to 0, 1, 2, 3, 4, 5, 6, and 7, respectively [11]. MAS shoulder and elbow (proximal upper limb) and wrist and finger (distal upper limb) scores were obtained. Possible MAS scores are 0, 1, 1 +, 2, 3, 4, and 5, and, for quantification, a score of 1 + was transformed to 1.5 [12]. Grip strength was measured (in kilograms) twice with a mechanical hand dynamometer, and the highest value was recorded. These assessments were performed by a licensed occupational

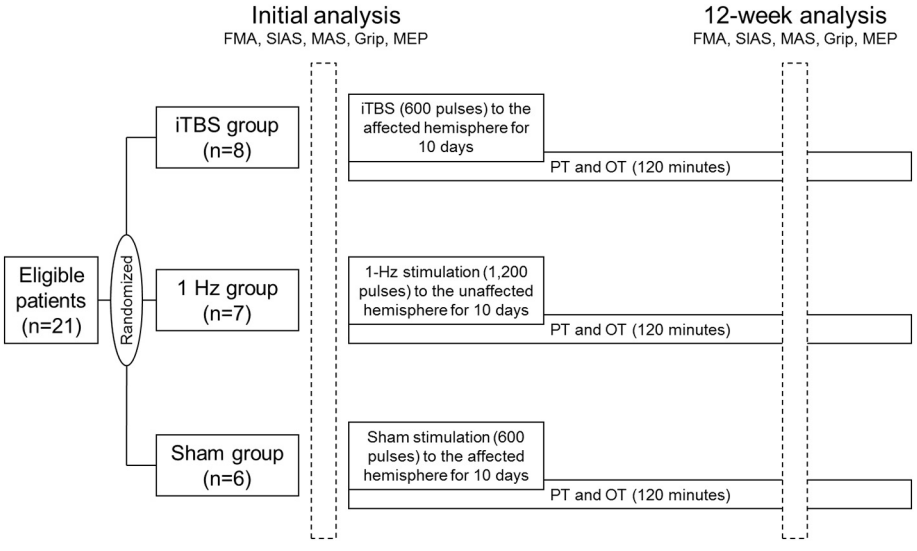

Fig. 1. Flowchart of the participants.
FMA, Fugl-Meyer Assessment; SIAS, Stroke Impairment Assessment Set; MAS, Modified Ashworth scale; Grip, grip strength; MEP, motor evoked potential amplitude; iTBS, intermittent theta-burst stimulation on the affected motor cortex; 1 Hz, 1-Hz stimulation on the unaffected motor cortex; Sham, sham stimulation.