ACRM
AMERICAN CONGRESS OF REHABILITATION MEDICINE

Archives of Physical Medicine and Rehabilitation

journal homepage: www.archives-pmr.org

Archives of Physical Medicine and Rehabilitation 2015;96:69-75

ORIGINAL ARTICLE

Corticospinal Integrity and Motor Impairment Predict Outcomes After Excitatory Repetitive Transcranial Magnetic Stimulation: A Preliminary Study

Chih-Jou Lai, MD, MS,[a,b] Chih-Pin Wang, MD,[c] Po-Yi Tsai, MD,[a,b] Rai-Chi Chan, MD,[a,b] Shan-Hui Lin, MD,[a] Fu-Gong Lin, PhD,[d] Chin-Yi Hsieh, MD[c]

From the [a]Department of Physical Medicine and Rehabilitation, Taipei Veterans General Hospital, Taipei; [b]National Yang-Ming University, School of Medicine, Taipei; [c]Department of Emergency, Mackay Memorial Hospital, Taipei; and [d]School of Public Health, National Defense Medical Center, Taipei, Taiwan.

Abstract

Objective: To identify the effective predictors for therapeutic outcomes based on intermittent theta-burst stimulation (iTBS).

Design: A sham-controlled, double-blind parallel study design.

Setting: A tertiary hospital.

Participants: People with stroke (N=72) who presented with unilateral hemiplegia.

Interventions: Ten consecutive sessions of real or sham iTBS were implemented with the aim of enhancing hand function. Patients were categorized into 4 groups according to the presence (MEP+) or absence (MEP−) of motor-evoked potentials (MEPs) and grip strength according to the Medical Research Council (MRC) scale.

Main Outcome Measures: Cortical excitability, Wolf Motor Function Test (WMFT), finger-tapping task (FT), and simple reaction time were performed before and after the sessions.

Results: MEPs and the MRC scale were predictive of iTBS therapeutic outcomes. Group A (MEP+, MRC>1) exhibited the greatest WMFT change (7.6±2.3, $P<.001$), followed by group B (MEP−, MRC>1; 5.2±2.2 score change) and group C (MEP−, MRC=0; 2.3±1.5 score change). These improvements were correlated significantly with baseline motor function and ipsilesional maximum MEP amplitude.

Conclusions: The effectiveness of iTBS modulation for poststroke motor enhancement depends on baseline hand grip strength and the presence of MEPs. Our findings indicate that establishing neurostimulation strategies based on the proposed electrophysiological and clinical criteria can allow iTBS to be executed with substantial precision. Effective neuromodulatory strategies can be formulated by using electrophysiological features and clinical presentation information as guidelines.

Archives of Physical Medicine and Rehabilitation 2015;96:69-75

Stroke is a major medical problem and the leading cause of disability worldwide.[1] Motor recovery after a stroke depends on the reorganization of the perilesional region, axonal regeneration within connected motor networks, and the unmasking of the potential secondary motor areas.[2,3] The postulated role of synaptic plasticity in poststroke motor recovery has awakened great interest in the applicability of noninvasive brain stimulation,[4,5] including repetitive transcranial magnetic stimulation (rTMS), which has shown promise in promoting motor relearning and enhancing neurologic recovery.[6] This is because rTMS generates long-term potentiation and long-term depression-like synaptic plasticity, which are associated with augmented neural plasticity.[7,8] The *N*-methyl-D-aspartate receptor–dependent aftereffects of high-frequency rTMS have been shown to upregulate cortical plasticity, leading to the consolidation of adaptive neuromodulation.[9,10] Participant responses to rTMS vary greatly; possible modulatory factors include the participant's age, the duration of the poststroke period, the lesion location, and the severity of baseline motor impairment.[10-12] Identifying the receptiveness of patients with various characteristics to rTMS

Supported by the Taipei Veterans General Hospital (grant no. V103C-168).
Clinical Trial Registration No.: NCT02006615.
Disclosures: none.

0003-9993/14/$36 - see front matter © 2015 by the American Congress of Rehabilitation Medicine
http://dx.doi.org/10.1016/j.apmr.2014.08.014

Table 1 Demographic data and clinical characteristics of all patients

Characteristics	Group A (n=21)	Group B (n=17)	Group C (n=17)	Group D (n=17)
Age (y)	62.6±11.6	60.4±10.4	63.4±12.1	62.1±10.5
M/F	17/4	14/3	13/4	13/4
Ischemic/hemorrhagic	15/6	12/5	13/4	13/4
Cortical±CR/BG	8	6	7	6
CR/BG	13	11	10	11
Right/left brain lesion	11/10	9/8	10/7	8/9
Lesion volume (cm^3)	37.0±21.4	39.5±28.4	34.7±23.6	38.2±20.6
NIHSS	11.8±3.8	11.4±4.1	12.1±3.7	11.4±3.5
Months poststroke	10.4±5.8	9.7±5.1	11.4±4.3	10.6±4.6

NOTE. Values are mean ± SD or n.
Abbreviations: BG, basal ganglia; CR, corona radiata; F, female; M, male; NIHSS, National Institutes of Health Stroke Scale.

conditioning may help determine which stroke patients should be targeted for conditioning and help predict therapeutic outcomes.

Elicited motor-evoked potentials (MEPs) recorded in the targeted muscles represent the excitability of intracortical connections, indicating the functional integrity of the corticospinal tract (CST).[13] The absence of detectable MEPs after ipsilesional stimulation soon after a stroke is considered a predictor of poor functional outcomes.[14,15] Applying focal rTMS to the target primary motor cortex activates both neural synaptic transmission to remote motor networks and crucial elements involved in the effective neural regeneration of new functions.[16]

The connection between a disrupted CST and the efficacy of intermittent theta-burst stimulation (iTBS), an excitatory rTMS paradigm for motor enhancement, has not been examined. We hypothesized that by determining the integrity of the CST and the severity of baseline motor impairment, the effectiveness of iTBS treatment in motor recovery could be predicted. Thus, we compared groups of motor-impaired stroke patients with variously categorized MEPs; we also sought to identify other possible contributing factors underlying the receptiveness of stroke patients to iTBS treatment.

Methods

Participants

Seventy-two stroke patients (15 women; mean age, 62.5y) who presented with unilateral hemiplegia secondary to a first-ever stroke were recruited from a rehabilitation center at a tertiary hospital. All fulfilled the following conditions: (1) a diagnosis of unilateral, ischemic, or hemorrhagic supratentorial stroke at least 2 months prior, as confirmed by magnetic resonance imaging; (2) no history of concomitant neurodegenerative diseases or brain surgery; (3) no aphasia, spatial neglect, visual field deficit, emotional problems, or communication problems; and (4) no rTMS contraindications. All patients underwent detailed clinical and neurologic examinations including the National Institutes of Health Stroke Scale, the distal Medical Research Council (MRC) scale of 0 to 5 points,[17] the FIM system,[18] and electroencephalography. All the patients recruited to the study gave their written informed consent before participating, in accordance with the 2008 Declaration of Helsinki. The study was approved by the local institutional review board.

Fifty-three patients were diagnosed with ischemic stroke and 27 with cortical involvement (with or without subcortical lesion). All patients were in the chronic stage of stroke, with a mean poststroke duration ± SD of 10.5±5.0 months. Other baseline demographic and clinical features are presented in table 1.

Electrophysiological measures and motor assessments were performed at inception (baseline), midterm in the 10-session intervention, and immediately after the 10 sessions of intervention. We divided the patients into 4 groups: 3 groups received a real iTBS treatment, and 1 group received a sham iTBS intervention. The real iTBS groups included patients (group A, n=21) who had inducible MEPs (MEP+) recorded from the paretic first dorsal interosseous (FDI) and exhibited preserved hand grip strength (MRC>1) before iTBS intervention; group B (n=17) included patients who had undetectable MEPs (MEP−) but exhibited preserved hand grip strength (MRC>1); and group C (n=17) included patients with undetectable MEPs and no evidence of hand grip strength (MEP− and MRC=0). Group D (n=17), to which the sham treatment was administered, had a patient composition similar to that of group A and included patients who exhibited positive MEPs (MEP+) and positive grip strength (MRC>1), but underwent a placebo iTBS treatment. Patients with both MEP+ and MRC>1 were randomly assigned to either group A or group D. No patient with a totally paretic hand grip presented with elicited MEPs. Figure 1 summarizes the criteria used for group categorization.

Interventions

Patients in the experimental groups underwent a real iTBS protocol administered using the Magstim Rapid[2,a] with a 70-mm

List of abbreviations:

aMT	**active motor threshold**
CST	**corticospinal tract**
FDI	**first dorsal interosseous**
fMRI	**functional magnetic resonance imaging**
FT	**finger-tapping task**
iTBS	**intermittent theta-burst stimulation**
MEP	**motor-evoked potential**
MRC	**Medical Research Council**
MT	**motor threshold**
RT	**reaction time**
rTMS	**repetitive transcranial magnetic stimulation**
WMFT	**Wolf Motor Function Test**