NEURAL REGENERATION RESEARCH
April 2017, Volume 12, Issue 4 www.nrronline.org

RESEARCH ARTICLE

Low frequency repetitive transcranial magnetic stimulation improves motor dysfunction after cerebral infarction

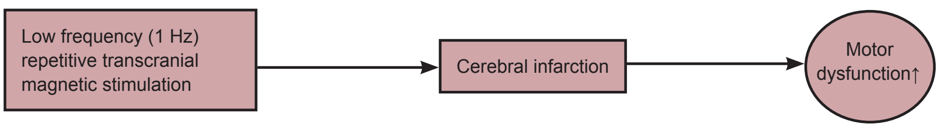
Zhi-yong Meng, Wei-qun Song*
Department of Rehabilitation, Xuanwu Hospital, Capital Medical University, Beijing, China

How to cite this article: *Meng ZY, Song WQ (2017) Low frequency repetitive transcranial magnetic stimulation improves motor dysfunction after cerebral infarction. Neural Regen Res 12(4):610-613.*

Funding: *This project was supported by the National Natural Science Foundation of China, No. 30540058, 30770714; the Natural Science Foundation of Beijing of China, No. 7052030; the Talents Foundation of Organization Department of the Beijing Municipal Committee in China; the Beijing Science Plan Project Fund of China, No. Z0005187040191-1; the Research Foundation of Capital Medical Development of China, No. 2007-2068.*

Graphical Abstract

Low frequency (1 Hz) repetitive transcranial magnetic stimulation helps improve motor function after cerebral infarction



Correspondence to:
Wei-qun Song,
songwq666@163.com.

orcid:
0000-0002-5053-5084
(Wei-qun Song)

doi: *10.4103/1673-5374.205100*

Accepted: *2017-03-07*

Abstract

Low frequency (≤ 1 Hz) repetitive transcranial magnetic stimulation (rTMS) can affect the excitability of the cerebral cortex and synaptic plasticity. Although this is a common method for clinical treatment of cerebral infarction, whether it promotes the recovery of motor function remains controversial. Twenty patients with cerebral infarction combined with hemiparalysis were equally and randomly divided into a low frequency rTMS group and a control group. The patients in the low frequency rTMS group were given 1-Hz rTMS to the contralateral primary motor cortex with a stimulus intensity of 90% motor threshold, 30 minutes/day. The patients in the control group were given sham stimulation. After 14 days of treatment, clinical function scores (National Institute of Health Stroke Scale, Barthel Index, and Fugl-Meyer Assessment) improved significantly in the low frequency rTMS group, and the effects were better than that in the control group. We conclude that low frequency (1 Hz) rTMS for 14 days can help improve motor function after cerebral infarction.

Key Words: *nerve regeneration; brain injury; repetitive transcranial magnetic stimulation; motor dysfunction; cerebral infarction; National Institute of Health Stroke Scale; Barthel Index; Fugl-Meyer Assessment; neural regeneration*

Introduction

Cerebral infarction is a common and frequently occurring disease, with high mortality and disability rates. As a consequence, improving motor function in patients with cerebral infarction has become a focus in basic and clinical research. Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive painless treatment that can affect the excitability of the cerebral cortex and effect changes in synaptic plasticity, which in turn enhance the recovery of neurological function (Hendricks et al., 2002; Rodger and Sherrard, 2016).

This study investigated the effect of 1-Hz low frequency rTMS on the recovery of motor function by analyzing neurological function scores in patients with subacute cerebral infarction.

Subjects and Methods

Subjects

Twenty patients with cerebral infarction combined with hemiparalysis were chosen from June 2012 to December 2012 in the Department of Rehabilitation Medicine, Xuanwu Hospital, Capital Medical University, China. Patients were collected in accordance with cerebral infarction standards. The 20 patients were randomly divided into a low frequency rTMS group (n = 10; 9 males; age: 64.8 ± 9.5 years) and a control group (n = 10; 8 males; age: 65.2 ± 9.7 years). All

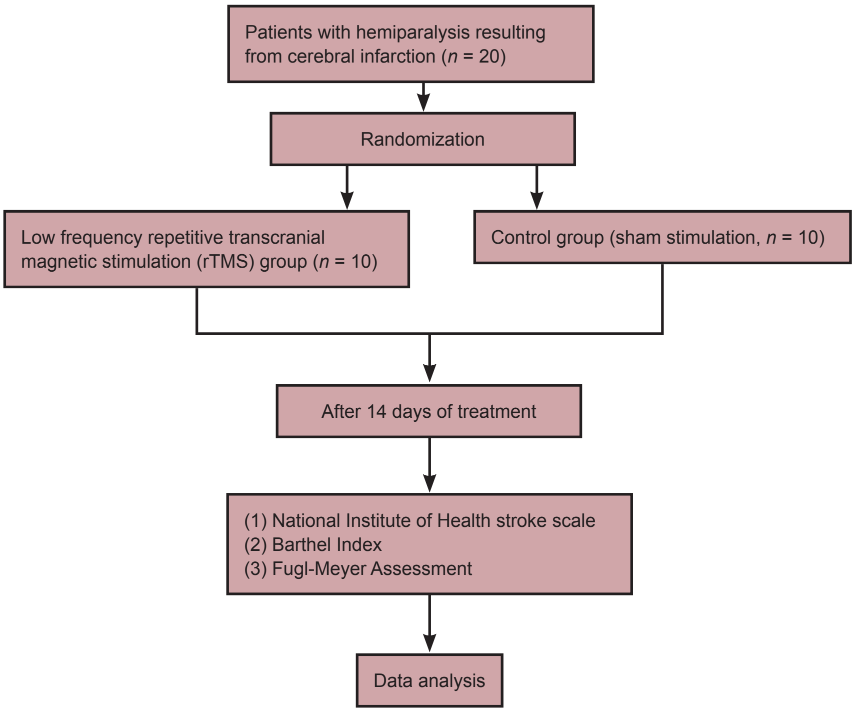


Figure 1 Flow chart of the study.

patients were right-handed. The study was approved by the Ethical Committee of Capital Medical University Xuanwu Hospital.

Inclusion criteria

Patients meeting all the following criteria were included in the study: (1) cerebral infarction of the internal carotid artery that was diagnosed based on clinical symptoms and signs, cranial computed tomography, or magnetic resonance imaging; (2) unilateral limb dysfunction resulting from unilateral cortical damage; (3) first-time stroke; (4) age range: 35–80 years; (5) signed informed consent before treatment by the patients and their families.

Exclusion criteria

Patients meeting any of the following criteria were excluded from the study: (1) use of cardiac pacemakers, implantable defibrillator, or other similar equipment; (2) presence of cerebral hemorrhage, subarachnoid hemorrhage, or transient ischemic attack; (3) worsening of the illness or emergence of new infarctions; (4) medical history of epilepsy; (5) failure of the heart, liver, lung, kidney, or other important organs; (6) severe cognitive or communicative barriers.

rTMS

rTMS was delivered with a Magstim Rapid stimulator (The Magstim Company, Ltd., Carmarthenshire, UK). The figure-8-shaped stimulating coil had a coil diameter of 70 mm. The site of stimulation, parameters, and motor threshold for the rTMS were set according to a previous study (Rossi et al., 2009). Stimulation frequency was 1 Hz and the intensity was 90% of motor threshold. The stimulation site was the contralateral primary motor cortex (M1) contralateral to the infarction. Continuous stimulation was delivered daily in one 30-minute session for 14 days. A total of 1,800 pulses were administered each day. In the control group, patients were given 30 minutes of sham stimulation once per day. Patients were able to hear magnetic stimulator, but did not receive any real magnetic stimulation. Rehabilitation training (exercise) was conducted twice a day for each group, with each session lasting 40 minutes. Therapeutic responses and adverse reactions were observed during all treatments.

Neurological assessment

Neurological function was scored in each group before the experiment and after 14 days of treatment. Functions were assessed using the National Institute of Health Stroke Scale (NIHSS; Vanacker et al., 2016). Additionally, the Barthel Index (BI) was utilized to assess daily living ability and the Fugl-Meyer Assessment (FMA) was employed to evaluate motor function of the limbs (Wei et al., 2011; Kaushal et al., 2014).

Statistical analysis

Data were analyzed using SPSS 17.0 software (SPSS, Chicago, IL, USA). Intergroup comparison was done by independent samples t test or paired t test. A mixed-effect model was used to analyze the influence of confounding factors. The dependent variables were NIHSS, BI, and FMA. The fixed effects were age, sex, course of disease, hypertension, diabetes, coronary heart disease, smoking, and drinking. Significance was set at $P < 0.05$.

Table 1 Changes in NIHSS, BI, and FMA scores for each group

Item	Before treatment	After 14 days of treatment
NIHSS		
Low frequency rTMS	10.85±1.82	7.08±1.34*#
Control	10.56±1.75	8.24±1.56*
BI		
Low frequency rTMS	38.85±4.85	55.24±4.98*#
Control	39.56±4.62	50.92±3.67*
FMA		
Low frequency rTMS	30.78±7.41	47.46±7.88*#
Control	31.85±9.72	42.24±8.57*

Data are expressed as the mean ± SD (n = 10). *P < 0. 01, *vs*. before treatment (paired t-test); #P < 0. 01, *vs*. control group (independent samples t-test). NIHSS: National Institute of Health Stroke Scale; BI: Barthel Index; FMA: Fugl-Meyer Assessment; rTMS: repetitive transcranial magnetic stimulation.

Table 2 Multivariate analysis of factors that might influence post-treatment motor function (*P* value)

Variable	NIHSS	BI	FMA
Age	0.778	0.304	0.113
Gender	0.797	0.342	0.615
Course of the disease	0.315	0.351	0.615
Hypertension	0.514	0.223	0.967
Diabetes	0.235	0.322	0.246
Coronary heart disease	0.365	0.507	0.447
Smoking	0.976	0.612	0.928
Drinking	0.165	0.194	0.086

Effects of age, sex, duration of disease, hypertension, diabetes, coronary heart disease, smoking, and drinking on FMA, NIHSS and BI scores had no statistical significance (P > 0.05). NIHSS: National Institute of Health Stroke Scale; BI: Barthel Index; FMA: Fugl-Meyer Assessment.

Results

Baseline data

None of the patients had new clinical symptoms. Before the experiment, NIHSS, BI, and FMA scores did not differ significantly between the two groups (P > 0.05; **Figure 1** and **Tables 1**, **2**).

Effect of low frequency rTMS on the recovery of motor function

Fourteen days after treatment, NIHSS scores significantly decreased, BI and FMA scores significantly increased in each group (P < 0.01). Further, NIHSS scores significantly decreased and BI and FM scores significanty increased in the low frequency rTMS group than in the control group (all P < 0.05; **Tables 1**, **2**).

Multivariate analysis results

The dependent variables were, NIHSS, BI, and FMA. The analysis showed that none of the factors (age, gender, duration, hypertension, diabetes, coronary heart disease, smoking, or drinking) significantly affected FMA, NIHSS and BI scores (P > 0.05).

Adverse reaction

None of the patients had any severe adverse reactions such as recurrent stroke or seizures. One individual in the low frequency rTMS group experienced dizziness, but the symptoms disappeared soon after treatment.

Discussion

The interhemispheric competition theory suggests that some motor function deficits in patients after stroke result from the loss of inhibition to the cortex contralateral to the injury (Hiscock et al., 2008). rTMS can help achieve regional cortical reorganization of function through the regulation of cortical excitability, which affects neural function (Reis et al., 2008; Liu and Liu, 2015; Hara et al., 2016). The effect of stimulation depends on the frequency and intensity of the stimulation. Generally, low rTMS (less than 1 Hz) can inhibit cortical excitability in the stimulated hemisphere (Murase et al., 2004), facilitate excitatory interhemispheric balance, increase contralateral hemisphere excitability, or reduce the excitability of the contralateral hemisphere to promote the recovery of motor function (Gao et al., 2010; Feng et al., 2016). The results indicated that they led to significantly improved motor function in patients (Ramakrishna and Kim, 2010) and indirectly supported the hemispheric competition theory.

Low frequency stimulation of the contralateral hemisphere not only can reduce the excitability of the contralateral cortex, but also can enhance the effect of functional exercise. Thus, all kinds of exercise training may improve motor function in patients with cerebral infarction. Kakuda et al. (2011) used low frequency rTMS (1 Hz) combined with occupational therapy in post stroke hemiplegic patients with spastic upper extremity, and found that the therapy promoted sports recovery and improved limb spasticity. In the current study, we combined low frequency (1 Hz) rTMS, delivered at 90% of motor threshold (1,800 pulses) to contralateral M1 with daily rehabilitation training. Our results showed that after 14 days of treatment, neurological function improved significantly in rTMS group than in the control group. However, Nichols-Larsen et al. (2005) reported that rTMS did not enhance the therapeutic effect of exercise therapy, possibly because of severe movement disorders in patients; in the short-term, the protocol was not enough to significantly improve motor function.

Lefaucheur (2006) believed that rTMS could promote the recovery of motor function in patients with cerebral infarction, but the duration of improvement was short and was only observed during stimulation or a few minutes afterward. A relationship between the duration and dose of stimulation and the therapeutic effect of rTMS could explain this result. However, many other studies have confirmed that rTMS also produces significant long-term effects (Fitzgerald et al., 2006; Chang et al., 2010). Khedr et al. (2010) studied the long-term effects of two different rTMS frequencies on motor stroke and found that rTMS stimulation significantly improved motor function.

Here, the long-term efficacy of rTMS has been confirmed. Because the brain is a functional network, the absence of motor function after cerebral infarction is not only associated with the local impairments that are directly related with the affected side or its related corticospinal tract, but it is also associated with corticospinal tract integrity and the whole brain. When local brain damage occurs, the network of non-damaged areas is activated, and compensation can gradually occur to alleviate the deficits. Different brain regions, such as dorsal premotor cortex, ventral premotor cortex, supplementary motor area, and top posterior cortex, contribute to the recovery of motor function. Moreover, rTMS promotes the functional reconstruction of the brain neural network, and plays a lasting regulatory role in modulating cortical excitability at the stimulation site and remote areas (Gilio et al., 2003; Quartarone et al., 2005).

In conclusion, low frequency rTMS is useful because it is painless, safe to use, convenient, and because it facilitates motor function recovery in patients with ischemic stroke.

Declaration of patient consent: *The authors certify that they have obtained all appropriate patient consent forms. In the form the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.*

Acknowledgments: *we would like to thank all the doctors from the Rehabilitation Department of Xuanwu Hospital of China for their help in this publication.*

Author contributions: *WQS designed this study and revised the paper. ZYM performed experiments, analyzed data and wrote the paper. Both authors approved the final version of the paper.*

Conflicts of interest: *None declared.*

Plagiarism check: *This paper was screened twice using CrossCheck to verify originality before publication.*

Peer review: *This paper was double-blinded and stringently reviewed by international expert reviewers.*

References

Chang WH, Kim YH, Bang OY, Kim ST, Park YH, Lee PK (2010) Long-term effects of rTMS on motor recovery in patients after subacute stroke. J Rehabil Med 42:758-764.

Feng JY, Shan L, Wang B, Jia FY (2016) Effects of ultra-low frequency transcranial magnetic stimulation on motor function and intelligence of children with spastic cerebral palsy: study protocol for a randomized parallel-cohort controlled trial. Asia Pac J Clin Trials Nerv Syst Dis 1:25-30.

Fitzgerald PB, Fountain S, Daskalakis ZJ (2006) A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. Clin Neurophysiol 117:2584-2596.

Gao F, Wang S, Guo Y, Wang J, Lou M, Wu J, Ding M, Tian M, Zhang H (2010) Protective effects of repetitive transcranial magnetic stimulation in a rat model of transient cerebral ischaemia: a microPET study. Eur J Nucl Med Mol Imaging 37:954-961.

Gilio F, Rizzo V, Siebner HR, Rothwell JC (2003) Effects on the right motor hand-area excitability produced by low-frequency rTMS over human contralateral homologous cortex. J Physiol 551:563-573.

Hara T, Abo M, Kakita K, Masuda T, Yamazaki R (2016) Does a combined intervention program of repetitive transcranial magnetic stimulation and intensive occupational therapy affect cognitive function in patients with post-stroke upper limb hemiparesis? Neural Regen Res 11:1932-1939.

Hendricks HT, Zwarts MJ, Plat EF, van Limbeek J (2002) Systematic review for the early prediction of motor and functional outcome after stroke by using motor-evoked potentials. Arch Phys Med Rehabil 83:1303-1308.

Hiscock A, Miller S, Rothwell J, Tallis RC, Pomeroy VM (2008) Informing dose-finding studies of repetitive transcranial magnetic stimulation to enhance motor function: a qualitative systematic review. Neurorehabil Neural Repair 22:228-249.

Kakuda W, Abo M, Kobayashi K, Momosaki R, Yokoi A, Fukuda A, Ito H, Tominaga A, Umemori T, Kameda Y (2011) Anti-spastic effect of low-frequency rTMS applied with occupational therapy in post-stroke patients with upper limb hemiparesis. Brain Inj 25:496-502.

Kaushal K (2014) Using Barthel index for assessment of disability: a comment on functional disability among elderly persons in a rural area of Haryana. Indian J Public Health 58:284.

Khedr EM, Etraby AE, Hemeda M, Nasef AM, Razek AA (2010) Long-term effect of repetitive transcranial magnetic stimulation on motor function recovery after acute ischemic stroke. Acta Neurol Scand 121:30-37.

Lefaucheur JP (2006) Stroke recovery can be enhanced by using repetitive transcranial magnetic stimulation (rTMS). Neurophysiol Clin 36:105-115.

Liu P, Liu BB (2015) Repetitive transcranial magnetic stimulation in a rat model of middle cerebral artery occlusion: variation of nerve regeneration microenvironment in infarcted brain areas and recovery of rat neurological function. Zhongguo Zuzhi Gongcheng Yanjiu 19:4333-4338.

Murase N, Duque J, Mazzocchio R, Cohen LG (2004) Influence of interhemispheric interactions on motor function in chronic stroke. Ann Neurol 55:400-409.

Nichols-Larsen DS, Clark PC, Zeringue A, Greenspan A, Blanton S (2005) Factors influencing stroke survivors' quality of life during subacute recovery. Stroke 36:1480-1484.

Quartarone A, Bagnato S, Rizzo V, Morgante F, Sant'angelo A, Battaglia F, Messina C, Siebner HR, Girlanda P (2005) Distinct changes in cortical and spinal excitability following high-frequency repetitive TMS to the human motor cortex. Exp Brain Res 161:114-124.

Ramakrishna R, Kim L (2010) Transcranial magnetic stimulation may provide benefit in acute ischemic stroke. World Neurosurg 73:427-428.

Reis J, Swayne OB, Vandermeeren Y, Camus M, Dimyan MA, Harris-Love M, Perez MA, Ragert P, Rothwell JC, Cohen LG (2008) Contribution of transcranial magnetic stimulation to the understanding of cortical mechanisms involved in motor control. J Physiol 586:325-351.

Rodger J, Sherrard RM (2015) Optimising repetitive transcranial magnetic stimulation for neural circuit repair following traumatic brain injury. Neural Regen Res 10:357-359.

Rossi S, Hallett M, Rossini PM, Pascual-Leone A; Safety of TMS Consensus Group (2009) Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 120:2008-2039.

Vanacker P, Heldner MR, Amiguet M, Faouzi M, Cras P, Ntaios G, Arnold M, Mattle HP, Gralla J, Fischer U, Michel P (2016) Prediction of large vessel occlusions in acute stroke: national institute of health stroke scale is hard to beat. Crit Care Med 44:e336-343.

Wei XJ, Tong KY, Hu XL (2011) The responsiveness and correlation between Fugl-Meyer Assessment, Motor Status Scale, and the Action Research Arm Test in chronic stroke with upper-extremity rehabilitation robotic training. Int J Rehabil Res 34:349-356.

Copyedited by Wang J, Li CH, Qiu Y, Song LP, Zhao M