The effects of high-frequency transcranial magnetic stimulation combined with transcutaneous electrical stimulation in a severe stroke patient

Soichiro Koyama,[1] Shigeo Tanabe,[2] Kazuya Takeda,[1] Hiroaki Warashina,[1] Hiroaki Sakurai,[2] Yoshikiyo Kanada,[2] Ryuji Okumura,[3,4] Jun Shinoda,[3,4] Junji Nagata,[5] Tetsuo Kanno[5]

[1]Department of Rehabilitation, Kawamura Hospital; [2]Faculty of Rehabilitation, School of Health Sciences, Fujita Health University; [3]Department of Clinical Brain Sciences, Gifu University Graduate School of Medicine; [4]Chubu Medical Center for Prolonged Traumatic Brain Dysfunction, Kizawa Memorial Hospital; [5]Department of Neurosurgical, Kawamura Hospital, Japan

Abstract

The case report describes the effects of 5 Hz repetitive transcranial magnetic stimulation (rTMS) combined with transcutaneous electrical stimulation (TES) in a patient with severe stroke. The patient was a 69-year-old male who was affected by a left middle cerebral artery infarction. The patient had no movement in his right hand. To assess the effects, cerebral blood flow and motor function were measured before and after treatment. This treatment delivered rTMS over the affected M1 with TES at the paretic wrist extensor muscles for 10 days. The regional cerebral blood flow (rCBF) in the entire brain was measured by positron-emission tomography. To evaluate the motor function, the Fugl-Meyer assessment (FMA) was used. After treatment, the rCBF was increased (except for the stimulated region), and the FMA score was slightly improved. These results suggest the potential therapeutic use of rTMS combined with TES for recovery in severe stroke.

Introduction

Stroke is one of the most common causes of death and the leading cause of chronic disability.[1] If motor dysfunction occurs, recovery is typically incomplete. However, recent rehabilitation methods based on neuroscience may reduce motor impairments.[1] One of the neuroscience rehabilitation methods, repetitive transcranial magnetic stimulation (rTMS), was used to modulate cortical excitability in the lesioned hemisphere. This cortical stimulation approach is noninvasive and painless. In particular, high-frequency rTMS (>5 Hz) stimulates the lesioned hemisphere and upregulates motor cortical excitability in the lesioned hemisphere.[2,3] Strafella *et al.* reported that regional cerebral blood flow (rCBF) in the entire brain was increased as cortical excitability was increased by TMS[4] and might reflect changes in synaptic activity within an interconnected neural system.

In addition, a previous study reported that rTMS with voluntary contraction could further induce changes in the corticospinal excitability.[5] However, this method cannot be used on patients who are unable to fully induce voluntary contraction. To resolve the problem, Koganemaru *et al.* proposed a modified method for stroke patients with moderate paralysis.[6] In the modified method, transcutaneous electrical stimulation (TES) was used to assist with voluntary contraction. This treatment, which was composed of high-frequency rTMS with TES-assisted voluntary contraction, could improve motor function in patients after stroke.[6] However, there are many patients with severe stroke who have no voluntary contraction at all, and it is not clear whether high-frequency rTMS combined with TES is able to improve motor function in patient with severe paralysis. The purpose of this case study was to verify whether rTMS combined with TES changed rCBF and motor function in a severe stroke patient.

Correspondence: Shigeo Tanabe, 98-1 Dengakugakubo, Kutsukake, Toyoake, Aichi, 470-1192 Japan.
Tel. +81.562.93.9000 - Fax: +81.562.95.6817.
E-mail: tanabe@2005.jukuin.keio.ac.jp

Key words: repetitive transcranial magnetic stimulation, transcutaneous electrical stimulation, positron-emission tomography, severely chronic stroke.

Contributions: KS, study execution, data analysis and manuscript writing; TS, study execution and design; TK, WH, KS, experiments performing; KY, NJ, KT, valuable help on the optics providing. All authors discussed results and commented on the manuscript.

Conflict of interests: the authors declare no potential conflict of interests.

Acknowledgements: we appreciate Ikuo Motoya for his helpful technical assistance. In addition, Tomoaki Kaneko and Yousuke Hayakawa provided intensive rehabilitation and acquired the motor function data.

Received for publication: 24 September 2012.
Revision received: 29 October 2012.
Accepted for publication: 13 November 2012.

Clinics and Practice 2012; 2:e89
doi:10.4081/cp.2012.e89

Case Report

The patient was a 69-year-old male affected by left ischemic cerebral infarcts approximately 24 months prior. He had no voluntary contraction in his right hand, spasticity in both paretic upper and lower extremities (modified Ashworth scale 1), no sensory depression, and no other higher brain dysfunction (*e.g.*, neglect). The patient was independent in activities of daily living. The patient was informed of the purpose of this study and gave informed consent to participate in this treatment, which was conducted after receiving approval from the ethics committee of our hospital. The protocol of rTMS with TES was determined and carried out by a medical doctor. The rTMS was performed using a transcranial magnetic stimulator (Magstim Super Rapid Magnetic Stimulator, Magstim Company, Dyfed, UK) with an air-cooled figure-eight coil (outer diameter, 9 cm). To record motor evoked-potential (MEP), surface electromyography (EMG) (MEB-9404, Nihon Kohden, Tokyo, Japan) was used. After cleansing the skin, electrodes (1cm diameter) were arranged over the belly-to-tendon montage of the first dorsal interosseous (FDI) muscle. The ground electrode was placed around the wrist. EMG signals were amplified and filtered at band pass 10–2000 Hz and digitized at a sampling rate of 5 kHz. The rTMS of biphasic magnetic stimuli was delivered over the M1 of the lesioned hemisphere at the paretic hand area. The coil was placed tangentially to the scalp, with the handle pointing 45° postero-laterally. Because MEPs were not elicited with maximal intensity of the stimulator output in this patient, the optimal positions of stimulation were determined as those symmetrically opposite to the optimal positions of the FDI muscles in the unlesioned hemisphere. The rTMS parameters were stimulation frequency 5Hz and stimulation intensity of 110% of the rest motor threshold (RMT) in the unlesioned hemisphere. RMT in the unlesioned hemisphere was defined as the lowest stimulation intensity required eliciting MEPs with peak-to-peak amplitude of 50 uV in the FDI in 5 out of 10 trials. TES was per-

formed using surface neuromuscular stimulator and isolator (stimulator: SEN-8203, isolator: SS-104J, Nihon Khoden, Tokyo, Japan). Wrist extensors (extensor carpi radialis longus and brevis, extensor carpi ulnaris, and extensor digitorum communis) were stimulated with a pair of self-adhesive rectangle electrodes (HV-BIGPAD7×4cm, OMRON Co. Ltd., Kyoto, Japan). One electrode was placed proximally over the forearm below the elbow, and the other was placed distally on the forearm (positioned for optimal joint movement). The TES parameters were set at a frequency 40 Hz with a plus width of 0.25 ms, and stimulation cycle of 500 ms on and 500 ms off. The stimulus pulse was a square monophasic waveform. The optimal location and stimulation intensity were identified in a range up to 30 mA as the level that produced 10° of extension of the paretic wrist measured from desk surface to palmar surface in the relaxed state. The treatment protocol was based on the previous report of rTMS with TES for assisted voluntary contraction.[6] The patient was seated on a comfortable reclining chair. The treatment had 10 cycles (1 cycle=1 min). Each cycle consisted of TES for the extensors for a period of 50 s followed by 5 Hz rTMS for 8 s, which was both preceded and followed by a resting period of 1 s. In addition, because implementation of repetitive stimulation and synchronous application with established rehabilitative treatments leads to more prominent or longer lasting performance improvements,[7] our case study included intensive occupational therapy for 1 h after the treatment. The treatment was carried out for two weeks excluding the weekend. To measure the effect of treatment, we assessed both the rCBF and the motor function before and after treatment. For evaluation of the brain rCBF, we used positron-emission tomography (PET) (ADVANCE NXi Imaging System, General Electric Yokokawa Medical System, Tokyo, Japan). The PET scanner provided 35 transaxial images at 4.25 mm intervals. The in-plane spatial resolution (full width at half maximum) was 4.8 mm, and the scan mode was the standard two-dimensional mode. The patient fasted for at least 6 h before PET. The rCBF was measured by the steady-state method. During PET, the patient was instructed to keep a supine position. The ^{15}O-CO_2 was inhaled at a dose of 500 MBq/kg for the measurement of the rCBF. Before the emission scan was performed, a 15-min transmission scan was performed to correct photon attenuation with a ring source containing ^{68}Ge. The emission scan was acquired for 10 min beginning 5 min after inhaling ^{15}O-CO_2. Arterial blood was manually sampled from the radial artery 3 times at 7, 7.5, and 8 min after the ^{15}O-CO_2 inhalant. During PET data acquisition, head motion was continuously monitored using laser beams projected onto ink markers drawn over the forehead skin and corrected manually as necessary. All PET images were transformed into standard brain size and shape by linear and nonlinear transformations using statistical parametric mapping (SPM2, Wellcome Department of Cognitive Neurology, London, UK) for anatomic standardization[8] in Matlab 7.7 (MathWorks Inc., Sherborn, MA, USA). Tracer accumulation in the regions of interest (ROIs) was analyzed as the standardized uptake value, which is the activity concentration in the ROIs at a fixed time point divided by the injected dose, normalized to the patient's measured weight. The maximum pixel values for each ROI were requested from local sites in units of activity concentration. For evaluation of motor function, we used a Fugl-Meyer Assessment (FMA) before and after the treatment period. The FMA scale is a performance test in which the patient is asked to make movements that are considered to reflect the sequential stages of hyperreflexia, flexion and extension synergies, and the ability to perform selective movements. The upper extremity motor function section consists of 32 items, which represent movement components rated on a three-point ordinal scale (0–2). The score of one item, the reflex activity, is doubled before calculating the sum score. The maximum sum score is 66, inferring optimal recovery. The FMA scale has been shown to be valid.[9]

Results

Figure 1 shows the entire brain region of rCBF before and after treatment. Table 1 shows the maximum ROI values before and after this protocol. The rCBFs in the entire brain region of the stimulated side were increased by the treatment. However, rCBFs in stimulation

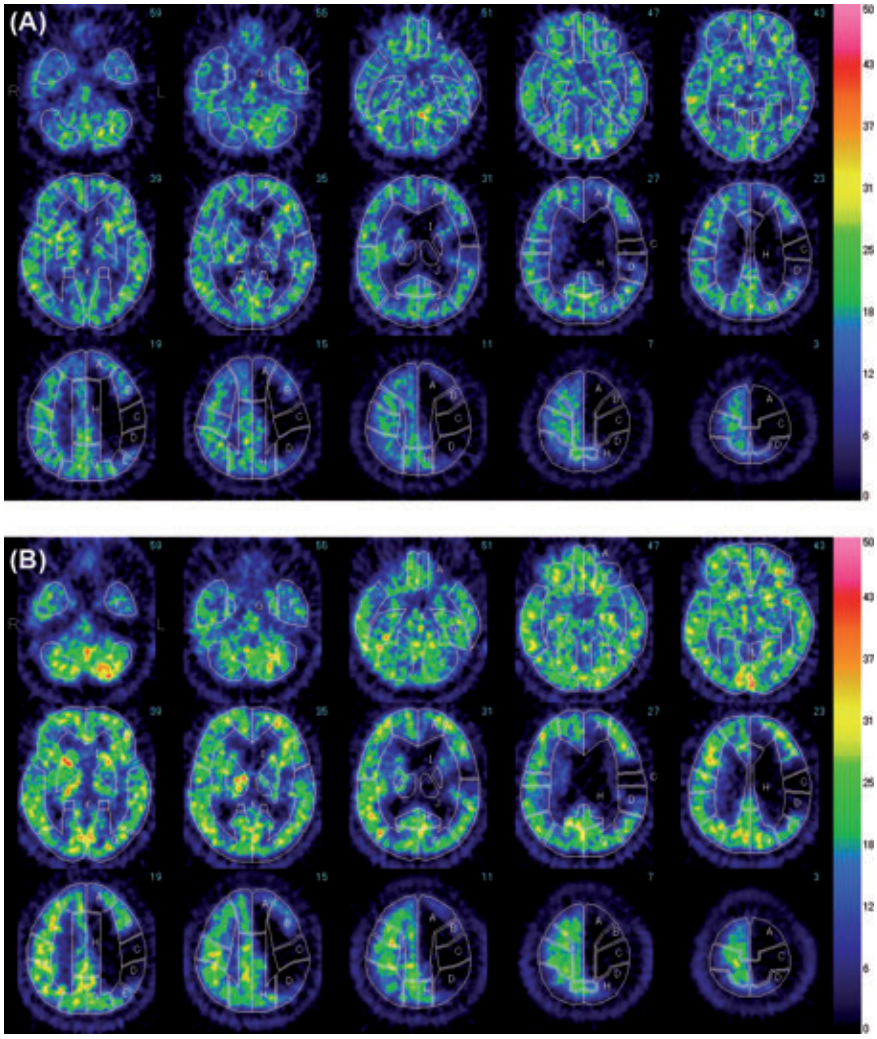

Figure 1. Positron emission tomography images of regional cerebral blood flow (A) before and (B) after treatment.

points such as M1 and the vertex were not increased. Therefore, this treatment could improve rCBF in the entire brain region except for the stimulated region. Table 2 shows the result of FMA scales before and after treatment. Motor function was slightly improved by the treatment.

Discussion

This case study provides important information about the effect of this treatment which was composed of high-frequency rTMS with TES in a severe stroke patient. The rCBF in the stimulated point was not increased by the treatment. This result was inconsistent with previous report[10] where rCBF in the stimulated point, compared with 10 cm above the vertex, was increased by rTMS. The difference suggests that the neuronal cells in the stimulated region might have atrophied in the patient in the present study.

On the other hand, rCBF was increased in areas distant from the stimulated area. This result is consistent with the previous report. From the cellular and molecular viewpoint, changes in rCBF in the unstimulated region after high-frequency rTMS were measured. Ridding *et al.* reported that a mechanism of high-frequency rTMS after-effects involved changes in synaptic activity between cortical neurons (LTD and LTP of synaptic connections).[11] Such LTD and LTP depend on the glutamatergic N-methyl-d-aspartate receptor (NMDAR).[12] NMDAR sensitivity was modulated by brain-derived neurotrophic factor (BDNF). Muller *et al.* reported that high-frequency rTMS increases the expression of BDNF in the unstimulated region.[13] Thus, improvement of rCBF, which reflect changes in synaptic activity in perilesional and distant brain regions, might be caused by these mechanisms. Generally, recovery from motor dysfunction after stroke means that the molecular and cellular substrates of plasticity are changed in both perilesional and distant brain regions such as the dorsolateral premotor cortex, supplementary motor area, and cingulate motor areas together considered to be the secondary motor areas.[14]

In this study, however, motor function improved only slightly. This result was inconsistent with a previous report using the combination of high-frequency rTMS and TES-assisted voluntary contraction in a patient with deficient voluntary contraction[6] where six weeks of high-frequency rTMS with TES improved movement function. The difference suggests that the treatment period in the present study might be too short. In addition, chronic stroke patients have various secondary disabling conditions like a muscle weakness and low endurance. These secondary disabling conditions can further contribute to poor rehabilitation outcomes.[15] Thus, in the present study, improvement of motor function might have been decreased.

Table 1. Maximum regions of interest of regional cerebral blood flow before and after treatment (mL/min/100 mL).

Segment	Right hemisphere (non-stimulus side) Before	After	Left hemisphere (stimulus side) Before	After
Callosomarginal	14.60	17.43	8.92	10.10
Anterior central convolution	15.76	19.32	11.34	13.43
M1	15.09	18.00	1.02	0.99
Vertex	13.15	14.98	4.84	4.57
Angular convolution	16.36	20.05	12.60	13.83
Temporal	17.07	20.19	14.87	16.76
Tritocerebrum	15.76	18.78	15.55	18.29
Around of callosum	15.84	18.58	11.41	12.88
Lenticular nucleus	18.26	21.55	14.57	17.87
Thalamus	13.31	17.34	7.59	8.72
Hippocampus	15.19	17.97	14.80	17.78
Cerebellar hemisphere	15.72	19.11	16.83	20.29

Table 2. Scores of Fugl-Meyer assessment scale before and after treatment.

	Before	After
Shoulder/elbow/forearm	12	14
Wrist	0	0
Hand	0	0
Coordination/speed	0	0
Total	12	14

Conclusions

Our case study verified the effect of high-frequency rTMS with TES in a severe stroke patient using assessment of rCBF and motor function. These results suggest the potential of this treatment method for recovery in severe stroke.

References

1. Feigin VL, Lawes CM, Bennett DA, Anderson CS. Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. Lancet Neurol 2003;2:43-53.
2. Berardelli A, Inghilleri M, Rothwell JC, et al. Facilitation of muscle evoked responses after repetitive cortical stimulation in man. Exp Brain Res 1998;122:79-84.
3. Pascual-Leone A, Valls-Sole J, Wassermann EM, Hallett M. Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. Brain 1994;117:847-58.
4. Strafella AP, Paus T. Cerebral blood-flow changes induced by paired-pulse transcranial magnetic stimulation of the primary motor cortex. J Neurophysiol 2001;85:2624-9.
5. Thabit MN, Ueki Y, Koganemaru S, et al. Movement-related cortical stimulation can induce human motor plasticity.J Neurosci 2010;30:11529-36.
6. Koganemaru S, Mima T, Thabit MN, et al. Recovery of upper-limb function due to enhanced use-dependent plasticity in chronic stroke patients. Brain 2010;133:3373-84.
7. Hummel FC, Cohen LG. Non-invasive brain stimulation: a new strategy to improve neurorehabilitation after stroke? Lancet Neurol 2006;5:708-12.
8. Friston KJ, Frith CD, Liddle PF, et al. The relationship between global and local

changes in PET scans. J Cereb Blood Flow Metab 1990;10:458–66.
9. Fugl-Meyer AR, Jääskö L, Leyman I, et al. The post-stroke hemiplegic patient. 1. A method for evaluation of physical performance. Scand J Rehabil Med 1975;7:13–31.
10. Siebner HR, Takano B, Peinemann A, et al. Continuous transcranial magnetic stimulation during positron emission tomography: a suitable tool for imaging regional excitability of the human cortex. Neuroimage 2001;14:883-90.
11. Ridding MC, Rothwell JC. Is there a future for therapeutic use of transcranial magnetic stimulation?. Nat Rev Neurosci 2007;8:559-67.
12. Stefan K, Kunesch E, Benecke R, et al. Mechanisms of enhancement of human motor cortex excitability induced by interventional paired associative stimulation. J Physiol 2002;543:699-708.
13. Müller MB, Toschi N, Kresse AE, et al. Long-term repetitive transcranial magnetic stimulation increases the expression of brain-derived neurotrophic factor and cholecystokinin mRNA, but not neuropeptide tyrosine mRNA in specific areas of rat brain. Neuropsychopharmacol 2000;23: 205-15.
14. Ward NS. Mechanisms underlying recovery of motor function after stroke. Postgrad Med J 2005;81:510-4.
15. Teixeira-Salmela LF, Olney SJ, Nadeau S, Brouwer B. Muscle strengthening and physical conditioning to reduce impairment and disability in chronic stroke survivors. Arch Phys Med Rehabil 1999; 80:1211-8.