Validation and the Future of Stimulation Therapy of the Primary Motor Cortex

Youichi SAITOH¹,²

¹Department of Neuromodulation and Neurosurgery Office for University-Industry Collaboration, Osaka University, Suita, Osaka;
²Department of Neurosurgery, Osaka University Graduate School of Medicine, Suita, Osaka

Abstract

The use of electrical motor cortex stimulation (EMCS) for post-stroke pain was established in Japan and has spread globally. EMCS has been used for the treatment of neuropathic pain, Parkinson’s syndrome, and recovery of motor paresis. Since 2000, repetitive transcranial magnetic stimulation (rTMS) has been developed for the treatment of various neurological disorders. rTMS is a non-invasive method with almost no adverse effects. In the USA, rTMS of the left dorsolateral prefrontal cortex was approved for the treatment of major depression in 2008. rTMS of the primary motor cortex (M1) has been studied worldwide for the treatment of neuropathic pain, Parkinson’s disease, motor paresis after stroke, and other neurological problems. New methods and devices for rTMS therapy are under development, and rTMS of the M1 is likely to be established as an effective therapy for some neurological disorders. The present review discusses EMCS and rTMS of the M1 concisely.

Key words: primary motor cortex, repetitive transcranial magnetic stimulation, motor cortex stimulation

Introduction

Tsubokawa was the first to use electrical motor cortex stimulation (EMCS) for intractable central post-stroke pain in 1990.¹⁴ Over the next 20 years, the indications for EMCS expanded to include neuropathic pain,²⁴,²⁶,³⁰ the recovery of motor paresis after stroke,²¹ Parkinson’s disease,⁴ and dystonia.²⁵ In 1995, Baker established transcranial magnetic stimulation (TMS), as a non-invasive method for cortical stimulation that could be used for physiological examination. Around 2000, repetitive TMS (rTMS) was developed, and has been expected to become a treatment option for neurological disorders, including Parkinson’s syndrome and depression, pain, recovery of paresis after stroke, and dystonia. In 2008, the Food and Drug Administration (FDA) approved rTMS therapy for major depression.

We had used EMCS for treatment of neuropathic pain (Fig. 1), but only half the patients responded.¹⁴,³⁰ Unfortunately, non-responders can be identified only after the test implantation of EMCS. Therefore, we started using navigation-guided rTMS for neuropathic pain in 2002 (Fig. 2). The response rate is almost the same as for EMCS; approximately 40% of cases have responded to rTMS of the primary motor cortex (M1).¹³ Parkinson’s syndrome has been reported to be affected by rTMS.²² In our institute, pure akinesia was first treated by rTMS of the M1, and remarkable improvement in movement was observed temporarily. Therefore, bilateral EMCS devices were implanted for a patient with pure akinesia.³³ In Parkinson’s disease, bilateral rTMS was thought to be effective for motor symptoms but not for non-motor symptoms. As the effectiveness of rTMS for Parkinson’s disease is consistently temporary, it is believed that consecutive treatments with rTMS are needed for Parkinson’s disease.⁵,³²

Safety guidelines for rTMS were reported in
Fig. 1 Scheme of electrical motor cortex stimulation.

Fig. 2 Scheme of navigation-guided transcranial magnetic stimulation.

Fig. 3 Efficacy of electrical motor cortex stimulation was approximately 50%. We considered that the primary motor cortex was difficult to stimulate because the main part of the primary motor cortex is located within the central sulcus. Therefore, we dissected the central sulcus and implanted electrodes within the central sulcus.

II. Repetitive transcranial magnetic stimulation (rTMS)

rTMS is a non-invasive method. The most popular coil type, the figure-8 coil, can stimulate a confined cerebral area. High-frequency (>1 Hz) stimulation appears to excite the cortex whereas low-frequency (≤1 Hz) stimulation seems to suppress cortical activity. rTMS should be used within the issued safety guidelines. The Magstim® (The Magstim Co. Ltd., Whitland, Carmarthenshire, UK) is the most popular device, but other types are available.

Results of Our Studies

I. Neuropathic pain

In our experience of EMCS, pain reduction of ≥50% was observed in 12 of 32 (36%) patients with ≥12 months follow up. In 10 of the 12 patients who received test electrodes within the central sulcus and on the precentral gyrus, the optimal stimulation was EMCS within the central sulcus. In 4 of these patients (40%), positive effects were maintained at follow up. On the other hand, in approximately 40% of the patients, high frequency rTMS (5 and 10 Hz) of the M1 reduced neuropathic pain significantly in comparison with sham stimulation. The pain reduction ranged from 3 hours to 1 day (Fig. 4). The pain reduction of rTMS was significantly correlated with that of EMCS during test stimulation.

II. Parkinson’s disease

EMCS was not used for Parkinson’s disease because deep brain stimulation (DBS) has been the standard surgical treatment for Parkinson’s disease in our institute. However, rTMS has changed our...
Fig. 4 After repetitive transcranial magnetic stimulation (5-Hz, 1500 pulses), significant pain reduction was obtained in patients with neuropathic pain for 3 hours (*) and continued for a day. The effect of stimulation on pain was rated by patients using a visual analogue scale (VAS) and the short form of the McGill Pain Questionnaire (SF-MPQ).

procedures. One patient with pure akinesia who did not respond to dopamine intake improved remarkably in response to bilateral high frequency rTMS of the M1. The patient received bilateral EMCS and the pure akinesia has been improved for a few years.33) For 21 cases with Parkinson’s disease, rTMS (10-Hz, 500 pulses, bilateral) of the M1 foot area showed significant improvements of Unified Parkinson’s Disease Rating Scale (UPDRS) III score including axial symptoms. The finger tapping test showed significant improvements after rTMS of the M1. Walking speed was also faster after rTMS of the M1. However, the improvements were temporary (unpublished data).

III. Recovery of motor paresis after stroke

Overall, we will examine 40 cases treated with rTMS (20 real rTMS and 20 sham). To date, treatment with rTMS plus rehabilitation showed significant motor recovery in comparison with the sham group. We are collaborating currently with the “Kaifukuki” rehabilitation hospitals, the Kansai Rehabilitation Hospital (Toyonaka, Osaka) and the Takarazuka Rehabilitation Hospital (Takarazuka, Hyogo). Ten patients in a “Kaifukuki state” who had cerebral hemorrhage or infarction between 10–56 days before rTMS were randomized to treatment groups of rTMS (5-Hz, 500 pulses, daily for 10 days) of the M1 hand area with usual rehabilitation or sham rTMS with usual rehabilitation (unpublished data).

Discussion

I. Neuropathic pain

EMCS is effective for 50% of patients with neuropathic pain.1,2,11 However, a craniotomy is required for electrode implantation, and it is difficult to predict successful pain reduction prior to electrode placement. Therefore, few patients wish to receive EMCS. On the other hand, rTMS of the M1 is non-invasive. The success rate may be lower than EMCS, but many patients wish to receive rTMS therapy due to the non-invasive nature of the treatment. In a meta-analysis study,23) rTMS of M1 has been effective for neuropathic pain. Five days of consecutive treatment was reported to be successful and safe.23) It is likely that daily rTMS of M1 for neuropathic pain will take over from EMCS in the future.

II. Parkinson’s disease

DBS for Parkinson’s disease has been performed all over the world, but EMCS has been used in limited circumstances.4,5,10) An Italian group reported that EMCS improved UPDRS scores, especially axial symptoms,4) but a Canadian group reported no improvement.32) Some patients with Parkinson’s disease cannot receive DBS because of older age or other contraindications. rTMS has been shown effective for Parkinson’s disease, but its effect seems milder than that of DBS.12,17,22) rTMS therapy has no side effects in patients with Parkinson’s disease. Therefore, patients with Parkinson’s disease who cannot or do not wish to receive DBS are candidates for rTMS therapy. To date, the most effective target is unclear, so future research will have to identify the most effective rTMS target for Parkinson’s disease.

III. Recovery of motor paresis after stroke

An EMCS trial has been reported in the USA.2) Patients aged 20 to 75 years who had experienced an ischemic stroke at least 4 months previously resulting in persistent moderate weakness of the arm were included. Ten patients were randomized: six patients to EMCS, four to the control group. No patient deaths, neurological deterioration, or seizures occurred. There were two infections from causes unrelated to the protocol. Of the eight patients who completed the treatment, the EMCS plus rehabilitation group showed significantly greater improvement in motor scores of the upper extremity than the control group. To date, EMCS and rTMS trials for the recovery of motor paresis after stroke have been conducted only for the chronic state.6) Only one report has investigated the effec-
tiveness and safety of rTMS for rehabilitation in the acute phase after cerebral infarction.\textsuperscript{16} We are doing a study of rTMS for rehabilitation in “Kaifukuki” and will report the safety and effectiveness in the near future. For rehabilitation of stroke, both low frequency rTMS of unaffected M1 and high frequency rTMS of affected M1 have been reported. The optimum procedure is difficult to decide, and some researchers have recommended combined rTMS.

IV. Mechanism

The detailed mechanism of stimulation of the M1 has been speculated for neuropathic pain, Parkinson’s disease, and recovery of motor paresis after stroke. Simply speaking, each mechanism seems to be different. In neuropathic pain, after M1 stimulation, the thalamus, insula, anterior cingulate cortex, and orbito-frontal cortex are activated.\textsuperscript{10} The pain threshold and emotional perception are modulated to reduce pain. In Parkinson’s disease, the delays of clinical benefits observed with EMCS may be due to synaptic plasticity, long-term potentiation, long-term depression, expression of secondary messengers, or polarization of brain tissue,\textsuperscript{7,19,25} and the immediate effects may be due to the dual effects of imposing a specific pattern of activity and suppressing an abnormal, disease-associated rhythmicity of oscillation in the corticobasal ganglia-cortical circuit.\textsuperscript{3,8,9,25} In the recovery of motor paresis after stroke, stimulation might improve motor performance on two ways: first, by increasing excitability of remaining pathways from the affected hemisphere and second, by improving the response of patients to standard therapy.\textsuperscript{10} rTMS has been used in two ways: low-frequency stimulation (≤ 1 Hz) to the motor cortex of the unaffected hemisphere to reduce the excitability of the contralesional hemisphere, or high-frequency stimulation (> 1 Hz) to M1 of the affected hemisphere. Further studies will be needed to clarify the mechanisms in all clinical uses.

V. Development of rTMS machine

The rTMS device has been developed and improved over time. In the USA, the NeuroStar machine (Neuronetics, Inc., Malvern, Pennsylvania, USA) has been approved by the FDA for treatment of major depression. Furthermore, new types of coils, such as the H-coil, have appeared.\textsuperscript{30} The combination of transcranial direct current stimulation and rTMS is expected to enhance the effects over only rTMS.\textsuperscript{20} Theta-burst stimulation is an easy way to control the excitability of the cortex.\textsuperscript{15} Quadrupulse rTMS can produce a broad range of motor cortical plasticity ranging from motor evoked potential (MEP) suppression to MEP facilitation depending on the interval of the pulses within a burst.\textsuperscript{11} We are currently developing a home system for rTMS therapy in conjunction with a medical instrumentation company (Fig. 5). We predict rTMS therapy will replace EMCS in the future.

Acknowledgment

Our research has been partly supported by Ministry of Health, Labour and Welfare and Ministry of Education, Culture, Sports, Science and Technology.

Conflict of Interest

The author declares that they have no conflict of interest.

References

6) Corti M, Patten C, Triggs W: Repetitive transcranial magnetic stimulation of motor cortex after stroke: A
32) Tanii N, Saitoh Y: Electrical stimulation of primary

Neurul Med Chir (Tokyo) 52, July, 2012


Address reprint requests to: Youichi Saitoh, MD, PhD, Department of Neuromodulation and Neurosurgery Office for University-Industry Collaboration, Osaka University, 2-1 Yamadaoka, Suita, Osaka 565-0871, Japan.
e-mail: neurosaitoh@mbk.nifty.com