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The effects of Task-Oriented Activity after applying Low Frequency Repetitive Transcranial Magnetic Stimulation on Cerebral Motor Evoked Potential Emplitude and Latency in Stroke Patients

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To investigate the effects of task-oriented activities under the residual effect after repetitive transcranial magnetic stimulation (rTMS) on cerebral motor evoked potential (MEP) amplitude, cerebral motor evoked potential (MEP) latency in stroke patients, this study conducted an intervention program on two groups (experimental group - TIL, control groups – GRT, each consisting of 10 patients) of chronic stroke patients. The program–which was conducted three times a week for 6 weeks–evaluated the MEP amplitudes, MEP latency before and after the experiment. In an inter-group test of MEP amplitude and MEP latency, all groups showed an increase between pre- and post-test evaluations. In an intergroup examination on MEP amplitude and MEP latency, a significant difference was observed between the TIL and GRT groups.

Keywords : Low frequency (1Hz) repetitive transcranial magnetic stimulation (rTMS), Motor Evoked Potential (MEP) amplitude, Motor Evoked Potential (MEP) latency

1. Introduction

Many stroke patients experience motor impairment in the hand and upper extremity on the opposite side of the affected cerebral hemisphere as a consequence of corticospinal tract damage [1]. To alleviate motor impairment, various rehabilitation therapies have been used in stroke patients, and the efficacy of these approaches has been well-established in the literature. Noninvasive brain stimulation is a method of stimulating a specific part of the brain in a safe way by using magnetic or electric stimulation without surgical treatment to achieve neuromodulation. Repetitive transcranial magnetic stimulation is currently used in clinical practice [2]. Transcranial magnetic stimulation is based on certain principles in which a magnetic coil placed over the scalp generates a magnetic field, which induces an electric field inside the tissue. The induced electric field frequency subsequently causes depolarization of the neural cells in the cerebral cortex when its frequency reaches the proper strength level and time frame [3]. For instance, the stimulation of the primary motor cortex (M1) can elicit motor-evoked potential (MEP) and background muscle activity as has been recorded by electromyogram (EMG). In 1985, Barker and colleagues introduced transcranial magnetic stimulation, having solved the technical challenges involved in bridging the scalp and skull with a magnetic field pulse of sufficient strength and rapid enough change over time [4]. In 1993, Pascual-Lenon *et al.* reported that repetitive transcranial magnetic stimulation, which rapidly and repeatedly applies transcranial magnetic stimulation, can safely control human brain activity [5]. Previous studies have reported positive therapeutic effects of repetitive transcranial magnetic stimulation, such as an improvement in upper extremity function and muscle tone following its use [6]. Fregni *et al.* (2006) reported that when low-frequency repetitive transcranial magnetic stimulation were administered daily for 5 days, the effect of improving upper limb locomotor function was maintained until 1 week after the end of stimulation [7].

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In addition to these repetitive transcranial magnetic stimulation treatments, a method of increasing the duration of the therapeutic effect by using task-oriented activities for stroke patients is proposed. Task-oriented approach is a treatment modality designed to help improve the ability and functions required for completing tasks and associated goals and problem-solving skills under different circumstances, and to learn effective rewarding strategies [8].

This study therefore aimed to investigate the effects of low-frequency repetitive transcranial magnetic stimulation applied over the cerebral motor cortex, and the subsequent task-oriented activities performed under the residual effect, during the rehabilitation of stroke patients by measuring changes in MEP amplitude, MEP latency of the affected cerebral motor cortex.

2. Theoretical Background

2.1. Mechanism of Repetitive transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation creates a magnetic field in a short time after the electromagnetic coil is placed on the outer skin of the head and turns into an electric field in the tissue. When the electric field wave reaches the appropriate intensity and time, depolarization of the neuron in the cerebral cortex occurs [3]. Sohn *et al.* (1991) stated that magnetic stimulation can be used to stimulate the cerebral cortex efficiently and safely without causing pain because the strength of the magnetic field is not reduced by any resistance from the presence of bone, hair or skin, and the stimulation does not form high current densities in the hair and skin [9]. Repetitive transcranial magnetic stimulation, which is repeatedly applied over a short period of time, has been known to change the activity of the cerebral cortex over a period of time [2]. Changes in cerebral cortical activity are influenced by the number of repetitive magnetic stimuli, intensity, frequency, and total number of stimuli, among which the frequency of stimuli is important [10]. Repeated transcranial magnetic stimulation treatment for stroke patients can be divided into two types, depending on the frequency of the magnetic pulse. The first type uses high-frequency repetitive transcranial magnetic stimulation ($\geq$ 1 Hz), which increases excitability when applied to the stroke-affected cerebral hemisphere. Low-frequency repetitive transcranial magnetic stimulation ($\leq$ 1 Hz), however, decreases excitability when applied to the unaffected cerebral hemisphere [11-13]. According to Corti *et al.* (2012), the effects of repetitive transcranial magnetic stimulation may last several minutes to hours [14]. In previous studies by Thut and Pascual-Leone (2010), low-frequency repetitive transcranial magnetic stimulation applied at an average intensity of 101 % motor threshold (80 %-110 % motor threshold) provided treatment effect for 31 minutes on average [15]. Therefore, in this study, low frequency (1Hz) repetitive transcranial magnetic stimulation was applied to the unsponsored cerebral hemisphere to activate the injured cerebral hemispheres through transcallosal inhibition to improve the impaired upper limb function.

2.2. Transcallosal Inhibition

According to the interhemispheric competition model, in a normal state, both cerebral hemispheres regulate and compete with the opposite cerebral hemispheres, respectively.

This competition is called transcallosal inhibition (TCI) because it inhibits each other through the corpus callosum. Neurons that regulate TCI are located in the primary motor area and project to the other side through the brain beams. The projected neurons stimulate the inhibitory neurons locally in the primary motor area of the contralateral cerebral hemisphere [16]. However, as with strokes, damage to one brain can alter the balance of cortical excitability between the motor and motor regions of both cerebral hemispheres. For example, as the activity of the primary motor area of the unsponsored cerebral hemisphere increases and the balance of the cerebellar tremor suppression (TCI) is broken, the damaged cerebral hemisphere receives a strong cerebral hemispheric inhibition from the unsponsored cerebral hemisphere and affects the movement damage [17]. When low frequency repetitive transcranial magnetic stimulation is applied to the unsponsored cerebral hemisphere, the unsponsored cerebral hemisphere is suppressed and the damaged cerebral hemisphere is suppressed through TCI suppression. Thus, the injured body can be activated.

3. Methods

3.1. Subjects

This study included 20 subjects who met the inclusion criteria among adult stroke patients hospitalized in the Department of Rehabilitation Medicine, hospital B located in Republic of Korea. The subjects included in this study were randomly divided into the two groups for participation. Patients who met the following inclusion criteria were included:

1) those who had been diagnosed with hemiplegia at least six months prior to the start of the study but after the stroke (hemorrhage/infarction);
2) those who had no cognitive impairment (MMSE-K $\geq$ 24); and

Patients were excluded if they had [18]
① Damage to the internal carotid artery;
② an intracranial metallic implant;
③ a history of seizure; and/or
④ a pacemaker or cardiac implant (either cable or metal).

Like magnetic resonance imaging, MRI uses a strong magnetic field which it is necessary to pay special attention to the person who is inserted into the head or eye part of the magnetic material by surgery or the like. Cardiac pacemaker, drug infusion pump, and hearing aid, etc [18].

3.2. Intervention methods

The study subjects were assigned to either the task-oriented activity including residual effect after low-frequency rTMS group (TIL), or the general rehabilitation training group (GRT). The TIL group underwent the application of low-frequency rTMS and performed task-oriented activities for 20 minutes each, and the GRT group received general rehabilitation training (i.e., physical therapy and occupational therapy) for 40 minutes. Each group performed its intervention program three times a week. Data were collected before and after the six-week intervention period for evaluation. This study was conducted from March 2017 to May 2017.

3.2.1. Low-frequency repetitive transcranial magnetic stimulation

Low-frequency repetitive transcranial magnetic stimulation was administered using a MagPro R30 (MagVenture, Farum, Denmark) (Fig. 1). It is a device that has been approved by the Seoul Regional Korea Food Drug Administration to import medical devices (a license number 732). A B65 butterfly coil (70 cm in diameter)

Fig. 1. (Color online) MagPro R30, Medtronic Inc., Skovlunde, Denmark.

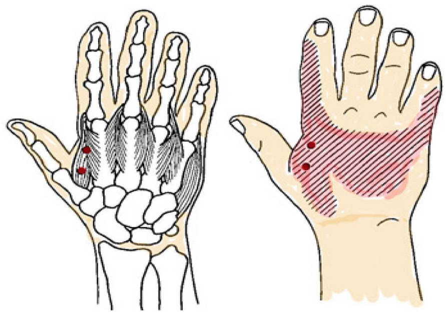

Fig. 2. (Color online) Attached surface electrodes: first dorsal interosseous muscles.

was connected to the device to deliver noninvasive magnetic stimulation to each subject while they lay in a supine position. To evaluate MEP threshold, each subject wore a swim cap on which the sites to be stimulated were marked, and the coil stimulator was placed tangential to the scalp with the handle pointing backwards at 45° away from the midline on the unaffected cerebral hemisphere. To measure MEPs from the hand muscles, Transcranial magnetic stimulation was targeted to the first dorsal interosseous (FDI) (Fig. 2). For a baseline MEP measurement, silver chloride electrodes were applied over the FDI, and a ground electrode was placed around the arm to obtain EMG data. The EMG data were recorded using a portable KEY POINT®.NET software, and EMG signals were amplified to 100 mV/div and filtered at 2 Hz-10 KHz. The site at which the largest MEP was elicited by transcranial magnetic stimulation was identified as the motor cortical area of the target muscle. Resting motor threshold was defined as the minimum stimulation intensity required to produce at least five MEPs out of 10 stimuli with amplitude of 50 μV or higher. During the study, 1,200 pulses of 1 Hz repetitive transcranial magnetic stimulation were applied to the unaffected cerebral hemisphere at a stimulation intensity of 120 % motor threshold to suppress cerebral motor cortex [19].

3.2.2. Task-oriented activities

The task-oriented program implemented in this study consisted of 10 tasks. 1) brushing their hair using a comb, 2) eating using a spoon, 3) folding laundry, 4) wearing clothes (patient uniform), 5) pouring and serving a drink kept in the fridge, 6) sweeping the floor using a broom, 7) putting laundry on a hanger, 8) cleaning windows, 9) ironing shirts, and 10) washing dishes manually.

3.3. Assessment methods

3.3.1. Assessment of cerebral MEP amplitude and latency

MEP amplitude, latency were measured in the same way as repetitive transcranial magnetic stimulation (low-frequency rTMS in this case) using MagPro R30 (Mag-Venture, Farum, Denmark) (Fig. 1).

3.4. Statistical analysis

Statistical analyses of collected data were performed using SPSS 18.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics and frequency analysis were used for the general characteristics of the subjects, and a normality test confirmed that all variables were normally distributed. A paired t-test was used to determine the difference in treatment results before and after the intervention within each group, and an independent sample t-test was used to determine the difference between the groups. The statistical significance was α = 0.05.

4. Results

4.1. General characteristics of subjects

The general characteristics of the experimental, control subjects are shown in (Table 1).

4.2. Comparison of treatment results before and after the intervention within the TIL group

Table 1. General characteristics of subjects.

Variables		TIL (N=10)	GRT (N=10)
Gender	Male	6	5
	Female	4	5
Age		42.20 ± 8.92	44.30 ± 4.96
Lesion type	Hemorrhage	5	7
	Infarction	5	3
Lesion side	Right	4	4
	Left	6	6
Time from stroke to rehab (months)		24.90 ± 6.15	27.40 ± 12.58

M ± SD M: mean SD: standard deviation, TIL: task-oriented activity including residual effect after low frequency rTMS group; GRT: general rehabilitation training group

Table 2. Comparison of results before and after with TIL group.

	Pre-test	Post-test	p
	M ± SD	M ± SD	
MEP amplitude (mV)	0.122 ± 0.07	0.324 ± 0.03	.000***
MEP latency (ms)	28.14 ± 2.69	24.11 ± 1.51	.000***

***p < .001
MEP amplitude: Motor evoked potential amplitude; MEP latency: Motor evoked potential latency

Table 3. Comparison of results before and after with GRT group.

	Pre-test	Post-test	p
	M ± SD	M ± SD	
MEP amplitude (mV)	0.123 ± 0.01	0.266 ± 0.01	.000***
MEP latency (ms)	29.12 ± 3.23	27.05 ± 3.71	.004**

***p < .001

Table 4. Comparison of results between the two groups.

	TIL (N=10)	GRT (N=10)	p
	M ± SD	M ± SD	
MEP amplitude (mV)	0.202 ± 0.02	0.143 ± 0.01	.000***
MEP latency (ms)	3.24 ± 2.10	2.07 ± 1.71	.033*

*p < .05, ***p < .001

The MEP amplitude increased to 0.122 mV and 0.324 mV, before and after the intervention in the TIL group. There were statistically significant differences ($p < 0.001$). And the MEP latency decreased to 28.14 ms and 24.92, before and after intervention. There were also statistically significant differences ($p < 0.001$) (Table 2).

4.3. Comparison of treatment results before and after the intervention within the GRT group

The MEP amplitude increased to 0.123 mV and 0.266 mV before and after intervention in the GRT group. There were statistically significant differences ($p < 0.001$). And the MEP latency decreased to 29.12 ms and 27.05 ms before and after the intervention in the GRT group. There were also statistically significant differences ($p < 0.01$) (Table 3).

4.4. Comparison of the difference in treatment results between the two groups

Concerning the changes in MEP amplitude before and after the intervention, the TIL showed an increase of 0.202 mV, which was statistically greater than the increase of 0.143 mV observed in the GRT group ($p < .001$). The changes in MEP latency was 3.24 ms in the TIL group, which indicates a more significant increase than 2.07 ms observed in the GRT group ($p < .05$) (Table 4).

5. Discussion

Various rehabilitation therapies have been introduced to improve the recovery of functional performance in stroke patients. Meanwhile, better functional outcomes have been reported when early treatment is started in a professional, comprehensive manner after the onset, when compared with in cases in which treatment was started later [2]. While a variety of rehabilitation options are available to help stroke patients overcome their functional impairments and return to pre-stroke activities, the use of repetitive transcranial magnetic stimulation in combination with task-oriented tasks has recently increased in popularity in the rehabilitation context. Transcranial magnetic stimulation has been proposed as an effective neurorehabilitation to show functional improvement in various areas such as exercise, cognition, and language in patients with stroke and Parkinson's disease. Nowak *et al.* (2008) applied low-frequency repetitive transcranial magnetic stimulation (1 Hz) to the primary motor area of the unaffected cerebral cortex in 15 stroke patients and reported the observation of substantially reduced excitability in the unaffected motor cortex and improved motor function of the affected hand [20].

In this study, MEP amplitude, latency was measured using repetitive transcranial magnetic stimulation. The pre- and post-intervention assessments revealed statistically significant differences in the treatment results in both the TIL and GRT groups, indicating that the intervention programs effectively changed MEP amplitude and MEP latency. When the two groups were compared with each other, the TIL group showed significantly greater increases in MEP amplitude than did the GRT group.

MEPs represent the overall activation level of the motor neurons that are connected with the cerebral cortex and neural tracts. That is, the magnetic pulses stimulate the neural tracts connected with the cerebral motor areas both directly and indirectly, and the excitability in the stimulated tracts causes the contraction of muscles in the periphery through α-motor neurons located in the involved spinal cord. As a result, potentials are elicited [21, 22]. The potentials elicited by the above process can contract peripheral muscles. The setting of task-oriented activities yielded positive results on cerebral cortex activation because the tasks required the use of the affected upper extremity. These findings confirm that a combination of repetitive transcranial magnetic stimulation and task-oriented activities was more effective in increasing MEPs in improving upper extremity function than general rehabilitation training. In a study by Migita *et al.* (1995) found that when low frequency repetitive transcranial magnetic stimulation was applied to the unaffected cerebral hemisphere after stroke, the amplitude of the motor-induced dislocation was increased in the biceps brachii and triceps brachii on the paralyzed side, the contraction force was increased [23]. Thus, the results of this study are consistent with those of the previous study, and underline the effectiveness of the use of low-frequency repetitive transcranial magnetic stimulation and a subsequent task-oriented approach treatment protocol in improving cerebral MEP.

When the two groups were compared with each other, the TIL group showed significantly greater increases in MEP latency than did the GRT group.

There are several reasons for the delayed activation latency in stroke patients: decrease in number of active pyramidal neurons, increase in temporal dipersion, slow activity of pyramidal neurons in lesion cortex, the slow activity of the corticospinal tract of the premotor cortex and the supplementary motor cortex, the slow regeneration of slow activity in invading muscles, and the contribution of nerve fibers with slow conduction from the normal cerebral hemisphere. Unlike the stimulation reflected by the motor-induced potential, the incubation period shows the excitability of the cerebral cortical inhibition circuit mediated through the GABAergic system [24]. The persistent latency expands the inhibitory neurons, expands the inhibition of the cerebral cortical motor neurons, and limits cellular activity [25]. Previous studies have shown that Traversa *et al.* (2000) actually showed a gradual decrease in latency with clinical improvement and a similar trend in patients with subacute stroke [26]. We can expect a shorter incubation period in patients with chronic stroke who are not sure for each individual, but whose functional status is relatively good [27, 28].

In this study, increased pre- and post-exercise induction potentials and decreased latency time in the intervention program showed that repeated and intense repetitive training of repetitive cranial magnetic stimulation and daily life-related task- Support the study that the latency latency may be reduced to improve the neural plasticity of the damaged cerebral hemisphere [29]. Recently, there have been studies on the effects of transcranial magnetic stimulation using EEG as well as brain imaging studies such as fMRI and PET. Especially, EEG can be used not only to measure the effect before and after TMS, but also to measure the effectiveness of transcranial magnetic stimulation [30]. Therefore, we think that it will be helpful to establish basis of new rehabilitation treatment and evaluation by combining transcranial magnetic stimulation and brain imaging technique in the future.

6. Conclusions

Noninvasive brain stimulation using repetitive transcranial magnetic stimulation is a new concept of neurorehabilitation that is different from existing rehabilitation, which is based on improvement of brain function through peripheral control. This study reports that an intervention combining low-frequency repetitive transcranial magnetic stimulation and task-oriented activities demonstrated significantly greater improvements in MEP amplitude, MEP latency in the affected cerebral cortex as compared with conventional rehabilitation training in stroke patients when performed three times a week for six weeks. Therefore, based on the present study, transcranial magnetic stimulation is a new neurorehabilitation and evaluation method that can be used safely and effectively for stroke patients, and it seems to be more likely to develop in the future.

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