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The Effect of Low-frequency Repetitive Transcranial Magnetic Stimulation on Muscle Tone Reduction and Cerebral Activity in Stroke Patients

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An intervention program was conducted with two groups of patients who had experienced stroke: one which received low-frequency rTMS and occupational therapy (rTMS-OT Group), and one which received occupational therapy only (OT group). The treatment was provided three times per week for 4 weeks followed by a 1-week evaluation of MEP amplitude and latency, and muscle tone. In an intergroup test of MEP amplitude and latency, and muscle tone, all groups showed increases between pre-and post-test evaluations. As a result of the study, during the treatment intervention of the experimental group and the control group, the experimental group rTMS-OTG and the control OTG group showed MEP amplitudes of 0.161 mV and 0.114 mV, respectively, and the experimental group showed more improvement. The MEP latency of the rTMS-OTG group was -2.83 ms and the MEP latency of the OTG group was -1.49 ms. The experimental group, rTMS-OTG, responded faster. However, in the case of muscle tone evaluation, there was no significant difference between the two groups. In conclusion, we determined that rTMS may be safely applied to the directly damaged cerebral cortex and is considered to be an effective treatment for patients recovering from stroke.

Keywords : repetitive transcranial magnetic stimulation (rTMS), motor-evoked potential amplitude (MEP amplitude), motor-evoked potential latency (MEP latency), muscle stiffness, Hemiplegia

1. Introduction

Stroke is a cerebrovascular disease that occurs as a result of hemorrhage and ischemia [1]. Following a stroke, many patients develop impaired contralateral upper extremity movement in the damaged cerebral hemisphere due to injury to the corticospinal tract [2]. Hemiplegia occurs as a general symptom of movement disorder after stroke [3], and upper extremity dysfunction, such as spasticity, occurs due to abnormal muscle tone. These problems make it difficult for patients to perform the functional movements required by the activities of daily living [4]. Spasticity results in movement weakness and clumsiness in the paralyzed extremity, which can cause pain and other complications. Therefore, the occurrence of spasticity reduces quality of life [5].

Various methods have been reported to recover upper extremity dysfunction to relieve hypertonia and stiffness in patients who have experienced stroke. Of these, repetitive transcranial magnetic stimulation (rTMS) has been reported to have a positive effect on hypertonia and cortical enhancement in recent studies. Transcranial magnetic stimulation (TMS) is a method of depolarizing nerve cells under a coil with magnetic field energy of approximately 2 T that is generated by applying a strong electric current to the electromagnetic coil [6, 7]. Among the factors that affect cortical excitability through TMS, the frequency of stimulation plays an important role. Generally, in normal individuals, high-frequency stimulation corresponding to a stimulation frequency of 5-20 Hz increases the excitability of the corticospinal tract, whereas low-frequency stimulation at 1 Hz reduces the excitability of the corticospinal tract for a short period of time [8-10]. The rationale behind TMS is a theory that states that under normal conditions each cerebral hemisphere controls the opposite hemisphere. Because these controls inhibit each other through the corpus callosum, this process is called transcallosal inhibition (TCI). Neurons involved in TCI are located in the primary motor area and are projected to the opposite side

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through girders to locally stimulate inhibitory nerve cells in the primary motor area of the contralateral cerebral hemisphere [11]. After a stroke, if the balance of TCI is disrupted along with an increase in the activity of the primary motor area of the non-injured cerebral hemisphere, the injured cerebral hemisphere receives strong interhemispheric inhibition from the non-injured hemisphere, which affects movement [12]. Therefore, when rTMS is applied to restore motor function after stroke if low-frequency (1 Hz) stimulation is applied to the non-injured hemisphere motor cortex, the increased excitability is reduced and the high-frequency (5 Hz or more) stimulation to the injured side cerebral hemisphere motor cortex is reduced. In short, rTMS operates on the principle of increasing excitability when stimulation is applied [13].

Previous reports have suggested that using such low-frequency rTMS affects motor function through spasticity and cerebral activation. For example, Valle *et al.* (2007) found that activation of the cerebral motor cortex through TMS increases the inhibitory effect on spinal excitability through the corticospinal tract and thus reduces hyper-activity of gamma and alpha neurons resulting in stiffness. Out of the patient groups provided 5 Hz, 1 Hz, and sham stimulation for 5 days, the 5-Hz application group reported a significant decrease in spasticity [14]. Another study by Naghdi *et al.* (2015) investigating the correlation between stiffness and motor function in patients recovering from stroke suggested that when low-frequency rTMS is applied to the primary motor cortex of an intact lower extremity, abnormal hypertonicity of the injured lower extremity is reduced and motor impairment is improved [15]. This induces the aforementioned local depolarization of rTMS in neurons, as it can activate or inhibit the cerebral cortex depending on stimulus size and location.

Therefore, this study investigated the effects of the application of low-frequency (1 Hz) rTMS to the motor cortex on the non-injured side of patients recovering from stroke by measuring the hypertonicity of the paralyzed upper extremity and the MEP amplitude of the cerebral motor cortex on the injured side of patients. In addition, MEP latency was measured to analyze the cerebral activity on the patient's injured side and to investigate how these changes might affect the rehabilitation of patients recovering from stroke.

2. Theoretical Background

2.1. Principles and Effects of TMS

The fact that magnetic stimulation of TMS is not weakened by objects with high resistance such as the skull or scalp and does not form a strong current density in the scalp, allows it to be used in the therapeutic and experimental setting with less pain. In addition, safe and effective control of the cerebrum can be obtained non-invasively [16, 17].

The effect of TMS can increase or decrease the activity of the corticospinal tract according to frequency, stimulation intensity, and coil direction. High-frequency TMS increases the activity of the cerebral cortex through stimulation at 5–20 Hz. Conversely, low-frequency rTMS suppresses cortical activity through stimulation below 1 Hz. In previous studies, 20-Hz high-frequency rTMS increased local blood flow in the frontal lobe, cingulate gyrus, insula, hippocampus, thalamus, and cerebellum, and 1 Hz rTMS increased local blood flow in the frontal and, medial temporal lobes, and basal ganglia, whereas blood flow to the amygdaloid body decreased. This allowed for confirmation of the opposite effects of high- and low-frequency rTMS [18]. The effect of low-frequency TMS can be explained by the theory of TCI, which is a model of competition between cerebral hemispheres. In normal individuals, the cerebral hemi-spheres control opposite cerebral hemispheres, and this balance can be controlled by the mechanism of inter-hemispheric inhibition through the corpus callosum [19]. In a related previous study, when rTMS was applied to the non-injured cerebral motor area of patients recovering from stroke, the activity of the cerebral motor cortex on the injured side was increased by the disinhibition mechanism of the cerebral hemisphere on the injured side [12].

3. Methods

3.1. Research Participants

Participants for this study included adult patients recovering from stroke who were admitted to the Department of Rehabilitation Medicine at B Hospital in Gyeonggi-do and received rehabilitation treatment between February and May of 2022. A total of 32 participants who met the criteria of the study were selected. Among them, 30 participants were randomly assigned to two groups of 15 participants each, except two who dropped out. The specific inclusion criteria were as follows:

1) Patients diagnosed with stroke (defined as cerebral hemorrhage and cerebral infarction) by a rehabilitation medicine doctor

2) Patients for whom more than 6 months have passed since the onset of stroke

3) Patients who voluntarily participated after hearing

the explanation of this study and obtaining consent

The exclusion criteria of this study were set according to the recommendations of Rossi *et al.* (2009) to prevent side effects when using rTMS [20], and were as follows:

1) Patients with pacemakers installed
2) Patients with metal hardware in their heads
3) Patients with a history of seizures

In addition, those with aphasia, cognitive impairment, unilateral neglect, and visual field defects, or psychiatric or orthopedic conditions were excluded.

3.2. Intervention program

The experimental group was known as the rTMS-Occupational Therapy group (rTMS-OTG), and the control group was known as the Occupational Therapy group (OTG). The rTMS-OTG group was subjected to low-frequency TMS for 20 min following occupational therapy (also 20 min), and the OTG was administered occupational therapy for 40 min for each session. Both groups were treated three times per week for 4 weeks. Specific details of the occupational therapy applied to both groups are shown in Table 1. The evaluation was performed before and after the intervention.

3.2.1. Low-frequency rTMS

MagPro R30 (Magventure, Farum, Denmark) was used to apply low-frequency rTMS (Fig. 1). A B65 butterfly coil stimulator with a diameter of 70 cm was connected to MagPro R30 and the participants were assessed while lying down while receiving non-invasive magnetic stimulation. After placing a hood on which coordinates were drawn on the participant's head, the coil stimulator was positioned at an angle of 45° from the center line with the handle portion facing backward in a tangential direction to the side of the head of the uninjured cerebral hemisphere. When measuring the MEP in the hand, the

Fig. 1. (Color online) MagPro R30, Medtronic Inc., Skovlunde, Denmark.
(MagPro R30 was used to apply low-frequency rTMS, A B65 butterfly coil stimulator, non-invasive magnetic stimulation)

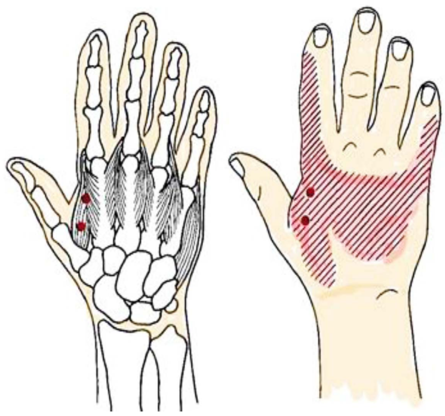

Fig. 2. (Color online) Attached surface electrodes: first dorsal interosseous.
(When measuring the MEP in the hand, the first dorsal interosseous (FDI) was measured as the target muscle)

Table 1. Treatment program for each group.
(Both groups were treated three times per week for 4 weeks. Specific details of the occupational therapy applied to both groups are shown in Table 1)

rTMS-OT group		OTG
1. Low frequency rTMS (20 min)	1 Hz, 1200 pulse, 120% MT	Occupational therapy (40 min)
2. Occupational therapy (20 min)	1. Upper extremity flexor stretching exercise 2. Grip the cup 3. Press a computer keyboard 4. Grip the small ball 5. Move the stoking cone 6. ROM arc exercise	1. Upper extremity flexor stretching exercise 2. Grip the cup 3. Press a computer keyboard 4. Grip the small ball 5. Move the stoking cone 6. ROM arc exercise

rTMS-OTG: repetitive transcranial magnetic stimulation and occupational therapy group first dorsal interosseous (FDI) was measured as the target muscle (Fig. 2).

Before the study, a silver-silver chloride electrode was attached to the intervertebral muscle to measure the exercise-induced potential, and the ground electrode was attached to the arm to measure the EMG value. EMG values were subsequently recorded through portable KEY POINT®.NET software, and the signal was amplified at 100 mV/div and subsequently filtered from 2 Hz to 10 kHz.

The point where the largest exercise evoked potential (MEP) appeared in the recorded potential of the FDI was judged as the motor cortex region of the corresponding muscle. The resting motor threshold was defined as the minimum stimulus intensity at which an MEP of 50 μV or higher was recorded in at least five or more of the 10 stimuli. The amplitude and latency of the MEP stimulated with an MEP of 120% latency values were measured 15 times to determine the average value [21].

3.3. Assessment

3.3.1. Assessment of cerebral MEP amplitude and latency

The evaluation of cerebral MEP amplitude and latency was measured in the same manner as in the rTMS application method using MagPro R30 for applying low-frequency rTMS. To measure the exercise-induced potential, a silver-silver chloride electrode was first attached to the FDI, and the ground electrode was attached to the arm to measure the EMG value. EMG values were subsequently recorded through portable KEY POINT®.NET software, and the signal was amplified at 100 mV/div and then filtered from 2 Hz to 10 kHz. The resting motor threshold was defined as the minimum stimulus intensity at which an MEP of 50 μV or higher was recorded in at least five or more of the 10 stimuli. The amplitude and latency of the MEP stimulated with an MEP of 120% latency values were measured 15 times to determine the average value [21].

3.3.2. Muscle tone assessment

A muscle tone tester (MyotonPRO, MyotenAS, Tallinn, Estonia) was used to measure the muscle tone of the upper extremity. This equipment has been proven to be reliable and valid for evaluating muscle tone in patients recovering from stroke [22].

In a study by Agyapong-Badu *et al.* (2013), it was reported that the intra-rater reliability correlation was as high as 0.94-0.99 [23]. Tendon hyperactivity and clasp-knife phenomenon have been reported in patients recovering from stroke due to central nerve damage, along with increased flexor tension in the upper extremity and increased extensor tension in the lower extremity [24]. Therefore, the long head of the biceps brachii was selected and measured among the flexor muscles of the upper extremities of patients in this study. The measurement method for the muscle tone test was derived a previous study from Louise *et al.* (2013), and the test method was as follows [25]: First, the participant aligned the forearm in a neutral position while being in a supine position and supported it with a pillow to support posture. Second, using a rolled towel under the wrist, the elbow was bent to approximately 10-15° to prevent excessive elongation of the biceps brachii muscle. The measurement position at the top needle of the muscle tone device was adjusted to identify the midpoint between the point outside the acromion of the scapula and the inside concave surface of the altar to determine the location of the muscle belly in the case of the long biceps muscle. Measurement was taken by maintaining a right angle to the muscle using a tape measure and tape, and a non-toxic marker to mark the skin (Fig. 3).

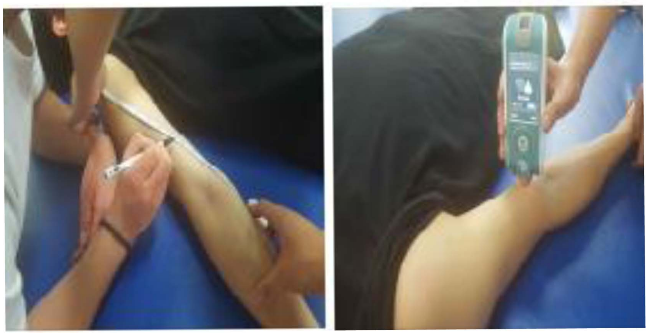

Fig. 3. (Color online) Location of testing site for biceps brachii.
(Measurement was taken by maintaining a right angle to the muscle using a tape measure and tape, and a non-toxic marker to mark the skin)

3.4. Statistical processing

The collected data was statistically analyzed using the SPSS 22.0 program for Windows (IBM Corp., Armonk, NY, US). Descriptive statistics and frequency analysis were performed for the general characteristics of the study participants, and as a result of normality verification on the data collected through the study all variables were found to be normally distributed.

A paired-sample t-test was performed to investigate differences in treatment before and after the intervention within groups, and an independent-sample t-test was performed for comparison between groups.

4. Results

4.1. General characteristics of study participants

The general characteristics of the participants of this study are presented in Table 2. As shown in Table 3, there was no significant difference among MEP, MEP latency, and muscle tone in terms of the homogeneity verification of the participants of this study. Therefore, the homogeneity of the participants was secured before data collection for this study began.

4.2. Comparison of effects before and after the intervention within the experimental group

In comparison of the MEP amplitude change in the experimental group, a significant increase (p<.001) was observed, from 0.154 mV before the intervention to 0.316 mV afterward. In the comparison of MEP latency change, a significant decrease (p<.001) was observed, from 26.14 ms before the intervention to 23.31 ms afterward. In the evaluation of muscle tone, muscle tone decreased (p<.001) before and after the intervention from 18.12 Hz before to 14.56 Hz after the intervention (Table 4).

4.3. Comparison of effects before and after the intervention within the control group

In a comparison of the MEP amplitudes in the control group, a significant increase (p<.001) was observed, from 0.160 mV before the intervention to 0.274 mV afterward. In the comparison of MEP latency change, there was a significant decrease (p<.001) from 27.26 ms before the intervention to 25.76 ms afterward. In the evaluation of muscle tone, a decrease was noted (p<.001) from 16.81 Hz before the intervention to 15.80 Hz afterward (Table 5).

4.4. Comparison between two groups before and after the intervention

In the comparison of the changes before and after the

Table 2. General characteristics of participants.
(The general characteristics of the participants of this study are presented in Table 2)

Variables		rTMS-OTG (N=15)	OTG (N=15)
Sex	Male	7	9
	Female	8	6
Age		43.13±2.45	43.93±1.03
Lesion type	Hemorrhage	8	7
	Infarction	7	8
Lesion side	Right	6	7
	Left	9	8
Time from stroke to rehabilitation (months)		20.00±1.24	19.07±1.38

M±SD
M: mean
SD: standard deviation
rTMS-OTG: repetitive transcranial magnetic stimulation and occupational therapy group
OTG: Occupational therapy group

Table 3. Homogeneity test of variables.
(there was no significant difference among MEP, MEP latency, and muscle tone in terms of the homogeneity verification of the participants of this study)

	rTMS-OTG (N=15)	OTG (N=15)	*t*	*p*
	M±SD	M±SD		
MEP amplitude (mV)	0.154±0.028	0.160±0.026	-0.521	.606
MEP latency (ms)	26.14±2.94	27.26±3.46	-0.952	.349
Muscle tone (Hz)	18.12±2.10	16.81±2.39	1.594	.122

M±SD
M: mean
SD: standard deviation
MEP: motor evoked potential
rTMS-OTG: repetitive transcranial magnetic stimulation and occupational therapy group
OTG: occupational therapy group

Table 4. Comparison of results before and after the intervention within the experimental group (rTMS-OTG). (Significant results were obtained in all items after intervention in the experimental group)

	Pre-test	Post-test	*t*	*p*
	M±SD	M±SD		
MEP amplitude (mV)	0.154±0.02	0.316±0.03	-14.029	.000***
MEP latency (ms)	26.14±2.94	23.31±1.75	5.105	.000***
Muscle tone (Hz)	18.12±2.10	14.56±1.93	7.418	.000***

***p<.001
M±SD
M: mean
SD: standard deviation
MEP: Motor-evoked potential
rTMS-OTG: repetitive transcranial magnetic stimulation and occupational therapy group

Table 5. Comparison of results before and after the intervention within the control group (OTG). (Significant results were obtained in all items after the intervention of the control group)

	Pre-test	Post-test	*t*	*p*
	M±SD	M±SD		
MEP amplitude (mV)	0.160±0.026	0.274±0.022	-14.029	.000***
MEP latency (ms)	27.26±3.46	25.76±3.47	5.105	.000***
Muscle tone (Hz)	16.81±2.39	15.80±2.36	7.418	.000***

***p<.001
M±SD
M: mean
SD: standard deviation
OTG: Occupational therapy group
MEP: Motor Evoked Potential

intervention between the two groups, the rTMS-OTG and OTG groups showed MEP amplitudes of 0.161 mV and 0.114 mV, respectively. MEP latency in the rTMS-OTG group was -2.83 ms and that in the OTG group was -1.49 ms. However, in the case of muscle tone evaluation, muscle tone in the rTMS-OTG group decreased by -3.56 Hz and that in the OTG group decreased by -1.00 Hz; however, there was no significant differences between the rTMS-OTG and OTG groups (Table 6).

5. Discussion

Various rehabilitation treatment methods have been proposed to restore function after stroke. Among them is rTMS therapy, in which the excitability of the cerebral cortex can be changed according to several variables such

Table 6. Comparison of results between the two groups. (After intervention, there was a statistically significant difference in MEP amplitude between the experimental group and the control group)

	rTMS-OTG (N=6)	OTG (N=6)	*t*	*p*
	M±SD	M±SD		
MEP amplitude (mV)	0.161±0.044	0.114±0.037	4.201	.000***
MEP latency (ms)	-2.83±2.14	-1.49±1.20	-2.436	.021*
Muscle tone (Hz)	-3.56±1.86	-1.00±0.58	-1.572	.127

*p<.05 **p<.01
M±SD
M: mean
SD: standard deviation
MEP: Motor Evoked Potential
rTMS-OTG: repetitive transcranial magnetic stimulation and occupational therapy group
OTG: occupational therapy group

as the level of magnetic stimulation (high or low frequency), duration (time), and intensity [26]. In a previous study, Nowak *et al.* (2008) performed low-frequency (1 Hz) rTMS in the primary motor area of the intact cerebral cortex in 15 patients recovering from stroke, reporting that movement improved [27].

In the present study, low-frequency rTMS was applied together with general rehabilitation treatment and the MEP amplitude and latency, and muscle tone were evaluated as indicators of the activity of the cerebral motor cortex on the injured side of patients recovering from stroke. The following results were obtained.

First, both rTMS-OTG and OTG groups showed significant differences in pre- and post-intervention evaluations of MEP amplitude and latency, and muscle tone within each group. Therefore, it was found that the intervention methods of the rTMS-OTG and OTG groups had therapeutic effects for increasing the MEP amplitude indicating cerebral activity, reducing the MEP latency period, and reducing muscle tone. We also found that when evaluating the MEP amplitude and latency between the two groups before and after the intervention, the rTMS-OTG group showed a significant increase in the amplitude of the exercise evoked potential than the OTG group, and the MEP latency also showed a significant decrease. These results suggest that the TCI of TMS, exercise therapy, and task application had a positive effect. First, TCI is based on the theory that in a normal brain state, both cerebral hemispheres control and compete with the other in the opposite cerebral hemisphere. Since the regulation and competition of the cerebral hemispheres inhibit each other through the corpus callosum in the cerebral medulla, this is called corpus callosum inhibition [28]. However, damage to one cerebral hemisphere as often happens during a stroke causes an imbalance in cortical activity between the motor areas of both cerebral hemispheres, and the injured cerebral hemisphere receives strong inhibition from the uninjured cerebral hemisphere, which affects motor performance 2[1]. Based on this theory, low-frequency rTMS was applied to the normal cerebral hemisphere in this study to decrease normal cortical activity, and it can be seen that the MEP was improved by reversing the activation of the injured cerebral hemisphere through TCI.

Additionally, we determined that the hand therapy program in this study had a positive effect on the improvement of cerebral motor cortex activity by combining occupational therapy with rTMS, which placed the upper extremity task on the injured side. Since absence of MEP is related to the excitability of the cerebral cortex, its absence during appropriate magnetic stimulation means that a neuron or neural stem is dead or has a very high motor threshold [22, 29]; its presence during rehabilitation treatment is considered to indicate a positive effect of the treatment. Our results are in line with those of a previous study that evaluated the effects of TMS on the primary motor area of the cerebral cortex, in which patients with high MEP in paralyzed upper extremity muscles within 30 days after stroke demonstrated a more positive recovery of function than patients with low MEP [30].

Patients recovering from stroke have delayed MEP latency due to a decrease in the number of pyramidal neurons; an increase in temporal dispersion; and slowed activity of the pyramidal neurons in the lesion motor cortex, premotor cortex, and auxiliary motor regions. This is a result of slow activity in the corticospinal tract of the supplementary motor cortex and nerve re-regulation in the affected muscle as well as the contribution of nerve fibers with slow conduction from the normal cerebral hemisphere [31]. Therefore, in this study, the decrease in the MEP latency in the experimental group is considered to be an indicator that MEP can be induced more quickly and exercise ability can be improved. In a previous study, Traversa *et al.* (2000) reported that a gradual decrease in the incubation period was accompanied by clinical improvement [32]. Therefore, it is estimated that the MEP incubation period will be shorter and tolerance for induced exercise will increase in the case of patients recovering from stroke with good function.

There was no significant difference in muscle tone between the two groups in this study, although the rTMS-OTG group showed a greater reduction in muscle tone than the OTG group. Therefore, it is difficult to generalize that low-frequency rTMS treatment in combination with occupational therapy is an effective method for reducing muscle tone. First of all, it is thought that there is a limit to inducing a decrease in muscle tone due to insufficient duration and frequency of treatment. However, in a study by Mally and Dinya (2008), 64 patients recovering from stroke with severe stiffness and inability to move the injured finger were divided into four groups and treated with continuous low frequency (1 Hz) twice per day for 1 week. It was studied whether active movement of the paralyzed arm was induced and stiffness was weakened when cranial magnetic stimulation was applied [33]. Based on the results of these previous studies, low-frequency rTMS intervention in combination with occupational therapy not only reduces spasticity but is expected to improve motor function.

In the present study, application of rTMS was shown to improve the neuroplasticity of the damaged cerebral hemisphere by increasing the exercise-evoked potential and decreasing the latency in the cortex on the injured side. However, it is difficult to generalize the results due to the small number of participants. In addition, the stimulation time of TMS and the duration of the post-effects have not been thoroughly investigated. Therefore, in the future, it will be necessary to recruit more participants to generalize the results and to assess the criteria for maximizing the effect of TMS and the duration of the effect after the intervention.

6. Conclusions

Our results suggested that rTMS treatment combined with low-frequency occupational therapy provided three times per week for 4 weeks showed improvement in the MEP of the damaged cortex and reduced MEP latency. Currently, various therapeutic methods are being applied to improve the motor function of patients recovering from brain injuries such as stroke. As TMS treatment improves brain plasticity for damaged brain functions and also includes occupational therapy and tasks, its application as a treatment is attracting attention. In conclusion, The difference between the results of this study and previous studies is that more objective research results were obtained using special equipment to measure MEP amplitude, latency, and muscle tone in stroke patients using TMS. Additionally, we determined that rTMS may be safely applied to the directly damaged cerebral cortex and can improve neurophysiological and body-kinesthetic functions, and is considered to be an effective treatment for patients recovering from stroke.

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