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Effect of Cerebral Motor Cortical Excitability and Hand Dexterity on Dominant Hemisphere Difference after 1 Hz Low Frequency rTMS Combined with Hand Manual Therapy in Chronic stroke

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The paper was to find out effects of cerebral motor excitability and hand dexterity used to 1 Hz low frequency repetitive transcranial magnetic stimulation (rTMS) combined with hand manual therapy (HMT) on dominant hand difference in chronic stroke patients. 16 stroke patients were classified into the dominant hand HMT with r TMS group (DHMT+rTMSG) and non-dominant hand HMT with rTMS group (NDHMT+rTMSG), and 1 Hz low-frequency rTMS with HMT was performed. Motor evoked potentials (MEPs) amplitude, latency and box and block test (BBT) were used to confirm cerebral motor activity and hand dexterity. In DHMT+rTMSG, MEPs amplitude, latency and BBT showed significant differences. In NDHMT+rTMSG, MEPs amplitude, latency only showing significant difference. In the comparison between groups, MEPs amplitude, latency showed significant difference. Therefore, the 1 Hz low frequency rTMS combined with HMT according to the dominant hand difference is considered to be an n approach applied in the recovery of hand function in stroke.

Keywords : 1 Hz low frequency repeated transcranial magnetic stimulation, motor evoked potentials, cortical motor activity, dominant hemisphere

1. Introduction

Transcranial magnetic stimulation (TMS) is widely used to test the conduction ability of the central nervous system. TMS is widely used for organizing motor cortex because it can easily record motor genetic potentials induced by magnetic stimulation by electromyography, and is recognized as an important equipment for studying the activity and plasticity of the cerebral motor cortex [1]. In addition, due to the advantage of being able to stimulate the cerebral cortex locally, it can improve the motor function of the upper limb of patients with brain injury, so it is used as new approach method for neuro-rehabilitation [2]. Therefore, TMS is one of the most non-invasive methods of local stimulation among the cerebral cortex, and can be used as an important evaluation and therapeutic equipment for exploring and activating the motor function of the cerebral motor cortex. Recently, a neurorehabilitation combined with TMS has been attempted to recover the upper limbs of stroke patients. However, there are very few approach that take into account the characteristics of the cerebral hemisphere in the rehabilitation of the upper limbs of stroke patients. Cerebral hemispheres of human have individual characteristics of left and right, which can affect the recovery of upper limb function in stroke patients. The dominant hand (DH) refers to components that is mainly used for performing functional activities, and the cortical motor function of the cerebral hemisphere can be developed asymmetrically according to the characteristics of DH [3]. The leading use of DH in the performance of the task appears as cerebral laterality. The difference between the distinct movements of the right and left hand movements of humans can be explained as a result of different cortical organization of the right and left cerebral hemispheres. Harris and Eng (2006) found that the presence or absence

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of damage to DH in daily life is a very important factor in the success of rehabilitation for the upper limb [4]. This shows that the DH is more dominant in performance accuracy and speed when performing tasks than the non-dominant hand. Therefore, the presence or absence of dominant hand paralysis can be an important keyword for exercise recovery. This is believed to be the result of not recognizing the correlation between the dominant cerebral hemisphere and the role of the patient's DH and NDH and motor recovery. Therefore, a specific rehabilitation approach considering the dominance of the cerebral hemisphere is required by the characteristic classification of the injured cerebral hemispheres of the right and left cerebral hemispheres efficiently for recovery of upper limbs in stroke patients. This study is to investigate the difference in cortical motor activity and hand function of 1 Hz low frequency repetitive transcranial magnetic stimulation (rTMS) combined with hand manual therapy (HMT) based on the difference in dominant hemisphere characteristics in the recovery of upper limbs in chronic stroke patients. In addition, it would like to present the therapeutic basis for the neurorehabilitation.

2. Materials and Methods

2.1. Participant

This study selected 16 patients with chronic stroke who visited the G rehabilitation hospital and received rehabilitation for upper limbs as subjects. The subject's selection criteria for this study are patients who have been diagnosed with a stroke for more than 6 months. The subjects of this study selected patients with a mini-mental status examination korean version (MMSE-K) score of 24 with no cognitive impairment and understanding the training process. In addition, patients who had experience of seizure and those who had implanted metal implants in the human body (metalic implant, cardiac pacemaker, cochlear implant) were excluded from the study.

2.2. Assessment methods

2.2.1. Transcranial magnetic stimulation (TMS)

TMS is currently used in clinical trials for the purpose of stimulating brain, muscle, and nerve system among human for comparative evaluation of the motor system of normal and patients and for improving the function of patients with brain injury. This study was conducted in 16 patients with chronic stroke to investigate the effect of 1 Hz low frequency rTMS in patients with dominant cerebral hemisphere injuries and patients with non-dominant cerebral hemisphere injuries on neuroplasticity of cerebral motor cortex. Through the MAG PRO R30 TMS device of this study, non-invasive rTMS was provided to the non-affected primary motor area (M1) (Fig. 1).

Fig. 1. (Color online) MagPro R30, Medtronic Inc., Skovlunde, Denmark. rTMS was applied using the 8 shaped coil of this equipment, and the activity of the cerebral cortex was measured before and after the intervention.

The MAG PRO R30 TMS stimulator is combined with a butterfly coil (MCF-B65) stimulator with a diameter of 70 cm. This stimulator can stimulate the cerebral cortex in an electrical form as a magnetic field is formed around the coil as instantaneous high current flows through it. Therefore, it is possible to conveniently provide non-invasive magnetic stimulation to the patient's cerebral hemisphere without pain. The maximum magnetic field of the TMS device in this study is 2.0 Tesla. The change in neuroplasticity in this study can be measured by the excitability change to the corticospinal pathway, which can be measured by the cerebral cortical activity in M1 of the cerebral hemisphere. In order to accurately measure the activity of the M1 corresponding to the first dorsal interosseous (FDI) muscle of the cerebral cortex, the study subject should take the supine position in the patient's bed provided in the TMS room in a comfortable state as much as possible. In order to accurately measure the motor evoked potentials (MEPs) of the corresponding muscle, the head was fixed by wearing a lower complexion hood with the coordinates of the stimulation drawn on the patient's cerebral motor cortex close contact with the scalp. In the cerebral stimulation hood worn by the study subjects, the center point is the intersection of the mid-sagittal line and interaural line, which connects from the nasion to the inion. There is a checkerboard pattern at 1 cm intervals. In this study, an EMG electrode was attached to the FDI muscle to find the location of the corresponding motor cortical region of the FDI muscle, and the motor hot spot was measured while giving a single repetitive magnetic stimulation. The EMG activity was measured with a portable KEY POINT.NET device, amplified to 100 mV/div, and filtered at 2 Hz~10 kHz. Motor hot spot (MHS) was the area where the largest MEPs appears in the recording potential during single rTMS, and the same point was determined as MHS, and after marking on the hood, the resting motor threshold (RMT) was measured. rTMS intensity setting of RMT is defined as the intensity at which the induced potential of 50 μV or more is measured in at least 5 times of 10 rTMS, and then stimulates the outer surface of M1 of the FDI muscle with an intensity of 120 % of the RMT intensity Thus, 15 times MEPs were measured [5].

2.2.2. Box and block test (BBT)

BBT is a hand function test that measures the gross manual dexterity of one hand. A 1-inch wooden block is placed in two separate boxes of 53.7 cm wide by 8.5 cm long. It could measure hand manipulation and coordination by carrying out the task of moving a 1-inch wooden block to the other box as quickly as possible for 1 minute. In this study, the number of blocks to which wooden blocks were moved by the damaged hand was calculated and scored.

2.3. Procedure

2.3.1. 1 Hz low frequency rTMS and dominant hand manual therapy (DHMT) and nondominant hand manual therapy (NDHMT) procedures

In this study, 8 patients with dominant cerebral hemisphere injuries and 8 patients with non-dominant cerebral hemisphere injuries, a total of 16 patients, applied 1 Hz rTMS for 20 minutes to the unaffected cerebral motor cortex based on the transcallosal inhibition concept. After 1Hz rTMS, HMT was performed. The clinical experience of completing HMT bobath therapist for more than 3 years was performed for 30 minutes each, 3 times a week, for a total of 12 weeks. In order to find out the difference in cerebral activity and dexterity of hand before and after intervention, MEPs and BBT of the affected cerebral hemisphere were performed twice before and after the study.

2.4. Data Analysis

This study used the SPSS 22.0 window program, and the general characteristics of the study participants were analyzed using descriptive statistics. In this study, the Wilcoxon signed rank test was performed to determine the before and after intervention effects of MEPs amplitude and latency in two group, and the Mann-Whitney U test was used to determine the difference in MEPs amplitude and MEPs latency between groups. All statistical significance levels were set as α=0.05.

3. Results and Discussion

3.1. General characteristics of subjects

The subjects of this study were 16 patients with chronic stroke. It was classified into 8 patients with dominant cerebral hemisphere injury (5 males, 3 female) and 8 patients with non-dominant cerebral hemisphere injury (5 males and 3 female). The age of the domninant hand manual therapy with repetitive transcranial magnetic stimulation group (DHMT+rTMSG) is 60.03 ± 14.25 years, the prevalence rate is 15.00 ± 4.57 months, and the age of the nondomninant hand manual therapy with repetitive transcranial magnetic stimulation group (NDHMT + rTMSG) is 56.00 ± 16.17 years and the prevalence rate is 19.37 ± 3.78 months.

Table 1. General characteristics of subjects.

Variables		DHMT+rTMSG (n=8)	NDHMT+rTMSG (n=8)
Gender	Male	5	5
	Female	3	3
Age		60.03 ± 14.25	56.00 ± 16.17
Lesion type	Hemorrhage	3	4
	Infarction	5	4
Handness	Right	8	8
	left	0	0
Time from stroke to rehab (months)		15.00 ± 4.57	19.37 ± 3.78

M±SD: M: mean, SD: standard deviation, DHMT+rTMSG: domninant hand manual therapy with repetitive transcranial magnetic stimulation group, NDHMT+rTMSG: nondominant hand manual therapy with repetitive transcranial magnetic stimulation group.

Table 2. Comparison of MEPs amplitude, latency before and after intervention in the groups.

Variables		Pre-test	Post-test	*z*	*p*
		M ± SD	M ± SD		
DHMT+rTMSG (n=8)	MEPs amplitude (mV)	0.12 ± 0.07	0.33 ± 0.16	-2.524	.012*
	MEPs latency (ms)	24.08 ± 0.85	22.56 ± 1.13	-2.103	.035*
NDHMT+rTMSG (n=8)	MEPs amplitude (mV)	0.12 ± 0.52	0.18 ± 0.57	-2.527	.012*
	MEPs latency (ms)	24.35 ± 1.49	23.56 ± 1.36	-2.371	.018*

M±SD M: mean SD: standard deviation *p < .05, MEPs: motor evoked potentials, DHMT+rTMSG: dondominant hand manual therapy with repetitive transcranial magnetic stimulation group, NDHMT+rTMSG: nondominant hand manual therapy with repetitive transcranial magnetic stimulation group.

3.2. Comparison of cerebral motor activity activity and hand dexterity before and after intervention in two group

3.2.1. Comparison of MEPs amplitude, latency before and after intervention in two group

MEPs amplitude of DHMT+rTMSG increased from 0.12 mV before intervention to 0.33 mV after intervention ($p < 0.05$) and MEPs latency decreased from 24.08 ms to 22.56 ms. MEPs amplitude of NDHMT+rTMSG slightly increased from 0.12 mV before intervention to 0.18 mV after intervention ($p < 0.05$), and MEPs latency decreased from 24.35 ms to 23.56 ms. And there was a significant difference in two groups ($p < 0.05$) (Table 2).

3.2.2. Comparison of BBT before and after intervention in groups

BBT of DHMT+rTMSG improved from 18 points to 25 points, showing a significant difference ($p < 0.05$). BBT of NDHMT+rTMSG improved from 18 points to 19 points, but there was no significant difference ($p > 0.05$) (Table 3).

3.3. Comparison of motor cortex activity and hand dexterity before and after intervention between two groups

3.3.1. Comparison of MEPs amplitude, latency BBT before and after intervention between two groups

In the comparison of amplitude and latency between DHMT+rTMSG and NDHMT+rTMSG, there was a significant difference in MEPs amplitude and latency between the two groups after intervention ($p < 0.05$) and there was no significant difference in BBT comparison between DHMT+rTMSG and NDHMT+rTMSG ($p > 0.05$) (Table 4, 5).

Table 3. Comparison of box and block test before and after intervention in the groups.

		Pre-test	Post-test	*z*	*p*
		M ± SD	M ± SD		
BBT (point)	DHMT+rTMSG (n=8)	18.88 ± 5.49	25.88 ± 8.86	-2.527	.012*
	NDHMT+rTMSG (n=8)	18.37 ± 4.03	19.00 ± 3.63	-1.890	.059

M±SD M: mean SD: standard deviation, *p < .05, BBT: box and block test, DHMT+rTMSG: domninant hand manual therapy with repetitive transcranial magnetic stimulation group, NDHMT+rTMSG: nondominant hand manual therapy with repetitive transcranial magnetic stimulation group.

Table 4. Comparison of MEPs amplitude and latency between two groups.

		DHPT+rTMSG (n=8)	NDHPT+rTMSG (n=8)	*z*	*p*
		M ± SD	M ± SD		
MEP amplitude (mV)	pre test	0.12 ± 0.07	0.12 ± 0.52	.000	1.000
	post test	0.33 ± 0.16	0.18 ± 0.57	-2.105	.035*
MEP latency (ms)	pre test	24.08 ± 0.85	24.35 ± 1.49	-.581	.562
	post test	22.56 ± 1.13	23.56 ± 1.36	-2.004	.045*

M±SD M: mean SD: standard deviation *p < .05, MEPs: motor evoked potentials, DHMT+rTMSG: domninant hand manual therapy with repetitive transcranial magnetic stimulation group, NDHMT+rTMSG: nondominant hand manual therapy with repetitive transcranial magnetic stimulation group.

Table 5. Comparison of BBT between two groups.

		DHPT+rTMSG (n=8)	NDHPT+rTMSG (n=8)	*z*	*p*
		M ± SD	M ± SD		
BBT	pre-test	18.88 ± 5.49	18.37 ± 4.03	-.053	.958
(point)	post-test	25.88 ± 8.86	19.00 ± 3.63	-1.791	.073

M ± SD M: mean SD: standard deviation, *p < .05, BBT: box and block test, DHMT+rTMSG: domninant hand manual therapy with repetitive transcranial magnetic stimulation group, NDHMT+rTMSG: nondominant hand manual therapy with repetitive transcranial magnetic stimulation group.

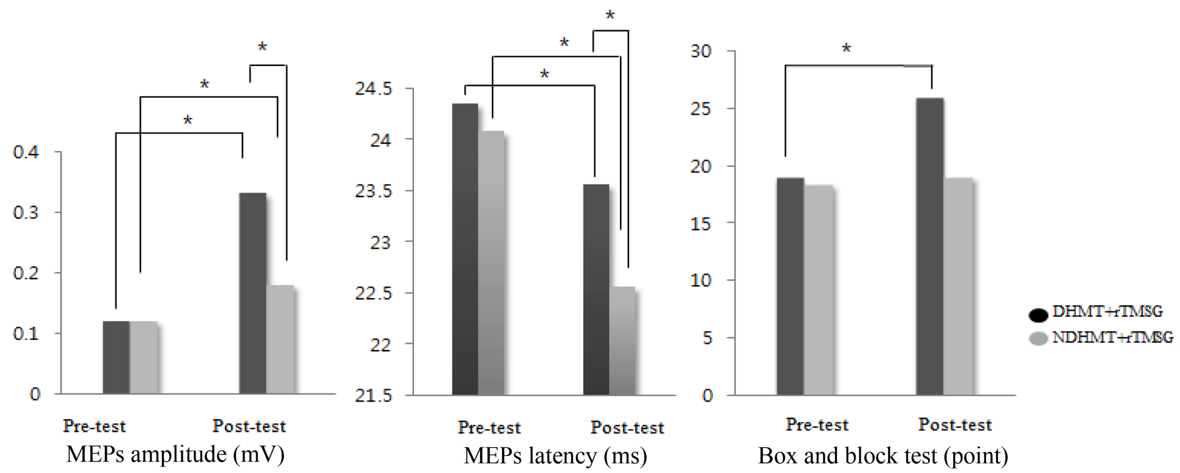

Fig. 2. Comparison of MEPs amplitude, latency and box and block test before and after intervention in groups and between groups.

3.4. Discussion

Transcallosal inhibition is based on the theory of interhemispheric competition, and it is explained that the motor cortex regions in both cerebral hemispheres inhibit the cerebral motor cortex opposite to each other, thereby maintaining the balance of activity between the cerebral hemispheres. Motor neurons in the M1 are said to locally inhibit the contralateral cerebral hemisphere through the corpus callosum, and this inhibition inhibits the cortical excitability of the contralateral cerebral hemisphere [6]. However, damage to the cerebral hemisphere due to a stroke does not normally activate the activity of interhemispheric transcallosal inhibition connected to the non-affected cerebral hemisphere, and transcallosal inhibition decreases. In other words, a decrease in the inhibitory output of the non-affected cerebral hemisphere results in suppressing the function of affected cerebral hemisphere. In addition, the cortical excitability of the injured cerebral hemisphere continuously decreases, thereby reducing the excitability of the corticospinal pathway of the affected cerebral hemisphere. The imbalance of interhemispheric competition results in a secondary learned nonuse syndrome due to disinhibition of the normal cerebral hemisphere [7]. Disinhibition of the injured side of the cerebral hemisphere has a negative effect on neurorehabilitation as the intact upper limb is used a lot in the process of daily life. In previous studies, the cerebral hemisphere to which 1 Hz rTMS was applied suppresses motor cortical excitability and excitability of the contralateral cerebral hemisphere, suggesting a mechanism and a new method for motor recovery in approach of neurorehabilitation [8]. Previous studies found that applying 1 Hz frequency rTMS for 25 minutes to the contralesional M1 by sham stimulation for 25 minutes increased motor performance in the injured hand.

It has been reported that 1 Hz low frequency rTMS in the injured cerebral hemisphere and pinch strength, movement acceleration, and cortical excitability can be effectively increased during 15 minutes of pinching task training [9, 10]. In this study, the 90 % RMT intensity and 1 Hz low frequency rTMS suggested in the previous study were stimulated in the non-dominant cerebral hemisphere of the dominant cerebral hemisphere injured patient and the right dominant cerebral hemisphere of the non-dominant cerebral hemisphere injury patient. Thus, we tried to confirm the correlation between the characteristics of the dominant cerebral hemisphere and the performance of the upper limb. As a result of the study, 1 Hz low frequency rTMS and HMT on the non-dominant cerebral hemisphere were performed in patients with dominant cerebral hemisphere injuries. It was confirmed that there was a difference in the effect on the activity of the motor cortex and the dexterity of the hand [11]. Based on these results, it is thought that 1 Hz low frequency rTMS and HMT can control the imbalance of affected cerebral hemisphere, and in particular, the presence or absence of dominant cerebral hemisphere damage can have a positive effect on the recovery of upper limb movement in neurorehabilitation. rTMS is applied to various clinical areas such as dementia, depressive symptoms, cognitive deficit, etc. Recently, in stroke rehabilitation, various intervention methods such as the effect of high-frequency rTMS of the ipsilateral cerebral cortex and the effect of low-frequency rTMS of the contralateral cerebral cortex have been attempted. In general, high-frequency rTMS (> 5 Hz) causes cortiocospinal pathway excitation of the lesion-side cerebral hemisphere and low-frequency rTMS (≤ 1 Hz) reduces corticospinal tract excitation. According to a recent study, it has been reported that high frequency rTMS changes excitability to the corticospinal pathway in the acute stroke rehabilitation, and that high frequency rTMS does not change the excitability to the corticospinal pathway in the chronic phase [12]. However, this study confirmed the change in corticospinal pathway activity in chronic stroke patients by training with 1 Hz low frequency rTMS combined HMT. These results are thought to have implications for neurorehabilitation of stroke in the future. However, since this study evaluated only a small number of subjects and simple hand dexterity, there are limitations in generalizing this. In future studies, it is necessary to apply a large number of subjects to determine how rTMS according to the frequency and presence of DH damage has on the recovery of motor function in stroke patients.

4. Conclusion

Through this study, the following results were confirmed. In DHMT+rTMSG in the two groups, MEPs amplitude increased from 0.12 mV to 0.33 mV, MEPs latency decreased from 24.08 ms to 22.56 ms, and BBT improved from 18 points to 25 points in DHMT+rTMSG, and significant difference. In NDHMT+rTMSG, MEPs amplitude increased from 0.12 mV to 0.18 mV, and MEPs latency decreased from 24.35 ms to 23.56 ms, showing a significant difference. Finally, in the comparison of cerebral motor activity between two groups, there was a significant difference in MEPs amplitude and latency. 1 Hz low-frequency rTMS in parallel with HMT according to the DH difference showed a difference in the enhancement of brain activity. Based on these results, it is determined that a neurorehabilitation strategy for DH characteristics is necessary for recovery of hand function after stroke.

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