

Effects of 1 Hz Low Frequency Repetitive Transcranial Magnetic Stimulation with Neuromuscular Electrical Stimulation Applied to Contralateral Cerebral Cortex on Muscle Activity, Muscle Tone and Upper Limb Motor Function in Stroke Patients

Jung-Woo Jeong¹, Man-Seok Han^{2*}, and Bo-Kyoung Song^{3*}

¹Department of Occupational Therapy, Bobath Memorial Hospital, Seongnam 13552, Republic of Korea

²Department of Radiological Science, Kangwon National University, Samcheok 25949, Republic of Korea

³Department of Occupational Therapy, Kangwon National University, Samcheok 25949, Republic of Korea

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This study was to investigate effects of NMES with 1 Hz low-frequency repetitive transcranial magnetic stimulation (LF-rTMS) applied to unaffected cerebral cortex on muscle activities, tone, and motor function of upper limb (UL) in stroke patients. 16 patients were randomly divided into two groups, and experimental group (EG) was subjected to 1 Hz LF-rTMS and neuromuscular electrical stimulation (NMES). In control group (CG), Facilitation of hand intrinsic muscles and NMES were performed. It was evaluated using electromyography (EMG), MyotonePRO, and Fugl-Meyer assessment (FMA). As a result, there were significant differences on EMG of the anterior deltoid, triceps brachii (TB), MyotonePRO, and FMA in the EG. CG showed a significant difference in EMG of TB. Between groups, there was a significant difference in the biceps brachii and TB. It's thought that 1 Hz LF-rTMS and NMES can have a positive effect to improve muscle activity and UL in stroke patients.

Keywords : magnetic stimulation, 1 Hz LF-rTMS, NMES, stroke, transcallosal inhibition upper limb motor function

1. Introduction

After stroke, more than 70 % experience difficulties in performing functional tasks such as activities of daily living (ADL) due to limitations in upper limb (UL) function recovery. Even after 6 months of onset, about 50 % of stroke patients are unable to use their hands smoothly in ADL due to decreased hand dexterity, which lowers the frequency, efficiency, and participation in task activities, making it difficult for independent and efficient ADL [1]. Therefore, recovery of UL motor function in stroke patients is a very important goal in the rehabilitation process [2]. rTMS, which is applied to the recovery of UL motor function in stroke patients, is a treatment that uses an electromagnetic coil to locally form a magnetic field and then stimulates a specific area of the cerebral cortex to facilitate or suppress cerebral activity. And it is a safe

treatment that can control the central nervous system (CNS) in a non-invasive way, not by invasive methods such as deep cerebral stimulation, electric spasm, or craniotomy [3]. Magnetic stimulation induced by the coil activates adjacent nerve cells in the cerebral cortex. In particular, although the effect on the cerebral cortex differs depending on the coil type, stimuli intensity, and frequency, the stimulation affects the cerebral cortex 2-3 cm below the scalp. It also activates the axon, not the cell body of the nerve with a high response threshold [4, 5]. In general, the frequency used in rTMS is divided into low-frequency repetitive transcranial magnetic stimulation (LF-rTMS) of 1 Hz or less and high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) of 5 Hz or more. LF-rTMS based on transcallosal inhibition (TCI). TCI is a competition model between cerebral hemispheres, and both cerebral hemispheres of normal adult compete or regulate the contralateral cerebral hemispheres, which can be explained by interhemispheric inhibition (IHI) through the corpus callosum [6]. In a previous study, rTMS was applied to the primary motor cortex (M1) on the contralateral side of stroke patients to activate M1 to confirm TCI explained as a disinhibition mechanism [7].

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*Corresponding author: Tel: +82-33-540-3383

Fax: +82-33-540-6788, e-mail: angio7896@naver.com

Tel: +82-33-540-3483, Fax: +82-33-540-3489

e-mail: bksong@kangwon.ac.kr

LF-rTMS stimulated the contralateral cerebral cortex to activate damaged M1, contributing to upper limb motor recovery. In another previous study, as a result of applying LF-rTMS to M1, which corresponds to the lower limb on the contralateral side of a chronic stroke patient, it helped to restore abnormal muscle tone of lower limb [8]. Neuromuscular electrical stimulation (NMES) is a method of increasing muscle activity through electrical stimulation of normal muscles that are innervated. In the skeletal muscle of stroke patients, the muscle activity varies according to the characteristics of task performance and rehabilitation content, and the original characteristics of the muscle fiber can be maintained through electrical stimulation of the change in the musculoskeletal muscle [9]. In particular, NMES can help reduce excessive muscle tone in stroke patients [10]. It is also applied to promote functional contraction patterns of muscles on the pharynx in dysphasia with stroke [11]. In a previous study, the use of NMES in combination with rTMS as an intervention method reported a positive effect in restoring of UL function. Etoh *et al.* (2015) helped to recover upper limb function in combination with NMES and LF-rTMS in subacute stroke patients. Tosun *et al.* (2017) showed that NMES and LF-rTMS were concurrently administered to patients with early stroke and had a positive effect on M1 involved in the UL on fMRI [12, 13]. In particular, positive results were confirmed by performing tasks or quantitative evaluation of UL function for acute and subacute stroke patients. Therefore, in this study, 1 Hz LF-rTMS with NMES were applied to chronic stroke patients to investigate the changes in muscle activity, muscle tone, and UL motor function.

2. Materials and Methods

2.1. Subject

This study was conducted only among stroke patients admitted to a rehabilitation hospital who agreed to the purpose and method of the study. Subjects in this study were those with an onset period of more than 6 months and less than 24 months after stroke diagnosis, those with a Korean-montreal cognitive assessment (K-MoCA) 23 point or higher, those with Brunstrom recovery stage 3 or higher, those who could understand the researcher's instructions, listened to explanation of the study, and actively consented to participate in the study were selected. On the other hand, patients with neurological complication such as convulsions and seizures, patients with pacemaker devices, and contraindications to rTMS were excluded. The 16 patients selected were randomly divided into two groups of 8 patients through a lottery method, one of the randomization methods, and the experimental group was subjected to 1 Hz LF-rTMS combined with NMES. The control group was treated with NMES and hand intrinsic muscle training. The experimental group (EG) was subjected to LF-rTMS 4 times a week for 3 weeks in the contralateral cerebral cortex, the frequency of stimulation was 1 Hz, 900 pulses were applied for 15 minutes, and NMES was performed for 25 minutes. The control group (CG) performed NMES for 25 minutes and facilitation of hand intrinsic muscle for 15 minutes.

2.2. Assessment methods

2.2.1. Muscle activity

To measure muscle activity, surface electromyography (EMG) was used, which records compound action potentials from nerves and muscle fibers. For surface EMG, signals were collected using QEMG-4 (LXM3204, LAXTHA, Korea) with input impedance of 10^{12} ohm and common mode rejection ratio (CMRR) of 90 dB at 20 Hz (Fig. 1). For surface EMG, the active and reference electrodes



Fig. 1. (Color online) Figure shows that (a) QEMG-4 (Laxtha, Korea) was used to measure muscle activity during the subject's functional reaching, and (b) MyotonPRO (Myoton AS, Estonia, Myoton, Ltd London) were used to measure muscle tone in the supine position. 1 Hz low-frequency repetitive transcranial magnetic stimulation was performed using (c) ALTMS[®] (Remed, Korea), and Neuromuscular electrical stimulation was performed using (d) NOVASTIM CU-FS100 (CU Medical Systems, Inc, Korea).

were placed parallel to the muscle fiber direction by maintaining a distance of 25 mm between the centers of the electrodes, and then attached to the muscle belly of the anterior deltoid (AD), biceps brachii (BB), triceps brachii (TB), and extensor carpi radialis longus (ECRL). Then, the subjects were asked to point their fingers at an object located 30 cm in front of the table in a sitting position, and muscle contractions occurring 3 times were measured. In the method of recording muscle contraction, the resting motor threshold (RMS) was first obtained, a window was set for each motion unit, and the overlap ratio was recorded based on 90 %. And after extracting the maximum contraction value over 3 times from 4 channels, the contraction of each muscle was standardized and the absolute value was recorded.

2.2.2. Muscle tone

Muscle tone was measured using MyotonPRO (Myoton AS, Estonia, Myoton Ltd London) (Fig. 1). MyotonPRO is a device that can measure muscle tension non-invasively. By giving a mechanical shock to the skin and muscles to induce muscle vibration, the state of muscle tension is measured by converting the tension state of the resting muscle into a frequency [14]. Agyapong-Badu *et al.* (2013) suggested the test reliability to MyotonPRO as 0.94 to 0.99 [15]. In this study, long head of BB was measured, and the test was to measure the middle of the biceps brachii after the subject placed the forearm in a neutral position.

2.2.3. Measurement of UL motor function

The Fugl-Meyer assessment (FMA) was used to evaluate the motor function of the UL. FMA developed by Fugl-Meyer *et al.* (1975) can evaluate UL motor function, postural balance, sensory function in stroke patients [16]. The items of the FMA consist of a total of 33 items and 66 points, including 18 items on the shoulder, elbow, forearm, 5 items on the wrist, 7 items on the hand, and 3 items on coordination. In FMA, the higher the score means the level of motor recovery. The intra-rater and inter-rater reliability of FMA are 0.99 and 0.98, respectively, and the test-retest reliability is 0.94 to 0.99 [17].

2.3. Procedure

2.3.1. Application of 1 Hz LF-rTMS

1 Hz LF-rTMS on the unaffected side of cerebral cortex was performed using an ALTMS[®] (Remed, Korea, 2018) device consisting of a 70 mm figure 8 coil (Fig. 1). The subject is seated comfortably on the rTMS equipment chair with the head fixed on the headrest, arms and

elbows extended, and wrist joints in a neutral state. The location of the stimulus is connected from the nasal root point to theinion and then intersected with the mid sagittal line and the inter aurial line. After taking the points, the coordinates are indicated by crossing the lines in a checkerboard pattern spaced 1 cm apart from the line. After that, the coil stimulator was applied after positioning it at an angle of 45 degrees from the center line to coordinates of the cerebral cortex on unaffected side. To confirm the location of M1, the subject's scalp was stimulated while moving little by little, and the position of the motor cortex was confirmed through the maximum motor evoked potential (MEP) of the first dorsal interosseous muscle (FDI). Resting motor threshold (RMT) is set as the minimum stimulation intensity at which MEP of 50 μ V or more is recorded in at least 5 out of 10 stimulations, and at 900 pulses in the contralateral cerebral cortex, 120 % of the motor threshold. As a standard, the stimulation frequency is 1 Hz, and 900 pulses are applied for 15 minutes [18].

2.3.2. Application of NMES

In this study, NOVASTIM CU-FS100 (CU Medical Systems, Inc, Korea) was used for NMES (Fig. 1). In NMES, pads are attached to the extensor digitorum communis (EDC) on the affected side of the subject for 25 minutes in a bipolar placement method on the distal and proximal parts of the muscle center, respectively. Using a tolerable 15-30 mA and peak voltage of 150 V, the contraction was allowed to occur. Using a biphasic wave, a stimulation frequency of 35 Hz and a pulse width of 200 μ V were applied for 12 seconds. The ramp time was set to 1 second, the on time and off time were 10 and 50 seconds, respectively, and the duty cycle was set to 1:5 [19].

2.3.3. Data Analysis

For the data analysis of this study, SPSS 18.0 for windows was used. For general characteristics of subjects, descriptive statistics and frequency analysis were used, and the Mann-Whitney U test was used to confirm the homogeneity of the two groups before the intervention. Friedman's test was used to investigate the changes in EMG, MyotonPRO, and FMA before, after, and 2 weeks after intervention within both groups, and Turkey's test was used for post hoc tests. The Mann-Whitney U test was used to investigate the changes in EMG, MyotonPRO, and FMA before, after, and 2 weeks after the intervention between two groups. All statistical analyzes were set at $\alpha = 0.05$ significance level.

3. Results and Discussion

3.1. General Characteristics of Subjects

The general characteristics of the subjects in this study are presented in Table 1. EG consisted of 5 males and 3 females, average age 51.626 ± 6.39 years, cerebral hemorrhage in 3, cerebral infarction in 5, right hemiplegia in 6, left hemiplegia in 2, and duration of stroke is 12.623 ± 2.66 months after onset. the K-MoCA score is 27.254 ± 1.83 points. In CG, 5 males and 3 females, average age 57.628 ± 6.73 years, 5 cerebral hemorrhage and 3 cerebral infarctions in injury type, 3 right hemiplegia, 5 left hemiplegia, duration is 12.374 ± 2.92 months after onset. K-MoCA score is 26.376 ± 1.76 points. There was no statistically significant difference in general characteristics between two groups before intervention ($p > 0.05$) (Table 1).

3.2. Comparison of changes in muscle activity and upper limb motor function before, after, and after intervention within the two groups

In the EMG conducted to examine the difference in muscle activity in two groups, AD in EG increased to 76.665 ± 8.00 % before, 78.228 ± 7.51 % after, and 78.425 ± 7.08 % in the test 2 weeks later. TB increased to 28.373 ± 5.15 % before intervention, 29.999 ± 5.04 % after intervention, and 33.600 ± 4.96 % after 2 weeks, showing a significant difference in EG ($p < 0.05$) (Table 2) (Fig. 2). CG increased to 29.478 ± 5.05 % before, 30.568 ± 4.33 % after, and 31.142 ± 3.92 % in the evaluation 2 weeks later in the TB, and there was a significant difference ($p < 0.01$) (Table 2) (Fig. 2). And in MyotonPRO, EG decreased to 236.122 ± 15.62 N/m before, 233.917 ± 15.47 N/m after, and 229.705 ± 14.91 N/m in the evaluation 2 weeks later, showing a significant difference ($p < 0.05$) (Table 2). CG decreased to 230.000 ± 10.98 N/m before, 228.315 ± 12.38 N/m after, and 229.307 ± 14.56 N/m after 2 weeks, but there was no significant difference (Table 2) (Fig. 2). In FMA, EG increased to 35.751 ± 8.24 point before intervention, 37.877 ± 7.54 point after intervention, and 38.121 ± 6.53 point the evaluation 2 weeks later, showing

Table 1. General characteristics of subjects

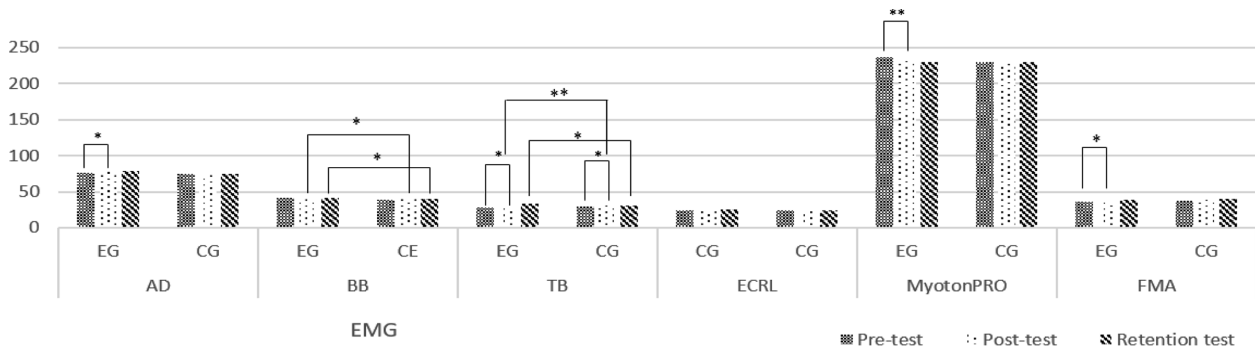
Variables		EG (N=8)	CG (N=8)	χ^2/t	p
Gender	Male	5(62.5 %)	5(62.5 %)	0.343	1.000
	Female	3(37.5 %)	3(37.5 %)		
Age		51.626 ± 6.39	57.628 ± 6.73	19.500	1.000
Side of stroke	Right	6(75.0 %)	3(37.5 %)	2.350	0.459
	Left	2(25.0 %)	5(62.5 %)		
Type of stroke	Hemorrhage	3(37.5 %)	5(62.5 %)	1.343	0.670
	Infarction	5(62.5 %)	3(37.5 %)		
Time from stroke to rehab (months)		12.623 ± 2.66	12.374 ± 2.92	11.000	0.991
K-MoCA (point)		27.254 ± 1.83	26.376 ± 1.76	14.100	0.330

M \pm SD: mean \pm standard deviation, EG: experimental group, CG: control group, K-MoCA: korean-montreal cognitive assessment

Table 2. Comparison of changes in EMG, MyotonPRO and FMA within groups

Variables		Pre-test	Post-test	Retention test	χ^2	p	Post-hoc
AD	EG	76.665 ± 8.00	78.228 ± 7.51	78.425 ± 7.08	7.750	0.021*	a>c, b>c
	CG	74.156 ± 10.40	74.625 ± 10.18	74.924 ± 10.71	1.000	0.607	
E	EG	41.149 ± 7.52	41.225 ± 7.21	41.837 ± 7.78	0.194	0.908	
	CE	39.298 ± 6.78	39.821 ± 5.81	39.500 ± 7.28	0.065	0.968	
G	EG	28.373 ± 5.15	29.999 ± 5.04	33.600 ± 4.96	14.250	0.005**	a>c, b>c
	CG	29.478 ± 5.05	30.568 ± 4.33	31.142 ± 3.92	7.750	0.021*	a>c, b>c
ECRL	CG	23.449 ± 3.85	23.959 ± 3.25	24.759 ± 4.15	5.250	0.072	
	CG	23.919 ± 2.81	23.592 ± 4.04	24.445 ± 3.79	5.250	0.072	
MyotonPRO (N/m)	EG	236.122 ± 15.62	233.917 ± 15.47	229.705 ± 14.91	7.750	0.021*	a>c, b>c
	CG	230.000 ± 10.98	228.315 ± 12.38	229.307 ± 14.56	0.839	0.657	
FMA (point)	EG	35.751 ± 8.24	37.877 ± 7.54	38.121 ± 6.53	6.889	0.032*	a>c, b>c
	CG	37.874 ± 6.28	39.251 ± 7.02	39.872 ± 7.77	2.000	0.368	

M \pm SD: mean \pm standard deviation * $p < 0.05$, ** $p < 0.01$, EG: experimental group, CG: control group, AD: anterior deltoid, BB: biceps brachii, TB: triceps brachii, ECRL: extensor carpi radialis longus, EMG: Electromyography, FMA: Fugl-Meyer assessment, post-hoc: Tukey's HSD, pre-test: c, post-test: b, retention test: a



EG: experimental group, CG: control group, AD: anterior deltoid, BB: biceps brachii, TB: triceps brachii, ECRL: extensor carpi radialis longus, EMG: Electromyography, FMA: Fugl-Meyer assessment

Fig. 2. Comparison of changes in EMG, MyotonPRO and FMA within groups and between groups.

a significant difference ($p < 0.05$) (Table 2) (Fig. 2). CG increased to 37.874 ± 6.28 point in the pre-intervention evaluation, 39.251 ± 7.02 point in the post-intervention evaluation, and 39.872 ± 7.77 point the evaluation 2 weeks later, but there was no significant difference (Table 2) (Fig. 2).

3.3. Comparison of changes in muscle activity, muscle tone, and UL motor function between the two groups

In the EMG conducted to investigate the difference in muscle activity between the two groups, there was a significant difference in the evaluation of the biceps and TB the evaluation after 2 weeks ($p < 0.05$). There was no significant difference in MyotonPRO and FMA between the two groups ($p > 0.05$) ($p > 0.05$) (Table 3) (Fig. 2).

Table 3. Comparison of changes in EMG, MyotonPRO and FMA between two groups

Variables		Pre-test	Post-test	Retention test	
E M G (%)	AD	EG	76.665±8.00	78.228±7.51	78.425±7.08
		CG	74.156±10.40	74.625±10.18	74.924±10.71
		χ^2	0.384	1.295	2.565
		p	0.825	0.523	0.277
	BB	EG	41.149±7.52	41.225±7.21	41.837±7.78
		CG	39.298±6.78	39.821±5.81	39.500±7.28
		χ^2	0.535	8.385	7.775
		p	0.765	0.015*	0.021*
	TB	EG	28.373±5.15	29.999±5.04	33.600±4.96
		CG	29.478±5.05	30.568±4.33	31.142±3.92
		χ^2	0.955	10.269	7.985
		p	.815	0.006**	0.018*
ECRL	EG	23.449±3.85	23.959±3.25	24.759±4.15	
	CG	23.919±2.81	23.592±4.04	24.445±3.79	
	χ^2	5.285	5.586	3.842	
	p	0.071	0.061	0.146	
MyotonPRO (N/m)	EG	236.122±15.62	233.917±15.47	229.705±14.91	
	CG	230.000±10.98	228.315±12.38	229.307±14.56	
	χ^2	1.299	1.114	0.377	
	p	0.522	0.573	0.828	
FMA (point)	EG	35.751±8.24	37.877±7.54	38.121±6.53	
	CG	37.874±6.28	39.251±7.02	39.872±7.77	
	χ^2	0.411	0.398	0.389	
	p	0.814	0.820	0.823	

M±SD: mean±standard deviation * $p < 0.05$, EG: experimental group, CG: control group, AD: anterior deltoid, BB: biceps brachii, TB: triceps brachii, ECRL: extensor carpi radialis longus, EMG: Electromyography, FMA: Fugl-Meyer assessment

3.4. Discussion

Many interventions have been introduced in the rehabilitation process to improve UL dysfunction that occurs in patients after stroke [20]. In rehabilitation of UL for stroke patients, Bobath approaches, virtual reality, robot therapy, imaginary training, mirror therapy, constrained induce movement therapy (CIMT), and functional electrical stimulation (FES) are representative interventions based on motor learning and re-learning theory for neurological condition [21]. In addition, non-invasive brain stimulation (NIBS) is an intervention method to restore UL function by activating the cerebral cortex using rTMS, and a positive effect has been reported through previous studies. LF-rTMS is suggested as an approach that can enhance inhibition by stimulating the cerebral cortex on the affected side. LF-rTMS promotes inhibitory activity through magnetic stimulation of cerebral the cortex on unaffected side, and secondarily increases the activity of the cerebral cortex on affected side, thereby restoring damaged upper limb function. This theory is called TCI. TCI is called the interhemispheric inhibition (IHI) model through the corpus callosum. Based on this theory, when performing a two-handed task or one-handed task in the UL, both cerebral hemispheres support regulated movement through inhibition of the contralateral cerebral hemisphere [6]. The use of LF-rTMS for activation of affected cerebral cortex in stroke patients is based on IHI. It is explained that inhibition of the cerebral cortex on the contralateral side through LF-rTMS can activate the cerebral hemisphere on the affected side by disinhibition of the neural circuit that is suppressing the affected cerebral hemisphere. Motor learning and relearning training in the rehabilitation process based on TCI have a positive effect on long-term potentiation (LTP) or long-term depression (LTD) of CNS [22]. NMES is used to prevent muscle atrophy and to treat abnormal muscle tone such as spasticity by inducing constant muscle contraction and relaxation through electrical stimulation to promote weakened muscle or to correct abnormal muscle contraction [23]. In a previous study, Zhang *et al.* (2019) reported activation of the cerebral cortex as a result of confirming MEP after applying NMES, 1 Hz LF-rTMS, and 10 Hz HF-rTMS to 60 patients with dysphagia after stroke [24]. Also, Khan and Chevidikunnan (2017) confirmed a positive change in MEP as a result of NMES on 10 stroke patients [25]. In this study, we investigated the effects of 1 Hz LF-rTMS and NMES on the contralateral cerebral cortex on muscle activity, muscle tone, and recovery of UL motor function in chronic stroke patients. In the EMG conducted to investigate muscle activity after intervention, the effect of the intervention was confirmed in the AD

and TB in EG and in the TB in CG. Etoh *et al.* (2019) confirmed the recovery of UL function by applying LF-rTMS and NMES to 20 stroke patients [26]. In particular, in this study, through a qualitative EMG test, it is judged that changes in the AD and TD have a significant effect as play an important role in the functional reaching. And in MyotonePRO, which was conducted to check muscle tone, significant changes were confirmed in the EG compared to CG after the intervention. In a previous study, when LF-rTMS was applied to the cerebral cortex on unaffected side of chronic stroke patients, the change in muscle tone on the affected side was confirmed [27, 28]. Therefore, it is judged that the change in muscle tone changed by applying LF-r TMS and NMES is a critical component that helps to perform of elbow extension such as reaching. Finally, in the FMA conducted to investigate the recovery of the subject's UL motor function, significant changes were confirmed in EG compared to CG. Vaziri *et al.* (2014) conducted a combination of 1 Hz LF-rTMS with NMES in the EG for 12 hemiplegic patients after stroke, and sham LF-rTMS with NMES in CG. Although there was a recovery in UL motor function, a significant change was confirmed only in EG in hand prehension [29]. Based on these results, NMES in combination with LF-rTMS was judged to be an approach that can positively change the recovery of UL motor function, although there is a difference between this study and evaluation tool. In the future, it is considered that it is necessary to conduct a study with a large number of subjects in order to generalize the research results presented in this study. In addition, if a neuroimaging linked research design is made in proving the correlation between cortical activation and recovery of UL motor function on NMES in parallel with rTMS applied to the unaffected cerebral cortex, the evidence of rTMS and various treatments in parallel with rTMS for UL recovery in stroke patients can be seen. It is believed that it can be presented clearly.

4. Conclusion

This study investigated how 1 Hz LF-rTMS and NMES applied to the contralateral side of a chronic stroke patient had any help on muscle activity, muscle tone, and UL motor function, and the following results were obtained. In the changes in muscle activity within the two groups, EG showed significant differences in AD and TB ($p < 0.05$), and CG showed a significant difference in the TB ($p < 0.05$). In MyotonPRO and FMA, there was a significant difference in EG ($p < 0.05$), but no significant difference in CG ($p > 0.05$). Also, in EMG between the two groups, there was a significant difference between the

BB and TB ($p < 0.05$), but there was no significant difference in MyotonPRO and FMA ($p > 0.05$). Through this, it is thought that 1 Hz LF-rTMS and NMES applied to the cerebral cortex of unaffected side can help recovery of muscle activity, and UL motor function in chronic stroke patients.

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