

A Comparison Study of Cerebral Cortical Activity at Chronic Stroke Patients According to Differences in Frequency of Repetitive Transcranial Magnetic Stimulation: Randomized Controlled Trial

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(Received 18 October 2023, Received in final form 15 December 2023, Accepted 15 December 2023)

This study aimed to characterize the cerebral cortical activity of chronic stroke patients according to differences in frequency of repetitive transcranial magnetic stimulation (rTMS). 20 chronic stroke patients were treated with 5 Hz high-frequency rTMS group (HFG) applied to the cerebral cortex on the damaged side and 1 Hz low-frequency rTMS group (LFG) applied to the cerebral cortex on the non-damaged side. The activity of the cerebral cortex was examined using electroencephalography (EEG) to changes in alpha waves (α -wave) and sensorimotor rhythm (SMR) wave. As a result, in two groups, HFG showed a significant difference in F3 and P4 for α -wave and in F3 and F4 for SMR wave ($p < 0.05$) ($p < 0.05$). In LFG, there was no significant difference in α -wave, but SMR wave showed a significant difference in F4 ($p > 0.05$) ($p < 0.05$). And in the comparison between two groups, α -wave showed a significant difference in F3 ($p < 0.05$). SMR wave showed no significant difference ($p > 0.05$). Through this, it is judged that 5 Hz high-frequency rTMS has a positive effect on cerebral cortical activity in chronic stroke patients compared to 1 Hz low-frequency rTMS.

Keywords : high frequency repetitive transcranial magnetic stimulation, low frequency repetitive transcranial magnetic stimulation, stroke, electroencephalography, sensorimotor rhythm wave

1. Introduction

Stroke is a major cause of death worldwide, and its incidence and prevalence are continuously increasing [1]. Patients who survive a stroke experience a negative impact on their physical and activity functions because of their limited recovery from brain damage [2]. The effective neuroplasticity of the damaged central nervous system in patients with stroke can be alleviated, improving the individual's quality of life and allowing the patient to return to various activities such as physical function, daily life, leisure activities, and work activities. To this end, treatment and rehabilitation training are required [3]. Neurorehabilitation programs are important for promoting functional recovery in patients with stroke. As the importance of effective neuroplasticity in neuro-

rehabilitation has been recognized, various interventions have been proposed for patients with stroke [4]. Among them, transcranial magnetic stimulation (TMS), as a non-invasive neuromodulation treatment, mainly modulates the excitability of the cerebral cortex and corticospinal tract, and has been proven safe [4]. The protocols commonly used for repetitive transcranial magnetic stimulation (rTMS) include high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) at a frequency of 5 Hz or higher and HF-rTMS at a frequency of 1 Hz or higher. Low-frequency repetitive transcranial magnetic stimulation (LF-rTMS) uses the following frequencies [5]. This either promotes or reduces the excitability of the cerebral cortex, depending on the frequency used [6]. Additionally, research results can be analyzed more accurately by combining various imaging techniques to determine the effectiveness of neuro-rehabilitation interventions [7]. Studies have demonstrated the effectiveness of intervention, mainly through changes in motor-evoked potential (MEP) [8]. Various studies have been conducted to prove the effectiveness of

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rTMS using functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) [9]. Specifically, non-invasive techniques such as fMRI, positron emission tomography (PET), TMS, EEG, and magnetoencephalography. Noninvasive techniques have been established as a new approach to understanding of recovery mechanisms in the study of brain function. In particular, EEG is very useful in examining changes in the functional and structural connectivity of the brain that occur due to disease and external stimulation [10, 11]. Previous research has reported that it has helped greatly in understanding the effects of cerebral cortex after intervention on central nervous system injuries such as Alzheimer's disease and stroke [12].

Although many studies have suggested the effectiveness of rTMS with respect to functional recovery after stroke [13], others have shown that the onset date, evaluation method, specific protocol and method applied, and individual patient characteristics may lead to differences in the effectiveness of rTMS. It was reported that there was [14, 15]. Therefore, this study considered it important to present the most efficient method by considering a continuous approach and the elements of the intervention methods applied in the neurorehabilitation of patients with chronic stroke. Accordingly, this study applied 5 Hz HF-rTMS and 1 Hz LF-rTMS to cortical activity in patients with chronic stroke and analyzed any differences in cerebral activity using EEG. Additionally, we aimed to understand the effects of rTMS by analyzing the brain waves in the cerebral cortex.

2. Materials and Methods

2.1. Patients

This study included patients with chronic stroke lasting over 6 months who were hospitalized in the department of rehabilitation medicine at hospital B, located in Gyeonggicity in South Korea. Prior to the study, all participants were presented with a recruitment document detailing the criteria and intervention. Subsequently, the research process was explained and patients who wished to participate in the study were selected. Participants were selected based on the following criteria: diagnosis of stroke by a neurologist or rehabilitation medicine specialist, a disease onset period of over 6 months, a score of 23 on the Korean version montreal cognitive assessment (K-MoCA), normal cognitive function, and independence. Patients who were able to sit and were at least in the third step of the Brunnstrom stage of upper extremity recovery were selected. Patients with metal objects attached to the body or with unstable medical disorders, such as seizures,

were excluded. Among the 22 selected patients, 2 had contraindications, did not meet the selection criteria, or were excluded for personal reasons. The 20 selected patients were randomly divided into two groups of 10 each by drawing lots. In the HF-rTMS group (HFG), 5 Hz HF-rTMS was applied to the cerebral hemisphere on the damaged side. In the LF-rTMS group (LFG), 1 Hz LF-rTMS was applied to the undamaged cerebral hemisphere. The HFG performed HF-rTMS on the injured cerebral hemisphere 3 times a week for 4 weeks, with a stimulation frequency of 5 Hz for 6 s of stimulation followed by 24 s of rest. A total of 900 pulses were applied over 15 minutes. In the LFG, LF-rTMS was performed on the uninjured cerebral hemisphere 3 times a week for 4 weeks, using a stimulation frequency of 1 Hz for 900 pulses over 15 minutes.

2.2. Assessment methods

2.2.1. Electroencephalography (EEG)

EEG is a medical imaging technique that measures the activity of electrical signals generated in the brain through terminals on the scalp, and can measure the electrical activity of both normal and damaged brains [16]. As current flows locally between the cell membranes and dendrites even during sleep or normal activity, when nerve cells in the brain are activated, measurement is possible in these states. This electrical flow generates local waves, and electrical signals are detected using EEG surface electrodes attached to the head above the cortical gyri. EEG can measure the current flow that occurs during the synaptic excitation of the cerebral cortex and dendrites. Unlike other brain tests, EEG has the advantage of being non-invasive and does not harm the human body. Additionally, it can confirm functional changes in the human brain within a short period of time, provide various data after the test, and has economic advantages; therefore, it has been used by many researchers [17]. In this study, changes in electroencephalographic measurements of the alpha wave (α -wave), sensorimotor rhythm (SMR) wave, and mid-beta-wave (mid- β -wave) were confirmed. EEG was measured while the patient was sitting in a comfortable chair in a treatment room isolated from the external environment, and body movements were minimized. EEG was measured using 8 channels on the scalp using monopolar derivation, and the attachment sites were sequentially Fp1, Fp2, F3, F4, and T3, and it was attached to T4, P3, and P4 (Fig. 1).

2.2.1.1. Alpha wave (α -wave)

α -waves have a frequency of 8-12 Hz and an amplitude range of 20-60 μ V, and the amplitude of the value



Fig. 1. (Color online) The electroencephalography (EEG) evaluation used in this study.

increases as the person is conscious and in a comfortable and relaxed, stable state. Particularly, α -waves are related to memory and information-processing speed in the brain. The α -wave is suppressed when eyes are opened, and increases when nervous or concentrating on an activity [18].

2.2.1.2. Sensorimotor rhythm (SMR) wave

SMR wave has a frequency of 12-15 Hz and appears when eyes are opened in a state of passive brain activity, attention is concentrated on external stimuli, or problems that require simple concentration are being solved while the body is in a comfortable and stable state. reported [18].

2.3. Procedure

2.3.1. 5 Hz HF-rTMS

Generally, HF-rTMS is a stimulation method that induces cerebral cortex excitability at a frequency of 5 Hz or higher. In this study, 5 Hz HF-rTMS was applied to the primary motor area (M1) of the cerebral cortex on the damaged side of patients [6]. A 70-mm 8-shaped coil



Fig. 2. (Color online) The rTMS equipment used in this study.

using ALTMS[®] (Remed, Korea, 2018) equipment was used (Fig 2). The stimulation point was checked by connecting an imaginary line from the nasion to theinion and a picture was taken at the junction of the midsagittal line and both interaural lines. The coil was placed on the cerebral hemisphere on the damaged side at an angle of approximately 45° from the centerline for the intervention. A total of 900 pulses were applied at an intensity of the resting motor threshold (RMT) 120% to activate the cerebral cortex on the damaged side using a frequency of 5 Hz for 15 min at a time, 3 times a week, for a total of 12 times over 4 weeks [6].

2.3.2. 1 Hz LF-rTMS

1 Hz LF-rTMS allows both cerebral hemispheres to control the contralateral cerebral hemisphere by using both hands in tasks such as writing. This is called transcallosal inhibition (TCI) and involves inhibition between the cerebral hemispheres through the transcallosus. This is known as the interhemispheric inhibition (IHI). Based on this, 1 Hz LF-rTMS was applied [18]. The same equipment and process were used as for the 5 Hz HF-rTMS.

2.4. Data analysis

Collected data were analyzed using SPSS 18.0 for Windows. Descriptive statistics and frequency analyses were used to determine the general characteristics of the participants. The Wilcoxon signed-rank test was used to determine changes in EEG waveforms before and after the intervention in both groups. The Mann–Whitney U test was used to compare EEG waveforms between the intervention after the intervention. The significance level was set at $p < 0.05$.

3. Results

3.1. General characteristics of subjects

The general characteristics of the participants were as follows: HFG included 6 men and 4 women, with an average age of 54.391 ± 5.12 years, Injury types is 6 cerebral hemorrhage, 4 cerebral infarctions, 5 right hemiparesis, and 5 left hemiparesis on the injured side. The mean disease duration after onset was 12.629 ± 3.01 months. and the K-MoCA score was 27.501 ± 2.14 points (Table 1). LFG included five men and five women, with an average age of 52.925 ± 4.51 years. Brain injury types is 4 cerebral hemorrhages, 6 cerebral infarctions, 4 right hemiparesis, and 6 left hemiparesis on the injured side. The mean disease duration after onset was 12.839 ± 3.92 months. and the K-MoCA score was 27.454 ± 2.93 points

Table 1. General characteristics of subjects

| Variables | | HFG (N=10) | LFG (N=10) | x ² /t | p |
|-----------------------------------|------------|---------------|---------------|-------------------|-------|
| Gender | Male | 6(60%) | 5(50%) | 0.435 | 0.771 |
| | Female | 4(40%) | 5(50%) | | |
| Age | | 54.391±5.12 | 52.925±4.51 | 7.291 | 0.664 |
| Side of stroke | Right | 5(50%) | 4(40%) | 0.273 | 0.152 |
| | Left | 5(50%) | 6(60%) | | |
| Type of stroke | Hemorrhage | 6(60%) | 4(40%) | 0.700 | 0.492 |
| | Infarction | 4(40%) | 6(60%) | | |
| Time from stroke to rehab(months) | | 12.629±3.01 | 12.839±3.92 | 1.225 | 0.268 |
| K-MoCA | | 27.501±2.14 | 27.454±2.93 | 5.403 | 0.667 |

M±SD M: mean SD: standard deviation, HFG: high frequency repetitive transcranial magnetic stimulation group, LFG: low frequency repetitive transcranial magnetic stimulation group, K-MoCA: korean version montreal cognitive assessment

(Table 1).

3.2. Comparison of changes in EEG before and after intervention within two groups

3.2.1. Results of the α -wave and SMR waves within two groups

The difference between α -waves before and after the intervention was measured using EEG. HFG was measured in the F3 and P3 areas (0.099±0.03 before intervention and 1.129±0.02 after intervention and 0.239±0.09 and 0.252±0.02 after intervention, respectively).

The difference was significant (both $p < 0.05$) (Table 2). The difference in LFG was not significant ($p > 0.05$) (Table 2). For SMR wave analysis, HFG was measured in the F3 area (0.051±0.02 and 0.089±0.01 before and after intervention, respectively), and the F4 area (0.059±0.03 and 0.084±0.01 before and after intervention, respectively), a significant difference (both $p < 0.05$) (Table 3). LFG was measured in the F4 area (0.039±0.01 and 0.078±0.01 before and after intervention, respectively), and a significant difference was seen (both $p < 0.05$) (Table 3). No significant differences were observed in the F3

Table 2. Comparison of alpha wave of electroencephalography within groups.

| Variables | Groups | Pre-test | Post-test | Z | p |
|-----------|--------|------------|------------|-------|--------|
| Fp1 | HFG | 0.073±0.01 | 0.075±0.02 | 0.720 | 0.426 |
| | LFG | 0.071±0.01 | 0.069±0.01 | 0.791 | 0.493 |
| Fp2 | HFG | 0.085±0.02 | 0.087±0.02 | 1.212 | 0.282 |
| | LFG | 0.096±0.02 | 0.086±0.03 | 3.250 | 0.197 |
| F3 | HFG | 0.099±0.03 | 1.297±0.02 | 3.723 | 0.048* |
| | LFG | 0.179±0.05 | 0.197±0.06 | 3.000 | 0.223 |
| F4 | HFG | 0.097±0.03 | 0.090±0.05 | 2.120 | 0.368 |
| | LFG | 0.128±0.03 | 0.162±0.04 | 1.531 | 0.217 |
| P3 | HFG | 0.239±0.09 | 0.252±0.02 | 7.957 | 0.024* |
| | HFG | 0.225±0.11 | 0.221±0.15 | 1.152 | 0.426 |
| P4 | HFG | 0.216±0.11 | 0.226±0.09 | 2.103 | 0.265 |
| | LFG | 0.151±0.06 | 0.162±0.09 | 1.750 | 0.663 |
| T3 | HFG | 0.115±0.07 | 0.101±0.05 | 1.834 | 0.266 |
| | LFG | 0.197±0.09 | 0.207±0.11 | 3.462 | 0.116 |
| T4 | HFG | 0.131±0.05 | 0.137±0.06 | 1.627 | 0.385 |
| | LFG | 0.187±0.03 | 0.194±0.94 | 1.649 | 0.403 |

M±SD M: mean SD: standard deviation, $p < 0.05^*$ HFG: high frequency repetitive transcranial magnetic stimulation group, LFG: low frequency repetitive transcranial magnetic stimulation group

Table 3. Comparison of sensorimotor rhythm wave of electroencephalography within groups.

| Variables | Groups | Pre-test | Post-test | χ^2 | p |
|-----------|--------|------------|------------|----------|--------|
| Fp1 | HFG | 0.025±0.01 | 0.026±0.01 | 4.327 | 0.055 |
| | LFG | 0.026±0.01 | 0.027±0.01 | 0.537 | 0.792 |
| Fp2 | HFG | 0.028±0.00 | 0.030±0.01 | 2.123 | 0.115 |
| | LFG | 0.024±0.01 | 0.021±0.01 | 1.300 | 0.497 |
| F3 | HFG | 0.051±0.02 | 0.089±0.01 | 6.192 | 0.035* |
| | LFG | 0.043±0.01 | 0.068±0.01 | 2.516 | 0.224 |
| F4 | HFG | 0.059±0.03 | 0.084±0.01 | 7.249 | 0.026* |
| | LFG | 0.039±0.01 | 0.078±0.01 | 7.567 | 0.032* |
| P3 | HFG | 0.039±0.03 | 0.039±0.01 | 1.242 | 0.433 |
| | LFG | 0.092±0.04 | 0.088±0.02 | 1.000 | 0.582 |
| P4 | HFG | 0.093±0.03 | 0.088±0.02 | 1.407 | 0.495 |
| | LFG | 0.059±0.03 | 0.076±0.03 | 1.750 | 0.417 |
| T3 | HFG | 0.079±0.01 | 0.069±0.02 | 2.161 | 0.193 |
| | LFG | 0.062±0.02 | 0.079±0.01 | 1.000 | 0.393 |
| T4 | HFG | 0.070±0.02 | 0.065±0.01 | 2.613 | 0.520 |
| | LFG | 0.069±0.02 | 0.070±0.01 | 1.750 | 0.395 |

M±SD M: mean SD: standard deviation, $p < 0.05^*$

HFG: high frequency repetitive transcranial magnetic stimulation group, LFG: low frequency repetitive transcranial magnetic stimulation group

Table 4. Comparison of alpha wave of electroencephalography between two groups.

| Variables | HFG (N=10) | LFG (N=10) | Z | p |
|-----------|-------------|-------------|--------|---------|
| Fp1 | 0.002±0.001 | 0.003±0.001 | -1.104 | 0.297 |
| Fp2 | 0.002±0.001 | 0.011±0.001 | -0.397 | 0.730 |
| F3 | 0.122±0.011 | 0.012±0.005 | -3.048 | 0.001** |
| F4 | 0.012±0.031 | 0.002±0.001 | -0.855 | 0.148 |
| P3 | 0.052±0.001 | 0.022±0.001 | -1.855 | 0.073 |
| P4 | 0.001±0.001 | 0.010±0.002 | -0.329 | 0.263 |
| T3 | 0.011±0.005 | 0.001±0.001 | -2.292 | 0.149 |
| T4 | 0.012±0.004 | 0.012±0.002 | -0.592 | 0.412 |

M±SD M: mean SD: standard deviation, $p < 0.01^{**}$

HFG: high frequency repetitive transcranial magnetic stimulation group, LFG: low frequency repetitive transcranial magnetic stimulation group

area ($p > 0.05$) (Table 3).

3.3. Comparison of changes cerebral activity before, after, and at 2 weeks of intervention between two groups

3.3.1. Results of α -wave and SMR waves compared between two groups

There was a significant difference between the two groups in the F3 area of α -wave after the intervention ($p < 0.05$) (Table 4). There were no significant differences in SMR waves in any area ($p > 0.05$) (Table 5).

4. Discussion

Upper extremity dysfunction after stroke limits patients'

activities of daily living and reduces their quality of life [19]. Recently, non-invasive brain stimulation therapy has been developed to improve upper extremity function and daily life performance in patients with stroke, and its effectiveness has been proven [20]. rTMS, which acts through cerebral interhemispheric control and in patients with stroke, HF-rTMS is applied to the cerebral cortex on the paralyzed side to increase excitability [5], and LF-rTMS is applied to the contralateral side of the injury to reduce interhemispheric inhibitory connections with the damaged cortex [6]. However, recent studies have raised several questions regarding individual differences among patients with stroke, rTMS application protocols, and evaluation tools [14]. Therefore, in this study, we

Table 5. Comparison of sensorimotor rhythm wave of electroencephalography between two groups.

| Variables | HFG (N=10) | LFG (N=10) | Z | p |
|-----------|-------------|-------------|--------|-------|
| Fp1 | 0.001±0.001 | 0.001±0.001 | -0.391 | 0.347 |
| Fp2 | 0.002±0.001 | 0.003±0.001 | -0.225 | 0.413 |
| F3 | 0.031±0.005 | 0.025±0.004 | -1.942 | 0.121 |
| F4 | 0.011±0.002 | 0.011±0.002 | -1.241 | 0.167 |
| P3 | 0.001±0.001 | 0.001±0.001 | -0.592 | 0.773 |
| P4 | 0.013±0.002 | 0.021±0.004 | -1.935 | 0.340 |
| T3 | 0.001±0.000 | 0.011±0.009 | -1.421 | 0.103 |
| T4 | 0.002±0.001 | 0.001±0.001 | -0.941 | 0.349 |

M±SD M: mean SD: standard deviation,

HFG: high frequency repetitive transcranial magnetic stimulation group, LFG: low frequency repetitive transcranial magnetic stimulation group

attempted to analyze the activity of the cerebral cortex using EEG after applying rTMS at different frequencies to patients with chronic conditions to investigate the changes in the cerebral cortex due to each protocol. In this study, we aimed to compare the effects of 5 Hz HF-rTMS and 1 Hz LF-rTMS on cortical activity in patients with chronic. We randomly divided the 20 patients into HFG and LFG. Their EEG were analyzed by subdividing the α -wave and SMR waves. First, by comparing changes in alpha waves through EEG, differences were observed before and after the intervention in the F3 and P4 areas in HFG, and no differences were observed in LFG. Alpha waves are waveforms that can confirm the state of cerebral arousal and concentration and are primarily used when checking the cerebral arousal state of an individual [18]. The F3 and P4 areas in the HFG are the primary motor and sensory areas, respectively, indicating that the activity of the patient's motor and sensory areas increased. A previous study using MEP after rTMS intervention reported significant improvement in MEP through theta burst stimulation combined with electrical stimulation therapy for 10 patients with stroke [21]. Additionally, another study reported activation of the cerebral motor cortex through MEP testing after applying 1 Hz LF-rTMS and 10 Hz HF-rTMS to 60 patients with stroke who developed dysphagia [22]. These results are consistent with those of this study, showing increased activity in the motor and sensory areas. Comparing the changes in SMR waves, differences were observed in the F3 and F4 areas in HFG after the intervention. In LFG, differences were observed only in the F4 area. The SMR wave is a waveform that appears when one begins to move the body or concentrate on an activity, and is a waveform that appears in cerebral activity that is more concentrated than the state of awakening [18]. The F3 and F4 areas of the subjects were motor areas that were observed to improve

movement [23]. In another study, 21 patients with stroke performed hand-centered therapy was performed after HF-rTMS, while hand-centered therapy was performed after sham HF-rTMS in another group. The accuracy of finger movements improved in the experimental group, and fMRI also showed that the activity of the sensorimotor cortical area increased [24]. In our study, brain waves also increased in the relevant motor areas. Particularly, an increase in the SMR wave can be an indicator of a positive correlation between the activity of the motor cortex area and movement improvement. Furthermore, when comparing brain activity between the two groups after the intervention, the α -waves showed improved results in the HFG. In a study by Sasaki *et al.* (2013) compared HF-rTMS, LF-rTMS, and sham rTMS in 29 patients with early stroke and reported improvements in hand grip strength and function after 2 weeks of HF-rTMS and LF-rTMS. Differences were confirmed in the post-maintenance phase results of the HFG [25]. In our study, HF-rTMS showed a more positive improvement than LF-rTMS did. These results indicate that HF, which directly stimulates the cerebral cortex on the damaged side rather than LF-rTMS, induces an indirect improvement on the damaged side by stimulating the cerebral cortex on the undamaged side. This is considered to be an advantage of rTMS. This study has some limitations. The results of the study cannot be generalized because of the small sample size. Additionally, there are limitations in understanding the advantages and disadvantages of more diverse TMS protocols by comparing only two methods such as HF-rTMS and LF-rTMS. Future research should attempt to compensate for these shortcomings, which will provide objective evidence to suggest appropriate treatments tailored to the characteristics of the subjects.

5. Conclusion

In this study, we compared EEG changes in patients with chronic stroke according to differences in rTMS frequency. Comparing the results within our two groups, significant differences were found in the F3 and P4 area in α -wave in HFG ($p < 0.05$), and analysis of SMR waves showed significant differences in the F3 and F4 area ($p < 0.05$) ($p < 0.05$). In HFG, a comparison of the SMR waves showed a significant difference in the F4 area ($p < 0.05$). A comparison of the two groups revealed a significant difference in the F3 area of α -wave ($p < 0.05$) but no significant difference in the SMR waves ($p > 0.05$). These results confirmed that high-frequency rTMS had a more positive effect on EEG changes in patients with chronic than low-frequency rTMS.

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