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Original Article

The Effect of rTMS with Rehabilitation on Hand Function and Corticomotor Excitability in Sub-Acute Stroke

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Objectives: Stroke is the leading cause of long-term disability. Hand motor impairment resulting from chronic stroke may have extensive physical, psychological, economical, and social implications despite available rehabilitative treatments. The best time to start treatment for stroke is in sub-acute period. Repetitive Transcranial Magnetic Stimulation (rTMS) is a method of stimulating and augmenting the neurophysiology of the motor cortex in order to promote the neuroplastic changes that are associated with motor recovery. The purpose of this study was to compare the effects of repetitive transcranial magnetic stimulation protocols plus routine rehabilitation on hand motor functions and hand corticomotor excitability in stroke patients with hemiplegia with pure routine rehabilitation programs.

Methods: This study was a randomized clinical trial which was performed on 24 patients with hemiplegia who were randomly divided in to three groups: received high frequency rTMS, received rehabilitation program with low frequency rTMSl, who were given only routine rehabilitation programs. The treatment was performed for 10 sessions, three times pre-post test and follow-up about neurophysiological contralesional hemisphere evaluations using record of MEP wave indices by single pulse TMS, and assessing functional wolf test and hand grip power of disabled hand by dynamometer.

Results: The results demonstrated that the rest MEP threshold reduction in experimental group which received high frequency magnetic stimulation was not statistically significant (P=0.387). There was significant reduction for active MEP threshold in the within group (P=0.031). Also there were statistically significant between obtained results from WOLF test and grip test.

Discussion: According to the results, it seems that Hf rTMS combined with routine physiotherapy can significantly improve hand functions and brain neurophysiology via specifically increase of contra-lesional corticomotor excitability in sever stroke patients. It indicated the role of neuroplasticity in nonlesioned hemisphere; but the hypothesis of movement improvement related cognitive balance can't be eliminated by exploring powerful approved effect of Hf rTMS on mood regulation.

Keywords: sub-acute Stroke; repetitive Transcranial Magnetic Stimulation; hand Motor function, brain contra-lesional corticomotor excitability

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Introduction

Stroke is described as a "brain attack". The disorder is the most common cause of disability in adults and disabilities caused by stroke often do not heal completely (1). Stroke is the leading cause of 10-12% of mortalities and is the first cause of long-term disabilities in the world. More than 50 percent of the survivors of this disease suffer from motor disabilities.(2, 3). Hemiplegia is a common symptom of this disorder due to damaging to Cerebrovascular Accident (CVA) (4). Hemiplegia is the functional limitations of more than 80 percent of people with brain stroke (5). So, despite the fact that most patients achieve a degree of independent mobility in the limbs, especially the upper limb, but many of them do not experience improvement in upper limb function properly (6, 7). Current treatments for this disorder to improve motor function after stroke include movement therapy, physiotherapy(8), occupational therapy, functional electrical stimulations (FES) and drug therapy. Due to restriction of every above mentioned, non-invasive

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treatments for brain stimulation have been at the forefront of researches (9). TMS enables the researchers to study changes of excitability of the primary motor cortex of damaged excitability hemisphere during recovery (10). Initial studies in this field report the results based on the increased activity of the healthy hemisphere in the patient's hand motion recovery that is reduced over time especially in patients with good recovery (11). Repetitive transcranial magnetic stimulation (rTMS) causes changes of synaptic activity that last more than stimulation time in the way that synaptic changes can occur as LTP (Long Term Potentiation) and LTD (Long Term Depression).rTMS can augment or reduce excitability of corticocortical routes based on the intensity of the stimulation, the stimulation frequency and coil place (12,13).

According to research conducted in recent years, rTMS may be an effective method in reducing the patient disability symptoms. And probably better effect is achieved when we have combination therapy (14). Unaffected hemisphere have an supporting role to functional recovery and cortical reorganization (15), and monitoring of its excitability may conclude information about mechanism of intervention in stroke patient. The pervious researches claimed effectiveness of physiotherapy and rTMS combination on functional improvement of upper limb (16). The main aim of this study was to compare the effects of repetitive transcranial magnetic stimulation protocols plus routine rehabilitation on hand motor functions and hand corticomotor excitability in stroke patients with hemiplegia with pure routine rehabilitation programs.

Methods

The study participants were selected randomly from the patients who referred to department of neurology in hospitals and clinics in Tehran as brain stroke. The inclusion criteria were noticed by clinical through simple method of population. To assess the strength of holding objects by hand and healing effect on it, hand held dynamometer pressure (Riester made in Germany) was used. To assess the functional ability of participants, wolf motor function test for assessing upper extremity function was used. To assess the motor evoked potential (MEP) parameters (peak to peak amplitude, latency and Diversion) using EMG system of company Neuro-EMG-MS (company NEUROSFT of Russia) with Neuro-MS.NET software is done with the capability to connect to the system Neuro-MS / D. The inclusion and exclusion criteria were as follow. For inclusion the existence of hemiplegic or hemiparesis at the prevalent side and after the first stroke, the conflict in the middle cerebral artery due to brain stroke, passing one to three months from the onset of stroke, in patients in the age range 30 to 65 years. The exclusion criteria included upper limb lasting damage, such as fractures, another neurological lesion such as Parkinson and multiple sclerosis, limitation of articular motion of upper limb for reasons other than stroke, history of epilepsy or a history of cardiac arrhythmias, the implants or clips inside the skull of the patient or the pacemaker in the heart, inability to work continuously in therapy sessions for 4 weeks for various reasons.

The participants divided to 3 groups for treatment randomly. The first group received conventional rehabilitation or routine physiotherapy of patients with upper extremity hemiplegia or hemi paresis. This means that after 10 minutes, Faradic Functional Electrical Stimulation on the extensor muscles of affected hand, routine and fixed exercises in the form of functional movements for 30 minutes will be taken by these patients. Exercise therapy is concluding active and active assistive upper limb motion of the forearm; wrist and fingers, strengthening the weakened muscles of the upper limb and motor control education of the affected side were used. Second and third group patients, were intervened with magnetic stimulations at a frequency of 1 Hz and 10 respectively beside routine physiotherapy. Stimulations were performed with frequencies 1 Hz and 10 kHz for at least 3 times a week for 10 sessions. Coil was placed in the motor cortex of healthy hemisphere touching the head. After finding the primarily motor region in a healthy side, the flow goes up somewhat, until when the first contraction is seen in the thenar muscles of the affected hand. This amount of magnetic stimulation intensity is considered as the patient's motion threshold and is different for every person. With intensity 60-80% of motor threshold (depending on the threshold of pain).And during treatment, patients were advised not to change the position of the head and coil position was fixed by coil holder. In the high frequency protocol, rest and stimulation duration were 20 seconds and 10 seconds respectively and for low frequency protocol, 1 HZ rTMS for 20 minute were done.

In order to record the motor evoked potentials (MEP) waves. the participants were kept in seated position and in the inner edge of the thenar prominence while the patient has a finger in the abduction. two active and reference electrodes were installed with a distance of two centimeters on the inside edge of the thenar prominence parallel to the direction of thumb and the ground electrode is placed on the Olecranon tuberosity. The magnetic stimulations were given using cooled angulated figure of eight coil connected to magnetic stimulation device. equipped with a single pulse and rTMS delivered to unaffected hemisphere. at rest and facilitation modes (mild muscle contractions) and using EMG system. MEP wave was recorded from the corresponding muscle. With short coil displacement. the best place to make potential was selected. Stimulation intensity was gradually increased until desired and repeatable response of muscle was recorded that was usually between 50 to 100 percent of maximum intensity. From 8-10 applied stimulations. the wave with lowest latency and highest amplitude was selected. The absence of the MEP was stated when no response more than 50 μv after 5 stimulators in 100% intensity was found (17). Time Peak to Peak Amp. latency and Duration. rest and active MEP threshold were extracted as variables. These parameters were measured and indicated in software Gain = 100μv. and displayed by the software. The coil direction in excitation time is parallel to the scalp and as coil handle in the position of posterolateral of skull. The MEP recording and WFMT were done in three session: the pretest. post-test and after 8 weeks of treatment.

Results

Lat variable (latency of MEP wave) in all three pre-test. post-test and Flow up were recorded in two high-frequency and control groups without changing the normal range. Amplitude has not had an effective change in each of the three groups. One of the most important variables used in determining the primary motor cortex excitability in the brain is rest MEP threshold briefly mentioned as rmep. which in all three groups showed significant changes in the MEP recording test processes. The rmep quantitative decrease represents an increase in excitability in unaffected hemisphere and its average number in the pre-test and post-test in high frequency group, was 96μv and 98μv respectively whereas recording of rmep was decreased to 82μv in follow up. (P=0.387) In the low frequency group. not notable changes in follow up (85μ v) were recorded compared to pre-test and post-test (81μ v) (Figure 1).

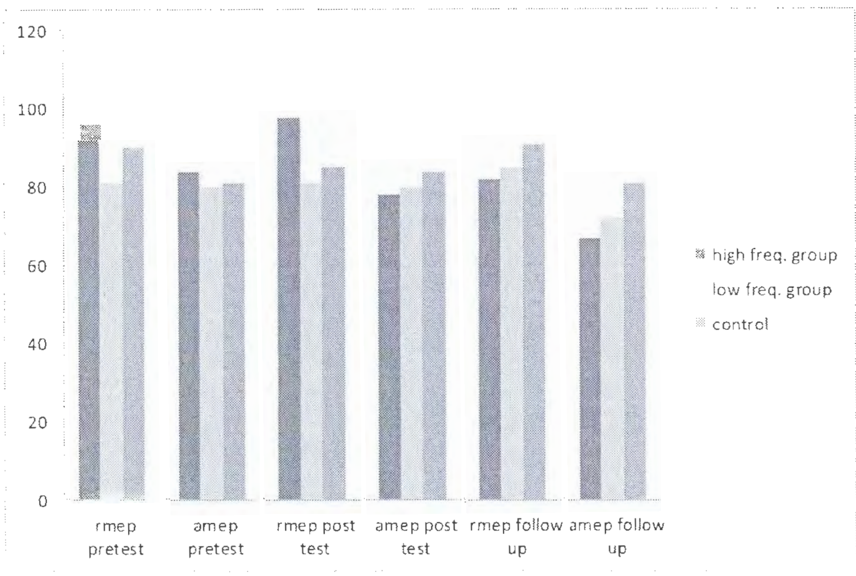

Fig. 1. Comparison of rmep and amep between groups in pretest. post test and follow up

In order to understand and facilitate in the recording of motor evoked potential and recording the aforementioned. the parameter called active MEP threshold was briefly defined with amep. Amep changes had a decreasing trend in the high-frequency group and recorded as 84μv in the pre-test. 78μv in the post-test and 67 μv in the follow up (P=0.598). In the control group from 81μv at pre-test it reached to 84µv in post-test and 81µv at follow up. Numerical changes of amep in the low frequency group, is greater than the control group and less than high-frequency group. Variable amep results, in low frequency group in the pre-test group is 80 µv, post-test is 80 µv, and in follow up is 72 µv. So that in high frequency group, it was more amep change in session than low frequency group and in the control group it had the least variation than two other groups (Figure 2).

In this, study variables rmep and amep expressed the identical trend. In high frequency group, the primary motor cortex excitability of healthy hemisphere after 8 weeks of treatment was significantly more change than the other two groups.

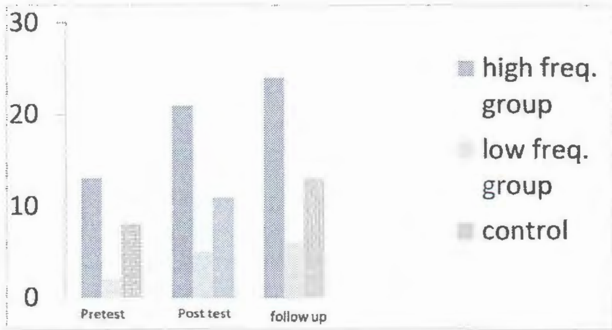

Fig 2. Comparison of grip power between three groups in pretest, post test and follow up

Variable dyn is characterized by the patient's grip strength that by investigating results in the three groups we saw slight increase grip strength. Most powerful patients at high frequency group in the pre-test applied 14N force (P=0.071) to dynamometer that in later steps of evaluation, increased to 21N and 24N. WIT variable indicates time of doing voluntary movement in a single-joint isolated movement, and WIG represents qualified movement grade in a single joint. In Wolf test, time of doing voluntary movement and grade of multi-joint functional movement was measured by variables WTF and WFG. WIT changes showed a trend of increased movement speed which was roughly similar in three groups and in three evaluation steps. However, change of WIG variable findings were evident only in high frequency group that was changed from grade 3 to 4. But in the other two groups, no obvious change was detected and it was near the grade 3 at all stages of the test. This is one of the most important functional changes caused by repeated magnetic excitations in high frequency, while no change was observed in the other two groups. WFG (functional Movement Grade) in the high frequency group in post-test promoted from grade 2 to 3. In the follow up grade 4 was recorded. In low frequency group and in all three steps, grade 1 was recorded (Figure 3). The latest parameter known as WOLF has been obtained by calculating mean of qualitative and quantitative test scores average of Wolf test.

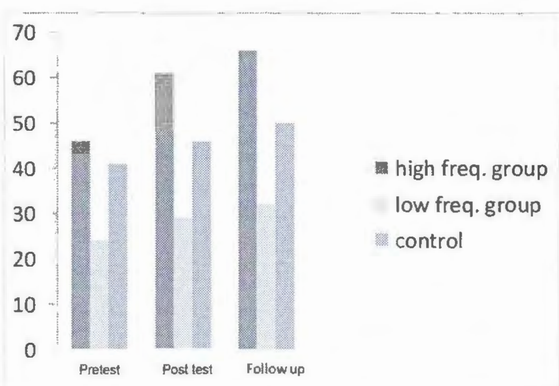

Fig. 3. Comparison of Wolf Score between three groups in pretest, post test and follow up

The greatest increase of score in post-test and follow up were related to high frequency group (P=0.081). The numerical change of wolf scores, in the high frequency group was equal to 20, but this numerical change in control group and low frequency group was equivalent to 8 assessed as a numerical improvement.

Discussion

The study aimed to investigate the application of high and low frequency rTMS (10Hz) on the primary motor cortex, and the potential impact of such interventions on grip strength and function of the affected hand and primary cortex excitability of non-affected hemisphere. After a stroke, disinhibition occurs in both hemispheres leading to activation of neuronal circuits, and leading to the hyper activity of neurons. After a while, with the improvement of motor function in the sub-cortical lesions, ICI increases in unaffected hemisphere and come near to normal state. While the ICI in affected hemisphere remains abnormal (18,19), the significance of improved functional tests in the present study, with the primary motor cortex increased excitability in the healthy hemisphere is likely indicating to continue unmasking intracortical circuits, and increased compensatory disinhibition mechanism in unaffected hemisphere. The above reasoning is apparently opposed to a research that knows increased ICI related to improving motor symptoms. It should be noted that, treatment intervention in high frequency, includes the aggregation effect of bilateral exercises of upper extremity (20), and electrical stimulations with rTMS, not the pure effect of high-frequency rTMS alone. In other words, the influential impress of bilateral exercises, plays role in increased excitability of unaffected cortex. The increased disinhibition of uninvolved hemisphere with impression of decrease rmep/amep in high frequency group is coming to pose the time outspread of compensatory continuing disinhibition phenomena. possible continuation of disinhibition is the inherent mechanism in the brain after stroke that plays an important role in creating and expanding time in contact with plasticity of brain, so that the remaining healthy have chance to creation of LTP/LTD with the compensatory performance of increased disinhibition (instead of increasing ICI). Although fMRI did not take place to identify the exact severity of the injury in our study, but looking at the extent of disability in the upper extremity in samples entered the present study and given the low scores obtained from Wolf motor function test of in the pre-test, the possibility of sever cortical lesion is strengthened. So Increased excitability occurred in the process of reducing rmep/amep in high frequency beside that reason mentioned above can be attributed to the extreme severity of the initial injury (19,21).

In order to determine the regional cerebral blood flow (rCBF) after high-frequency rTMS over the primary motor cortex of affected hemisphere, a study was done by koyama, with the use of PET method. It was found that, rCBF increases in the primary motor cortex of no stimulated side (22). In our study increase of excitability of unaffected hemisphere is proportionated with Koyama's result that propagation of rCBF in M1 of unaffected side is occurred after high frequency stimulation of affected M1 so contralesional neuronal membrane excitability may be raised that can be congruent with increase of rCBF. Prevalence of cognition injuries in sub acute stage in epidemiological studies in Western countries is emerged as 22-44% from the third month after the stroke lesion and in Tehran 68% has been reported. Cerebrovascular lesion in brain stroke patients, indirectly influence people's motivational and cognitive ability which is referred as to mood disorders after stroke and includes a wide range of disorders such as mood disorders (23,24).

According to the findings of this study, it can be said that mobility improvement in patients with brain damage may be acceptably associated with improvements in mood and cognition. Probably improvement function of stroke patients is influenced by improving mood and psychological conditions and the findings of fMRI, show the increased excitability in frontal cortex upraise after magnetic stimulation of motor cortex in stroke patients in chronic phase (25). Already it's confirmed and accepted that high frequency rTMS can use as a powerful instruments in treatment of major deep depression (MDD). Combination of high-frequency rTMS as well as rehabilitation program increases uses dependent plasticity. Koganemaru et al in 2009, in a study explored brain stroke patients in the chronic phase (24 months after the injury) to combination therapy (physiotherapy, perpherial nerve stimulations, and high-frequency rTMS (26). our results showed parallel development of increased corticospinal excitability along with grip strength, and increased function of the affected hand extensor muscles. The motor evoked potential of the unaffected hemisphere was recorded and evidence suggests that unaffected hemisphere is a source of plasticity changes in the reorganization of motor output after the occurrence of cerebrovascular ischemic lesion. With regard to the issues raised in this study and previous studies, it seems that application of rTMS with the frequency 10Hz in the motor cortex of the affected hemisphere in stroke patients, in the sub acute phase leads to broaden the time of effective plasticity of brain, in increasing the motor output of pyramidal pathway, and enhancing the effects of routine physiotherapy to improve the strength and upper extremity function in patients affected by stroke.

Conclusion

According to the results, Hf rTMS combined with routine physiotherapy can significantly improve hand functions and brain neurophysiology via specifically increase of contralesional corticomotor excitability in sever stroke patients that is representative of the role of neuroplasticity in unaffected hemisphere. But the hypothesis of movement improvement related cognitive balance can't be eliminated by exploring powerful approved effect of HfrTMS on mood regulation.

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