Original Research

Effect of High Frequency Transcranial Magnetic Stimulation (TMS) on Extensor Digitorum Communis Muscle Strength in Ischemic Stroke Patients

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ABSTRACT

Background: Stroke may disrupt a patient's motor function, consequently affecting the quality of life. A stroke surviving brain has the ability to repair itself through neuroplasticity mechanism. Transcranial Magnetic Stimulation (TMS) is a non-invasive device which can be used to stimulate the lesioned part of the brain in hope of triggering neuroplasticity.
Aims: To find prove of the repetitive Transcranial Magnetic Stimulation (rTMS) effect on extensor digitorum communis muscle strength improvement in ischemic stroke patients.
Methods: Subjects suitable with the inclusion criteria (N=18) were divided into two groups, control group and intervention group. The control group underwent conventional therapy exclusively every day for 5 days in a row, while the intervention group underwent rTMS therapy and conventional therapy every day for 5 days in a row. Extensor digitorum communis muscle strength was measured using surface electromyography (sEMG) before and after treatment.
Result: Significant increase of sEMG numbers were found on control group (p=0,003) and intervention group (p=0,001). The increase from the intervention group was not different when compared to the control group (p=0,067).
Conclusion: TMS can increase extensor digitorum communis muscle strength but with no difference with a conventional therapy.

Keywords: *Transcranial Magnetic Stimulation, TMS, neuroplasticity, surface electromyography, Extensor digitorum communis muscle strength, subacute ischemic stroke*

Introduction

Stroke is an acute neurologic deficit brought by occlusion or hemorrhage of brain vessel, causing focal or global symptoms lasting more than 24 hours. Stroke is the third leading cause of death in the world, behind heart disease and cancer. The American Heart Association estimated that there are 780.000 new and recurrent cases of stroke each year, with 600.000 patients suffering from a first attack and 180.000 patients suffering from a recurrent attack. Stroke causes the highest level of disability compared to any other disease. National Stroke Association stated that 10% stroke survivors recovered completely without any disability, 25% recovered with mild disability, 40% suffered moderate to severe disability requiring long term care.[1,2] Stroke incidence rate according to 2013 Indonesian Riskesdas showed an increased number, from 8,3 per 1000 people in 2007 to 12.1 per 1000 people in 2013.[3]

Depending on the degree of damage suffered, brain can utilize its own plasticity properties and reorganize itself. Some studies documented cortical organization change happening after stroke, especially in the lesioned side. Another thing needed to be put in perspective is the functional balance between both hemispheres controlled by interhemispheric inhibition. Stroke attacked hemisphere can go through twice the damage of the non lesioned side, which is caused by the stroke itself and the imbalance of inhibition and excitation [4,5].

Some certain amount of muscle strength and range of motion of the upper and lower extremity are needed as a requirement to perform independent daily living activities. A functional shoulder range of motions are -65^0 - 105^0 abduction-adduction, 0^0 - 121^0 elbow flexion, -40^0 - 38^0 wrist flexion –extension[6].

Transcranial magnetic stimulation (TMS) was introduced as a non-invasive tool for the investigation of the motor cortex. TMS is based on an electromagnetic coil applied to the scalp producing an intense, localized magnetic field which either excites or inhibits a focal cortical area. The repetitive application (rTMS), causing longer lasting effects, was used to study the influence on a variety of TMS frequencies to cerebral functions. Low-frequency (≤1 Hz) rTMS is likely to cause inhibition of neuronal firing in a localized area, whereas high-frequency (≥1 Hz) rTMS inversely leads to neuronal depolarization under the stimulating coil and to indirectly affect areas being connected[16-18].

Safety in Repetitive Transcranial Magnetic Stimulation (rTMS) is also an important aspect of consideration. Dizzines and convulsion are adverse events possible to happen, but a metaanalysis from Hsu et al stated there was only 1 study found reporting an adverse event of mild headache[7].

Several trials were done to investigate the effect of rTMS on upper limb motor function in patients with stroke. High frequency rTMS over the primary motor cortex (M1) in the affected hemisphere could improve motor learning performance in patients with chronic stroke and have a positive, long-term effect on motor recovery in acute and subacute patients with stroke.[5,7] However, other reports did not show measurable therapeutic effects of rTMS on motor function after stroke. There were inconsistent findings and methodological discrepancies across these trials, there is a lack

of consensus regarding the effect of rTMS on motor recovery in patients with stroke.[7,19]

Objective muscle strength measurement was done in this study using surface electromyography sEMG on extensor digitorum communis muscle as an extensor of wrist. Our hypothesis is rTMS may increase extensor digitorum communis muscle strength.

Material and Methods

This study was an experimental study with a randomized control two group design, done on subacute ischemic stroke patients. The subjects of this study were 18 subacute ischemic stroke patients, from Dr. Soetomo General Hospital Rehabilitation Medicine Outpatient Clinic, who suited the inclusion criteria and did not have any of the exclusion criteria. Inclusion criteria were subacute ischemic stroke, hemiparesis, could comprehend instruction, was willing to be the study subject and to follow the study protocol, and signed the informed consent. Exclusion criteria were unstable clinical condition, history of convulsion, history of head injury, present pregnancy during study period, aphasia, occipital lobe lesion only, contracture of the wrist and hand, and usage of metal medical device. Drop out criteria of the subject were unwillingness to follow the study protocol, a development of unstable clinical condition during study period, a development of headache which worsen with rTMS during study period with Wong Baker Scale ≥4. Subjects drew a lottery to conclude whether the subject entered the control or intervention group. Initial sEMG evaluation was done before starting the treatment. Subjects in the control group underwent conventional therapy for 5 days in a row, while the intervention group underwent a conventional therapy and rTMS for 5 days in a row. Repetitive Transcranial Magnetic Stimulation done using Neuro-MS/D, 8-shaped coil, 10Hz, 100% motor threshold, 750 pulses per day, targeted on primary motor cortex area (M_1). Another sEMG evaluation was done after the treatment period was over, followed by data analysis. Analysis of data was done using SPSS version 20 to do comparison of sEMG value of the control group before and after the treatment, comparison of sEMG value of the intervention group before and after the treatment, comparison of the initial data from the control and intervention group, and comparison of data taken after treatment period. All study subject had signed the informed consent form and this study had ethical clearance from the ethical committee of Dr. Soetomo General Hospital.

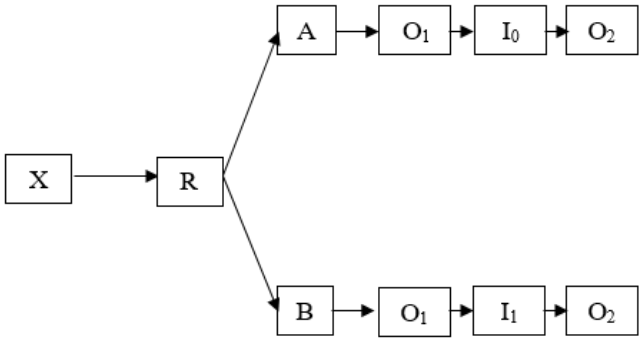

Figure 1. Study pathway. X: Subject; R: Randommization; A: Control Group; B: intervention Group; O_1= First sEMG; O_2: Final sEMG; I_0: Conventional Therapy; I_1: Conventional Therapy + repetitive Transcranial Magnetic Stimulation

Figure 2. Transcranial Magnetic Stimulation Neuro-MS/D

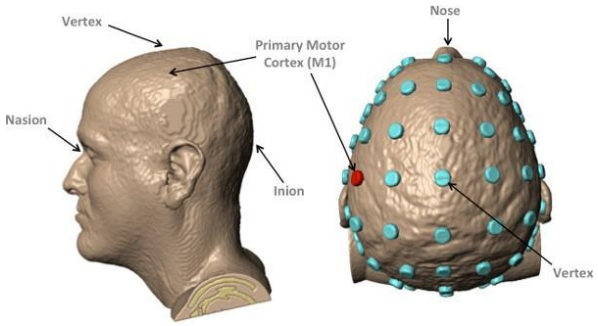

Figure 3. Coil placement on primary motor cortex (M_1)

Result

All 18 subjects were randomized into control and intervention group, all followed the study protocol from the start to the end. There was no difference found on the demographic data of the subjects and on the initial sEMG value (showed in table 1, table 2, and table 3). There was significant sEMG value difference before and after treatment found on control group (table 4), there was also significant sEMG value difference before and after treatment found on intervention group (table 5). But no difference between control and intervention group was found on after treatment sEMG value (table 6).

Discussion

All subjects of this study were clinically stable subacute ischemic stroke patients. The average age of subjects in intervention group was 56 years old, the control group was 55 years old, both group age were homogenous and did not influence the result of the study.

Table 1. Demographic Data

	Group		N	Mean	SD	*p-value*
Age (years old)	Intervention		9	55.56	± 9.1	0.82*
	Control		9	54.9	±9.9	
Sex	Intervention	Male / Female	6 3	6/3		0.26**/
	Control	Male / Female	8 1	8/1		0.58***
Initial muscle strength (MMT)	Intervention		9	2.11	±1.27	0.75
	Control		9	2	±1.32	
Spasticity level	Intervention		9	1.33	±0.5	0.58
	Control		9	1.56	±0.73	

Sample size (N); average (*mean),* standard deviation (SD); significant p if p<0,05. *Mann-Whitney test. **Pearson Chi-Square test. *** Fisher's Exact test.

Table 2. Control and intervention group comparison of initial sEMG

Group	N	Mean (mV)	SD	t	*p-value*
Intervention	9	63.79	±34.03	-1.67	0.11*
Control	9	106.34	±68.66		

*Independent sample t-2 test; sample size (N); millivolt (mV); average (mean), standard deviation (SD); significant p if p<0,05.

Table 3. Intervention group comparison of sEMG before and after treatment

sEMG	N	Mean (mV)	SD	t	*p-value*
Before	9	63.79	±34.03	5.3	0.001*
After	9	143.27	±75.07		

*Paired t test: sample size (N); millivolt (mV); average (*mean),* standard deviation (SD); p=0,001

Table 4. Control group comparison of sEMG before and after treatment

sEMG	N	Mean (mV)	SD	t	*p-value*
Before	9	106.34	±68.66	4.17	0.003*
After	9	149.89	±91.06		

*Paired t test: sample size (N); millivolt (mV); average (*mean),* standard deviation (SD); significant p if p<0,05.

Table 5. Control and intervention group comparison of after treatment sEMG

sEMG	N	Mean (mV)	SD	t	p
Intervention	9	79.48	±45.02	1.97	0.067*
Control	9	43.54	±31.34		

*Independent sample t-2 test; sample size (N); millivolt (mV); average (*mean),* standard deviation (SD); p=0,067

There were 6 (66.7 %) male subjects and 3 (33.3 %) female subjects in the intervention group, 8 male subjects (88.9%) and 1 female subject (11.1%) in the control group. No difference of sex between both groups was found.

Stastitical analysis was done to the initial muscle strength and spasticity level, as part of sEMG evaluation, to affirm whether there was any difference between both group before starting the treatment. Result showed there was no difference of those two parameters between both groups.

Exercise can enhance the process of neuroplasticity by increasing angiogenesis, neurotropic factors, the blood brain barrier integrity, brain vasomotor activity, and mitochondria biogenesis, also by moderating apoptosis and inflammation occuring on the brain.[9] Exercise increases expression of

angiogenic growth factor such as vascular endothelial growth factor (VEGF) and caveolin-1, playing major parts in neovascularization and improvement of vascular density. Exercise also increases brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and insulin-like growth factor (IGF-1), where BDNF holds a key role in neuroplasticity. NGF plays a role in nerve cells development and neuronal activities. IGF-1 stimulates autophagy mechanism, helping containment of apoptosis and necrosis of the ischemic brain area, so as to prevent widened cell deaths, and trigger neurogenesis.[8-10]

Neuroplasticity requires energy coming from the mitochondria, but an ischemic stroke causes mitochondrial damage. Exercise can increase the biogenesis of mitochondria after ischemic stroke by increasing the amount of mitochondria DNA and biogenesis factor of mitochondria such as mitochondrial transcription factor A and nuclear respiratory factor 1 (NRF-1).[9]

The above descriptions explain how exercise benefits post stroke recovery, and those are in concurrant with the result of this study shown by the increase of musle strength gained in the control group after 5 days of conventional therapy.

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive, painless modality that can be used to modulate cortical excitability. High-frequency rTMS facilitates cortical excitation of the treated side hemisphere, while a low-frequency rTMS decreases cortical excitation of the treated side hemisphere and increases the contralateral excitation.[7]

One important molecule of neuroplasticity is the BDNF (Brain Derived Neurotrophic Factor). A study by Wang et al showed rTMS therapy for 5 days increased BDNF affinity to TrkB (*Tropomyosin receptor kinase B*).[11] The above result concurs with this study wherein the usage of rTMS for 5 days in a row gave significant improvement on the subjects condition. The rapid improvement of symptoms is expected to bring good adherence and vigorous response to rehabilitation program from the patient, and to improve the patients quality of life.

BDNF is a growth factor neurotropin similar to nerve growth factor (NGF), neurotropin 3 (NT-3) dan neurotropin 4 (NT-4). These factors are responsible in triggering progenitor cells to proliferate, differentiate, and grow cells, they also take a role in regeneration process, neuron survival, remodelling and organization of sinaps, plasticity regulation, and repair of brain tissue. Neurotropin effect is mediated by Tyrosine kinase specific transmembrane receptor, the TrkB is a signal transduction receptor for BDNF.[12-14]

This study shows a higher improvement of extensor digitorum communis muscle from the intervention group compared to the control group, but the difference is not significant. This is different with the finding from Khedr et al, and Hsu et al. This maybe caused by the short period of intervention, by the psychologic condition of the subject during data collection, and or maybe caused by the timing of the data collection immediately after the last intervention (day 5).[5,7]

A study done by Lopes-Ibor in 2008 found headache or unpleasant sensation on the head as an adverse event of TMS usage, they occur on 4.5% of the subjects. They also didn't found any direct evidence of TMS causing death or epileptic seizure. These foundings

concur with previous studies stating there were no findings of headache, seizure, or death as an adverse effect of TMS, thus proving the safety of TMS.[15]

The weaknesses and difficulties of this study are small number of subjects and no blinded. The psychological influence (motivation, spirit, etc) of each subject were not identified and researcher did not differ each subject daily activity.

Conclusion

A rehabilitation program of rTMS and conventional therapy for 5 days in a row can increase extensor digitorum communis muscle strength of subacute ischemic stroke patients. The increase was not significantly different with patients who underwent only the conventional therapy.

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