Effect of High Frequency Transcranial Magnetic Stimulation on Upper Extremity Motoric Function in Subacute Stroke Ischemic Patient at Dr. Soetomo General Hospital Surabaya

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Abstract: Stroke cause motoric function disturbances that can decrease quality of life. Damaged brain caused by stroke have an ability to repair itself which is called neuroplasticity. Transcranial Magnetic Stimulation (TMS) was introduced as a non-invasive tool that could stimulate damaged brain hemisphere to increase neuroplasticity. This study aimed to prove and determine the effect of Repetitive Transcranial Magnetic Stimulation (rTMS) on upper extremity motoric function in subacute stroke ischemic patient. Eighteen subjects included in inclusion criteria, divided into 2 groups, control and intervention group. Control group had conventional therapy for 5 days consecutively and intervention group had conventional therapy and rTMS for 5 days consecutively. Upper extremity motoric function was evaluated with Fugl-Meyer Assessment (FMA). It was done before and after the intervention had completed. There were increasing of FMA score in control group 53.2 to 57.4 (p=0,012) and intervention group 40.3 to 54.1 (p=0,000). The increasing of FMA score in intervention group was higher 13.7 vs 4.2 (p=0,000). Combination of conventional and TMS therapy improved upper extremity function better than single conventional therapy in subacute stroke ischemic patient.

1 INTRODUCTION

Stroke by definition is rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin. Stroke is the third caused lead to death after cardiac disease and cancer. The American Heart Association estimate there are 780.000 stroke patients per year. Stroke is the most disabled disease. According to National Stroke Association about 10% stroke may fully recovered without sequelae, 25% may have sequelae, 40% may have moderate to severe handicap (Zorowits, 2010; Jauch et al., 2013).

Stroke prevalence according to Riset Kesehatan Dasar (Riskesda) Health Ministry of Republic Indonesia was increasing from 8.3 per 1000 people at 2007 become 12.1 per 1000 people at 2013 (Riskesdas, 2013).

The brain has ability to "plastic" and able to reorganize itself up to a certain degree of damage. Many studies have documented the changes in cortical organization that occur after motor stroke, particularly on the side of the lesion. In addition, there is a balance of function between the two hemispheres that is controlled by interhemispheric inhibition. The stroke affected hemisphere can be doubly disabled, by the stroke itself and by an imbalanced inhibition from the non-stroke hemisphere (Khedr *et al.*, 2009; Khedr *et al.*, 2010).

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 cerebral functions. Low-frequency (≤1 Hz) rTMS is likely to cause

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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 (Guse *et al.*, 2009).

Safety is an important consideration because rTMS could induce potential adverse effects such as headaches and seizures. Twelve of the studies reported that all patients tolerated the intervention well without any adverse events; only 1 study reported 4 subjects with mild, benign side effects of headaches (2 subjects), anxiety (1 subject), and fatigue (1 subject) (Lopez-Ibor *et al.,* 2008; Hsu *et al.*, 2012).

Several trials have investigated 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 (Khedr *et al.*, 2010; Hsu *et al.*, 2012). 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 (Chang *et al.*, 2010; Hsu *et al.*, 2012).

The Aim of this study is to prove and determine the effect of Transcranial Magnetic Stimulation (TMS) on upper extremity motoric function in subacute stroke ischemic patient. The hypothesis of this study is TMS may increase upper extremity motoric function in subacute stroke ischemic patient.

2 METHODS

This study is an experimental randomized clinical trial with two group design. Subjects were 18 subacute stroke ischemic patient who fulfilled inclusions criteria that come to Physical Medicine and Rehabilitation Outpatient Clinic Dr. Soetomo General Hospital. The inclusions criteria were subacute ischemic stroke, hemiparesis, willing to follow instructions, willing to participate in this study and signed an inform consent form. Exclusion criteria were instability condition, seizure history, brain injury history, pregnancy, aphasia, occipital lobe lesion, wrist or hand contracture, metallic medical equipment user. Drop out criteria were unwilling to participate in this study, instability condition while participating, headache along this study and increase with rTMS intervention, Wong Beker Pain Faces Scale > 4. Randomization was done to divide subjects into 2 groups. 9 subjects in control group did conventional therapy. 9 subjects in intervention group did conventional therapy + repetitive Transcranial Magnetic Stimulation. Conventional therapy for 5 days. Repetitive Transcranial Magnetic Stimulation for 5 days with Neuro-MS/D, 8-shape coil, 10Hz, 100% Motor threshold, 750 pulses per day, placed in primary motor cortex area (M_1).

Motoric function of upper extremity evaluated with Fugl-Meyer Assessment (FMA) before and after intervention had done (day-0 and day-5). The Data from control and intervention group will be evaluated intra-group and inter-group and analyze with SPSS version 20. Intra-group data will be analyzed with normality and homogeneity test. Intra-group data will be analyzed with normality and homogeneity test. If the data has normal distribution and homogenous, paired t test will be used, otherwise Wilcoxon Signed Rank Test. Inter-group data will be analyzed with normality and homogeneity test. If the data has normal distribution and homogenous, independent t test will be used, otherwise, Mann-Whitney test will be used. All participants signed an informed consent form approved by the Dr. Soetomo General Hospital human subjects' committee prior to participation in the study.

3 RESULTS

The eighteen subacute stroke ischemic patients fulfilled inclusions criteria were randomized and divided into control and intervention group. All subjects completed all sessions. Control and intervention groups' age and gender means in table 1. The FMA score before intervention between 2 groups showed in table 2. The analysis showed no difference at subjects' demographic data and FMA score before intervention. FMA score at control and intervention group increased after intervention and statistically significant intragroup. Intervention group FMA score more significantly increased compare to control group.

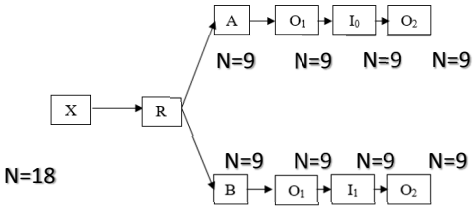

Figure 1: Study pathway. X: Subject; R: Randomization; A: Control Group; B: intervention Group; O1= First Fugl-Meyer Assessment; O2: Final Fugl-Meyer Assessment; I0: Conventional Therapy; I1: Conventional Therapy + repetitive Transcranial Magnetic Stimulation.

Table 1: Demographic Data.

	Group		N	Mean	SD	P score
Age	Intervention		9	55,556	± 9,098	0,824
	Control		9	54,889	±9,892	
Sex	Intervention	Male Female	6 3	6/3		0,257* / 0,576**
	Control	Male Female	8 1	8/1		
Manual Muscle Testing (Baseline)	Intervention		9	2,11	±1,269	0,748
	Control		9	2,00	±1,323	
Spasticity (Modified Ashworth Scale)	Intervention		9	1,33	±0,500	0,580
	Control		9	1,56	±0,726	

Sample size (N); standard deviation (SD)
* *Chi-Square test*
** *Fisher's Exact test*

Table 2: Fugl-Meyer Assessment score at control and intervention group before intervention.

Groups	N	Mean	SD	t	p
Intervention	9	40.333	±13.209	-1.969	0.067
Control	9	53.222	±14.532		

* Independent t-2 test; sampel size (N); Standar deviation (SD); p>0,05

Table 3:. Fugl-Meyer Assessment score at control group before and after intervention.

FMA Score	N	Mean	SD	t	p
Before	9	53.222	±14.532	3,223	0.012
After	9	57.444	±11.303		

* Independent t test; sampel size (N); Standar deviation (SD); p<0,05

Table 4: Fugl-Meyer Assessment score at intervention group before and after intervention.

FMA Score	N	Mean	SD	t	p
Before	9	40.333	±13.209	10,271	0.000
After	9	54.111	±13.336		

* Independent t test; sampel size (N); Standar deviation (SD); p<0,0001

Table 5: Increasing of Fugl-Meyer Assessment score at control and intervention group after intervention.

FMA Score	N	Mean	SD	t	p
Intervention	9	13.777	±4.024	5,096	0.000
Control	9	4.222	±3.929		

* Independent t test; sampel size (N); Standar deviation (SD); p<0,0001

4 DISCUSSIONS

There was no significantly difference Fugl-Meyer Assessment score before intervention in both group. This result may prevent ceiling effect bias. Not only Fugl-Meyer Assessment score at control group after intervention increased but also at intervention group.

Fugl-Meyer Assessment score increase in control group in line with other study that stated exercise may enhance neuroplasticity. Physical training (conventional therapy) upregulate the expression of neurotrophic factors. It may improve neural proliferation and survival and synaptic and axonal plasticity by enhancing synapse formation, dendritic growth, and remodeling. Numerous recent studies indicated that early training promotes neuroplasticity by acting on brain vasomotor activity and angiogenesis, neurotrophic factor and apoptosis marker expressions, brain inflammatory processes, blood brain barrier (BBB) integrity, and muscle activation control (Ploughman *et al.*, 2009; Zhang *et al.*, 2013; Pin-Barre *et al.* Rajan *et al*., 2017).

Fugl-Meyer Assessment score at Intervention group had more increase compare to control group significantly. This study result was in line with the other studies before. The meta-analysis study from Hsu *et al.,* suggests a clinically positive effect of rTMS on motor recovery in the affected upper limb of patients with stroke (Hsu *et al.*, 2012).

Transcranial Magnetic Stimulation may be capable of producing lasting changes in clinical outcome after stroke. the combination of TMS with conventional therapy leads to improved re-learning of movement that produces lasting changes in the organization of cortical motor output (Khedr *et al.*, 2009; Khedr *et al.*, 2010).

Study from Rajan *et al.,* showed that 5-day rTMS enhances brain-derived neurotrophic factor (BDNF) binding affinity for TrkB, BDNFTrkB signaling, and NMDA receptor–TrkB interaction[14]. BDNF is one of Neurotrophin that play a significant role in the proliferation, migration, and phenotypic differentiation of cells (neurogenesis) and ensure their functional and structural integrity (Lasek-Bal *et* al., 20015; Rajan *et al*., 2017).

Repetitive Transcranial Magnetic Stimulation is safe. There was no side effect in this study. Lopez-Ibor study on 2008 stated that only 4.5 % felt mild and limited to transient scalp discomfort or pain. There have been no deaths or epileptic seizures reported in more than 10.000 treatment sessions in published studies. The side effects are minimal and well tolerated. There are no verified auditory or cognitive deficits after rTMS (Lopez-Ibor *et al.,* 2008).

The limitations of these study are small number of subjects and no blinded.

5 CONCLUSIONS

This study showed that combination of conventional therapy and repetitive Transcranial Magnetic Stimulation in 5 consecutive days improve upper extremity motoric function significantly compare to conventional therapy alone in subacute stroke ischemic patient.

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