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Effect of Transcranial Magnetic Stimulation with Rehabilitation Program on Motor Function and ADL in Upper Extremity Ischemic Stroke: A Randomized Controlled Trials

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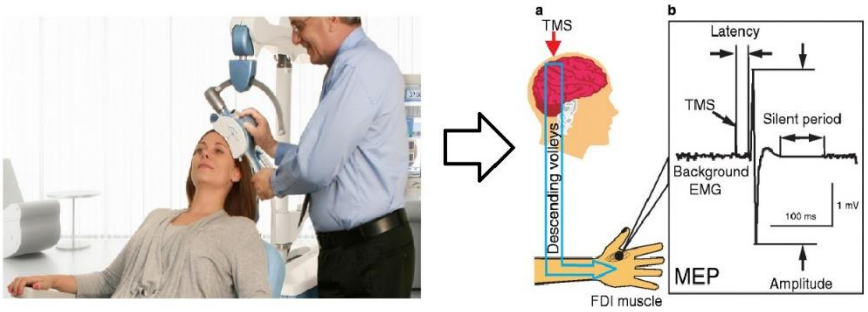
ABSTRACT

Ischemic stroke becomes the reason why some neural networks as well as cortico-subcortical excitability change either in the evidently spared contralateral hemisphere of the upper extremity or in the affected area. The processes are modulated through recent non-invasive brain stimulation techniques. In particular, a rehabilitation program and non-invasive instrument called transcranial magnetic stimulation (TMS) has already been implemented to examine the changes in brain plasticity caused by stroke and used as a therapeutic modality to securely increase the function of motor and activities of daily living (ADL). This study investigated the effect of low-frequency TMS with rehabilitation programs in post-ischemic stroke patients to improve the upper extremity's motor function. Randomized controlled trial was conducted in this study by dividing 11 patients into two groups which fulfilled the present inclusion criteria. Wolf Motor Function Test (WMFT) and Upper Extremity Fugl Meyer Assessment (UEFMA) were used to ADL of day 7 and to measure the levels of motor function, respectively. The study results showed a considerable difference in TMS with the rehabilitation program which was achieved on day seven on both groups. The total score of UEFMA and WMFT considerably increased from the condition before intervention (UEFMA intervention-control: 19.83-6.00; WMFT intervention-control: 20.67–4.00, $p < 0.001$). Therefore, low-frequency TMS with a rehabilitation program is recommended since it shows a considerable increase in the motor function of the upper extremity and ADL among the patients with post-ischemic stroke.

GRAPHICAL ABSTRACT

Effect of Transcranial Magnetic Stimulation with Rehabilitation Program

on Motor Function and ADC In Upper Extremity Ischemic Stroke



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Introduction

A stroke is a clinical disorder in which cell death is caused by insufficient blood supply to the brain. There are two key forms of stroke: Ischemic stroke due to loss of blood supply and haemorrhagic stroke due to bleeding. They both trigger parts of the brain to stop functioning properly. Signs and signs of a stroke can include failing to lift or feel on one side of the body, comprehension or speech disturbances, dizziness, or lack of vision on one side. The prevalence of stroke is around the world, and this disease makes the survivors need or highly rely on the help of motor function due to upper extremity dysfunction [1–3]. To resolve this situation, it needs to increase motor function and activities of daily living (ADL) to patients with post-ischemic stroke [4].

Previous research by Smith et al. [5] shows that TMS and rehabilitation programs have increased the recovery of motor function and activities of daily living (ADL) of patients with post-stroke. The motor function and ADL could be measured using the Upper Extremity Fugl Meyer Assessment test (UEFMA) and Wolf Motor Function Test (WMFT) [6]. Furthermore, both tests have been considered a good instrument for measuring ADL upper extremity and motor function in patients with post-ischemic stroke [7]. Clinical study has shown that intensive motor training combined with low-frequency TMS has been introduced to increase the motor impairment and function of patients suffering from mild to moderate stroke [8].

The aim of this study was to examine how low-frequency TMS and rehabilitation program to the patients with post-ischemic stroke would help to increase the motor function of upper extremity.

Background

It is estimated that 95% of stroke survivors experience dysfunction of upper extremity [9]. In addition, about 80% of them cannot recover the full function of their hands and arms [10]. In this case, stroke commonly causes disruption in the cortical excitability equilibrium between the two hemispheres. The homonymous motor representation and cortical excitability increase in the affected hemisphere and decrease in the unaffected hemisphere [11].

The increasing dysfunction may affect ADL and patient's quality of life [12]. Many studies show that intensive motor training with low-frequency TMS is able to increase motor function and daily activity on the upper extremity in patients with post-ischemic stroke [13].

Association between TMS combined Rehabilitation Program and Motor Function with ADL

TMS can be defined as a non-invasive, painless treatment and to change the excitability of cerebral cortex impact changes in synaptic plasticity, which finally boost the neurological function recovery [14]. A rehabilitation program is a clinical therapeutic and grounded movement of control strategy by implementing the principles of motor control, motor learning, and neuroplasticity [15].

Motor function mainly deals with active movement training such as controlling convulsions, improving muscle strength, and adjusting the patterns of movement [16]. Meanwhile, the upper extremity function mainly deals with ADL performance and social participation. It is feasible to have independent ADL in stroke patients [17]. Current evidence confirms that rehabilitation program and low-frequency TMS are able to lower the corticospinal excitability in the non-lesioned hemisphere [18]. And when stroke is related to the increase of certain proteins at the molecular level that plays a role in neuroplasticity, i.e. decreased caspase3, increased expression of Bcl-2, Mid Kine (MK), Brain-derived Neurotropic Factor (BDNF), anti-platelet endothelial cell (PECAM-1) will inhibit the apoptosis of nerve cells and increase the strength of synaptic nerve transmission [19].

Furthermore, some studies have supported that low-frequency TMS shows capability to increase ADL and motor function in the affected arms [20]. Finally, TMS combined with rehabilitation programs has been reported as most effective application in upper extremity post-ischemic stroke patients [21].

Material and methods

This study is a feasibility study of an observer-blinded stratified block-randomized controlled trial with TMS and rehabilitation program (intervention group) versus TMS (control group) for motor function upper extremity post-ischemic stroke. 11 patients were recruited based on an inclusion criterion, admitted from Pura Raharja hospital and had signed informed consent by the requirements of the local ethics committee in Indonesia. The study was conducted from October until December 2020.

A convenience sampling method was used in this study to randomly divide the participants into two groups, control, and experimental groups. The treatment group was six subjects who received TMS and rehabilitation program. The rehabilitation program control group was five subjects who received TMS after diagnosis of upper extremity dysfunction of post-ischemic stroke.

The group receiving upper extremity motor dysfunction experimental using the validated TMS and rehabilitation program and rehabilitation program and the group receiving upper extremity motor dysfunction control underwent TMS routine hospital procedures (Table 1).

Table 1: TMS an application for groups

Provisions	Provisions Treatment group	Provisions Control group
Time	20 minutes TMS and 60 minutes rehabilitation program.	20 minutes
Focus of treatment	Motor stimulation in cortex area, recovery of neurological function, and improvement of the phrase upper extremity motor function.	-
Day 1 until 7	TMS activities combined with the rehabilitation program selected by the patients are grasping a glass with/out a handle, manipulating a cart, manipulating a pen while writing and drawing, manipulating a spoon and hand while eating, handling oranges and handyman activities.	TMS

Mann-Whitney Test was conducted to statistically compare the differences in motor function between control and experimental groups. In this case, statistical significance was set at 5%. For statistical analysis, SPSS software v. 23 was chosen by the authors. Figure 1 below shows 11 participants, where 6 of them were put in the experimental group, and the rest were in the control group, while the treatment was completed on 7th day.

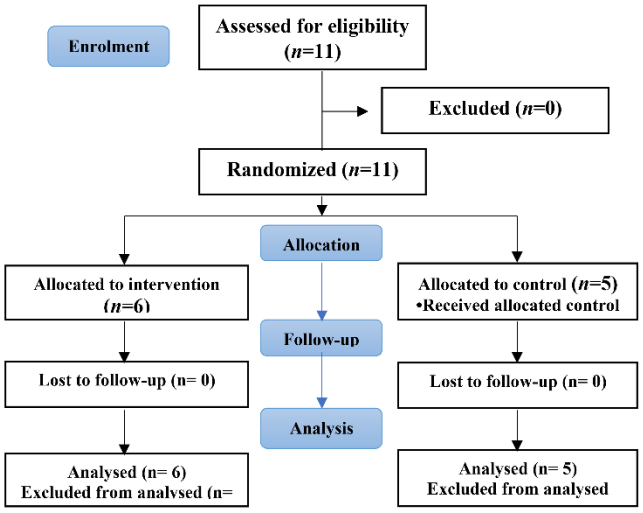

Figure 1: Participant Flow Chart

Eligibility criteria

Patients diagnosed as ischemic stroke with decreased motor function and ADL have mild to moderate impairment of an upper extremity referring to the UEFMA and WMFT, have normal/corrected hearing and vision, can follow easy commands set in the Mini-Mental State Examination.

Exclusion criteria

Patients without aphasia and stroke patients without all complications were excluded from the study.

TMS

The low-frequency TMS was applied over M1 at the non-lesioned hemisphere, especially in the extensor digitorum muscle (1 Hz, 90% [rMT], 1,200 pulses). The stimulation was distributed through the figure-eight air-cooled coil with a Magstim Rapid 2 stimulator at the motor cortex.

Rehabilitation Program

For ASAP process, specific training was adapted with modification from the basic procedures. This process includes priority task selection, task collaboration, task analysis, and self-efficacy evaluation to improve motor function and ADL in the upper extremity.

Research instruments

Cognitive functions (MMSE)

All participants took a pre-test measurement once they were recruited. MMSE measurements were conducted before treatment on the 1st day. The inter-rater reliability of the MMSE was 0.83 [22].

Upper Extremity Fugl Meyer Assessment

UEFMA was used to measure motor function in which UEFMA had a maximum score of 66 [23]. The motor functional of UEFMA evaluates aspects of movement, coordination, and speed [24]. The participants in the control and experimental groups took pre-test and post-test of the treatment on 7th day. The inter-rater and intra-rater reliability was 0.97 [25].

Wolf Motor Function Test

WMFT was conducted pre-test and post-test on the 7th day to improve the activity daily living on motor function upper extremity between two groups. Inter-rater reliability was high, between 97 to 99 [26].

Result and Dissection

Of the 11 patients with upper extremity, post-ischemic stroke consisting of 6 patients receiving TMS with the rehabilitation program and another 5 patients receiving TMS, were included in the study. There were no differences between the ages and sex in the control and experimental groups (Table 2).

Table 2: Demographic characteristic of the patients

The characteristic	Experimental group		Control group		p-value
	N = 6	%	N = 5	%	
Age					
< 60 years	4	66.7%	1	20%	0.705
> 60 years	2	42.3%	4	80%	
Mean (minimum: maximum)	56.00 (47-64)		65.00 (58-70)		
Median	55.50		65.00		
Sex					
Male	4	66.7%	3	60%	0.354
Female	2	42.3%	2	40%	
Location of lesion					
Right	6	100%	2	40%	1.000
Left	-	-	3	60%	

Demographic characteristics of the patients are presented in Table 2. Most upper extremity post-ischemic stroke patients were at the ages of more than 60 years and predominantly male gender. Patients receiving TMS and rehabilitation programs mostly had a left lesion, while the patients receiving TMS mostly had a right-side lesion, i.e., the control group.

The present study on demographic characteristics showed a significant difference between the two groups, the effects of a single session of low-frequency TMS combined with rehabilitation program on motor dysfunction upper extremity on post-ischemic stroke the mean age of subjects was 60,09 years, over 63% were male, and 72,73% had right lesions. Demographic characteristics showed that all characteristics, including the sex and location of the lesion, had significant differences.

The use of low-frequency TMS in post-stroke refers to the interhemispheric inhibition model. In this case, to suppress stroke, it needs to increase transcallosal inhibition from the contralesional M1 to the ipsilesional M1 [27], while rehabilitation program is conducted to improve in functional reorganization and neuroplasticity [28], due to synaptic circuits can be changed by synaptic transmission through synaptic change proteins [29]. It can be seen that TrkB pathway activation can improve cognition and has a correlation with synaptic density increase [30]. Where neuronal plasticity occurs, BDNF and TrkB are upregulated. Therefore, it can be said that BDNF is a molecular mediator of synaptic plasticity function and structure, and it plays an important role in memory consolidation and memory formation [31].

Some rehabilitation programs which are combined can improve the motor function better, i.e. raise of hand, grip, grasp, and pinch, and ADL on task-specific, i.e. hand to box, extend elbow weight, turn the key in the lock, lift paper clip, and lift basket, in stroke patients [32]. Therefore, we examined if the combination of 1 Hz TMS is able to affect the upper extremity in patients with post-ischemic stroke [33]. It is suggested that intensive motor training combined with TMS is able to improve the WMFT log performance time from 3.23 (1.70–4.07) to 2.51 (1.36–3.86) and the total score of UEFMA from 48 (34–58) to 51 (38–57) in patients with mild to moderate stroke [13]. The motor function showed significant differences between TMS with the rehabilitation program and TMS on the 7th day of upper extremity post-ischemic stroke (Table 3).

Table 3: The Paired t-test analysis between pre-test and post-test motor function and ADL of upper extremity post-ischemic stroke after TMS.

	UEFMA			WMFT			p- value
	Median	Mean	SD	Median	Mean	SD	
Treatment group							
Pre-test	31.50	31.50	2.881	20.50	20.83	2.317	0.001
Post-test	51.50	51.33	31.41	42.50	41.50	8.313	0.001
Control group							
Pre-test	31.00	29.00	4.301	17.00	18.00	3.391	0.001
Post-test	36.00	35.00	5.099	21.00	22.00	2.000	0.001
Paired t-test $p < 0.05$							

Table 3 indicates that both groups' motor function had significant difference ($p < 0.05$) on 7th day. On average the increase motor function, i.e. raise of hand, grip, grasp and pinch, in the values of pre- and post-on the treatment group were p (95% CI [31.50-51.33], p = 0.001), pre- and post-on the control group were p (95% CI [29.00-35.00], p = 0.001), respectively; the difference in the value of motor function on treatment and control group was p (95% CI [19.83-6.00], p = 0.001). The ADL in both groups showed a significant difference ($p < 0.05$) on day 7. On average, the increase ADL, i.e. hand to box, extend elbow weight, turn the key in

lock, lift paper clip, and lift basket, in the values of pre- and post-on the treatment group were (95% CI [20.83-41.50], p = 0.001), pre- and post-on the control group were (95% CI [18.00-22.00], p = 0.001), respectively; the difference in the value of ADL on treatment and control group was (95% CI [20.67-4.00], p = 0.001).

TMS is able to standardize the size of transcallosal inhibition and affect the information interaction of functional brain regions [32]. The left hemisphere mainly deals with the preparation of movement from almost "routine" activities, such as actions to reach something [34]. On the other hand, the right hemisphere functions to identify and respond to unforeseen environmental stimuli [35]. Few studies have revealed combined application of low TMS and rehabilitation program considerably improved motor function of the affected upper extremity in the patients with post-ischemic stroke, and the beneficial effects [36], and indicated that low-frequency TMS over the intact hemisphere was effective to be applied for chronic stroke [37-42].

Conclusion

TMS combined with rehabilitation programs significantly affects functional connectivity [38], neural improvement and allows for the plasticity of neurons and motor circuits system because of a series of motion skills using neuro rehabilitation program. Previous studies have mostly examined chronic stage stroke and applied TMS based on the low-frequency TMS model developed specifically in chronic stroke patients. The method of TMS with rehabilitation program already changed their combined working ability of multiple brain regions, such as decreasing connectivity between the primary motor and premotor areas, increasing inhibition on the affected hemisphere, and functional connectivity of these abnormalities have substantial correlation with the degree of motor function decline and provide functional change of ADL.

Although TMS research has shown modest results, with the small sample sizes, it is difficult to generalize the results of the study and the characteristics of the patients, especially sex of improving motor function and ADL for seven days. Low-frequency TMS combined with a rehabilitation program is advised because of a significant improvement in upper extremity motor function and ADL in the patients with post-ischemic stroke.

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Authors' contributions

All authors contributed toward data analysis, drafting and revising the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

We have no conflicts of interest to disclose.

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