Jurnal RSMH Palembang
Journal Homepage: http://jurnalrsmh.com/index.php/JRP

The Effectivity of Repetitive Transcranial Magnetic Stimulation on Motor Function of Acute Ischemic Stroke Patients in Dr. Mohammad Hoesin General Hospital Palembang

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ARTICLE INFO

Keywords:
Acute ischemic stroke
Motor function
Repetitive transcranial magnetic stimulation

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All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/JRP.v4i1.44

ABSTRACT

Background: More than 60% of stroke patients suffered from long-term disability due to motor impairment despite underwent intensive rehabilitative therapies. Non-invasive brain stimulation such as repetitive Transcranial Magnetic Stimulation (rTMS) has been reported in improving motor function after stroke through the mechanism of neuroplasticity. Research related to the use of rTMS as adjunctive therapy in ischemic stroke cases has mostly been carried out in chronic stroke patients and until now only a few studies have assessed the effectivity of rTMS in patients with acute stroke. Therefore, this study aims to assess whether rTMS can improve motor function in patients with acute ischemic stroke. **Methods:** This research was a randomized controlled trial and carried out acute ischemic stroke patients in Dr. Mohammad Hoesin Hospital Palembang. A total of 22 patients were randomly divided into a control group with standard therapy (11 subjects) and a treatment group with standard therapy and 5 sessions of rTMS (11 subjects). Improvement of motor function was assessed with motor strength using the Medical Research Council (MRC) scale performed before and after the intervention on the four limb segments. Bivariate analysis with Paired T-Test was used to compare the strength before and after the intervention in each group and the Mann Whitney Test used to compare the differences of motor strength between groups. **Results:** All subjects in both groups completed the study and no adverse effects were found in the rTMS group. The MRC scale after the intervention increased in all segments in both groups, but significant differences were only found in the treatment group (hand grip (p=0.011), shoulder abduction (p=0.001), hip flexion (p=0.001), and toe dorsiflexion (p =0.002)). Comparison of differences in motor strength between the two groups using the Mann Whitney Test revealed that the improvement was more significant in the rTMS group compared to the control group (p=0.024, p=0.031, p=0.016, and p=0.021). The motor strength in the rTMS group start to increase on the second and third day and particularly reached the peak on the fourth day after the procedure. Multivariate analysis showed no effect of confounding factors such as age, sex, BMI, comorbidities, onset, lesion location, NIHSS, and mRS inthe improvement of motor strength. **Conclusion:** rTMS therapy can improve motor function in acute ischemic stroke patients and can be considered as an adjuvant therapy in assisting the recovery of post-stroke motor impairment.

1. Introduction

Motor impairment is the leading cause of long-term disability due to stroke worldwide.[1] Even after extensive rehabilitation, more than 60% of stroke patients continue to experience motor impairment.[2] Cortical reorganization induced by neuroplasticity is an important part of motor recovery after stroke.[3] It has been reported that noninvasive brain stimulation, such as repetitive transcranial magnetic stimulation (rTMS), can promote brain plasticity by modifying cortical excitability.[4]

The potential therapeutic value and mechanism underlying the action of cortical stimulation depend on the time between stroke onset and treatment application including the acute, subacute, and chronic phases. Commonly, the acute phase of stroke is defined as the first one to three weeks following the onset of stroke which corresponds to an acute hospital setting though others mention up to 2 weeks from stroke onset. The subacute phase is defined as the period of time immediately after discharge from the acute care unit until the chronic phase, usually 6 months after stroke onset.[5,6,7]

In the acute phase, there is loss of function in the stroke-lesioned region and connected areas, altering modulation control, mainly through transcalosal projections to homologous contralesional hemispheric regions.[8,9] Studies in animal and human models showed that the early post-stroke phase is critical for enhancing neuroplasticity.[10,11] Even though functional recovery is not stable until several months after stroke, early intervention may increase the potential benefit.[5] However, evidence supporting the early use of plasticity-induced interventions for stroke rehabilitation is still limited.[12]

Study related to the use of rTMS as adjunctive therapy in ischemic stroke cases has mostly been carried out in chronic stroke patients and until now only a few studies have assessed the effectiveness of rTMS in patients with acute stroke. Therefore, this study aims to assess whether rTMS can improve motor function in patients with acute ischemic stroke.

2. Methods

Twenty-two patients with acute ischaemic stroke participated in this study. The patients were recruited from the Department of Neurology, Dr. Mohammad Hoesin General Hospital, Palembang from 1-30 November 2022. The inclusion criteria were as follows: 1) age more than 18 years; 2) onset of stroke up to 2 weeks; 3) hemiparesis symptom. The exclusion criteria were as follows: 1) recurrent ischemic stroke; 2) usage of intracranial metallic implants, cardiac pacemaker, or cochlear implant; 3) uncontrolled seizures; 4) disturbance of consciousness or severe systemic disease; 4) aphasia; 5) patients undergoing thrombolytic therapy and/or mechanical thrombectomy. The drop out criteria were as follows: 1) development of serious adverse effects of rTMS such as seizure, syncope, etc.; 2) unwillingness to complete the study; 3) died before completing the study.

All patients gave their written informed consent before participating in this study. This study was approved by Health Research Review Committee of Mohammad Hoesin General Hospital (No. 175/kepkrsmh/2022).

The patients were randomly allocated into two groups. The control group received standard therapy for the management of acute ischemic stroke including medical and physical therapies while the treatment group received standard therapy and 5 session rTMS.

The rTMS procedure was performed using Neurosoft MS-D TMS machine with a figure-of-8 coil and was carried out in 5 sessions for 5 consecutive days during initial hospital admission. Each session lasted for approximately 15 minutes. The resting motor threshold (RMT) was determined as minimum output of the stimulation that evoked target movement of the finger. The excitation was performed on the ipsilesional hemisphere using high frequency-rTMS (10 Hz) and followed by inhibition on contralesional hemisphere using low frequency-rTMS (1 Hz).

Motor strengths of the affected limb in four segments including shoulder abduction, hand grip, hip flexion, and toe dorsiflexion using Medical Research Council (MRC) scale were evaluated before and after 5 days treatment protocol. We also assessed daily motor strength as additional data.

The data analysis was using the SPSS for Windows version 22.0 software package. The changes in motor strength of four limb segments in each group were compared before and after 5 days of treatment using Paired T-test. Then the differences of MRC scale were compared between the two groups using the Whitney Test. Multivariate analysis was used to determine the effect of confounding factors on the changes in motor strength using linear regression analysis. The level of significance is set at p <0.05.

3. Results

All patients completed the study protocol and no adverse effects were found in rTMS group. Baseline characteristics and clinical demographic profiles of the patients are shown in Table 1. There were no significant differences between the two groups (p>0.05). Baseline motor strength assessed using the MRC scale showed no significant difference between the two groups.

Table 1. Baseline characteristics and clinical demographic profiles of the study participants.

Variable	Group		*P*
	rTMS n (%)	Control n (%)	
Age			
<45 years old	1 (9.1)	2 (18.2)	1.000[a]
>45 years old	10 (90.9)	9 (81.8)	
Gender			
Male	7 (63.6)	6 (54.5)	1.000[a]
Female	4 (36.4)	5 (45.4)	
Body mass index			
< 18.5	0	0	1.000[b]
18,5 – 25,0	6 (54.5)	5 (45.4)	
>25,0	5 (45.4)	6 (54.5)	
Hypertension			
Yes	9 (81.8)	8 (72.7)	1.000[a]
No	2 (18.2)	3 (27.3)	
Diabetes mellitus			
Yes	5 (45.4)	6 (54.5)	0.670[c]
No	6 (54.5)	5 (45.4)	
Dyslipidemia			
Yes	4 (36.4)	6 (54.5)	0.392[c]
No	7 (63.6)	5 (45.4)	
Heart disease			
Yes	3 (27.3)	4 (36.4)	1.000[a]
No	8 (72.7)	7 (63.6)	
Onset			
<3 days	2 (18.2)	1 (9.1)	
3-7 days	8 (72.7)	9 (81.8)	1.000[b]
7-14 days	1 (9.1)	1 (9.1)	
Lession location			
Cortex	5 (45.4)	3 (27.3)	
Subcortex	4 (36.4)	6 (54.5)	0.993[b]
Both	2 (18.2)	2 (18.2)	
NIHSS			
Mild (≤5)	3 (27.2)	1 (9.0)	0.993[b]
Moderate (6-14)	4 (36.4)	5 (45.5)	
Severe (≥15)	4 (36.4)	5 (45.5)	
mRS			
Mild (0-2)	3 (27.2)	1 (9.0)	
Moderate (3-4)	4 (36.4)	5 (45.5)	1.000[b]
Severe (5-6)	4 (36.4)	5 (45.5)	
MRC (baseline)			
Hand grip	2.09 ± 1.45	1.73 ± 1.49	0.568[d]
Shoulder abduction	2.09 ± 1.45	2.00 ± 1.55	0.888[d]
Hip flexion	2.09 ± 1.45	2.18 ± 1.40	0.882[d]
Toe dorsiflexion	2.09 ± 1.45	2.18 ± 1.40	0.882[d]

[a]Fisher test
[b]Kolmogorov-Smirnov test
[c]Chi-square test
[d]Independent T-test

The motor strength increased in all segments (handgrip, shoulder abduction, hip flexion, and toe dorsiflexion) in both groups, but after comparing the mean value before and after the intervention in each group using paired T-test, significant differences were only found in rTMS group (hand grip (p=0.011), shoulder abduction (p=0.001), hip flexion (p=0.001), and toe dorsiflexion (p=0.002)). Figure 1 shows the improvement of motor strength from the first to the fifth day of intervention in both groups. In rTMS group, the motor strength started to increase on the second and third day and reached the peak on the fourth day.

Table 2. Comparison of the MRC scale before and after therapy in rTMS and control groups.

MRC scale	rTMS		*p*	Control		*p*
	Before	After		Before	After	
Handgrip	2.09 ± 1.45	2.73 ± 1.55	0.011*	1.73 ± 1.49	1.82 ± 1.47	0.341
Shoulder abduction	2.09 ± 1.45	2.91 ± 1.38	0.001*	2.00 ± 1.55	2.27 ± 1.56	0.082
Hip flexion	2.09 ± 1.45	3.18 ± 1.17	0.001*	2.18 ± 1.40	2.45 ± 1.44	0.082
Toe dorsiflexion	2.09 ± 1.45	3.09 ± 1.30	0.002*	2.18 ± 1.40	2.45 ± 1.44	0.082

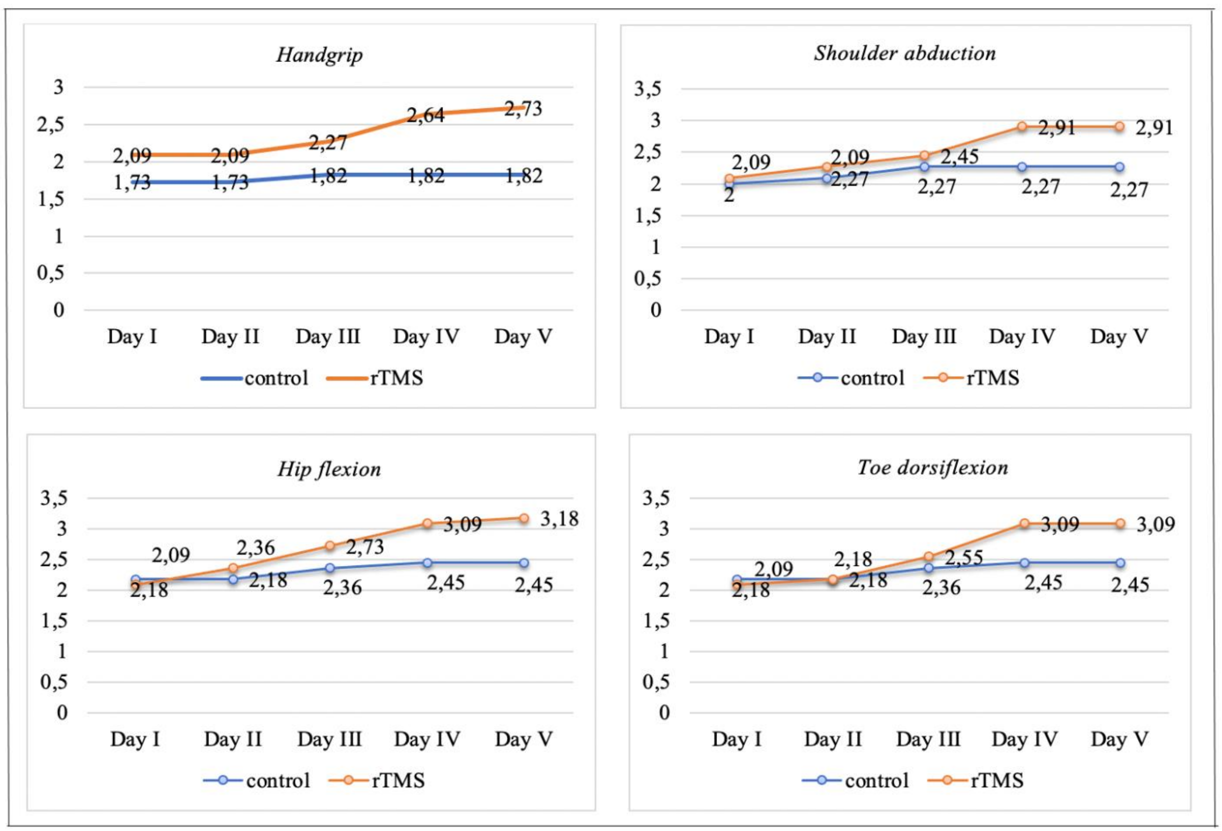

Figure 1. Changes in motor strength (MRC scale) in handgrip, shoulder abduction, hip flexion, and toe dorsiflexion from the first to the fifth day in the rTMS and control groups.

Comparison of the differences in motor strength in the two groups using the Mann Whitney Test showed that more significant improvements were found in the rTMS group compared to the control group in all segments (p=0.024, p=0.031, p=0.016, and p=0.021).

Multivariate analysis was performed to determine whether confounding factors such as age, sex, BMI, hypertension, diabetes, dyslipidemia, heart disease, onset, lesion location, NIHSS, and mRS influenced the changes in motor strength, but none of them had an effect on motor strength improvement (p>0.05).

Table 3. Comparison of the difference in the MRC scale between the two groups.

MRC scale	rTMS		Control		p
	Median (min-max)	Mean ± SD	Median (min-max)	Mean ± SD	
Handgrip	1 (0-2)	0.64 ± 0.67	0 (0-1)	0.09 ± 0.30	0.024*
Shoulder abduction	1 (0-2)	0.82 ± 0.60	0 (0-1)	0,27 ± 0.47	0.031*
Hip flexion	1 (0-2)	1,09 ± 0.83	0 (0-1)	0,27 ± 0.47	0.016*
Toe dorsiflexion	1 (0-2)	1,00 ± 0.77	0 (0-1)	0,27 ± 0.47	0.021*

*p<0,05.

4. Discussion

Our result showed that rTMS as an adjuvant therapy for acute ischaemic stroke patients can significantly improve motor function compared to standard therapy alone. There was an increase in motor strength in both rTMS and control groups, but only the rTMS group reported a statistically significant difference. This finding is consistent with the results of several studies demonstrating an improvement in motor strength in acute ischemic stroke patients after receiving rTMS therapy.[5,7,13]

The differences of the MRC scale between the two groups also revealed that the improvement of motor strength was more significant in rTMS group compared to the control group. This result is in concordance with studies reported by Kim et al. and Khedr et al. that there was a significant difference between the rTMS and control groups measured by percentage of improvement in motor strength.[7,14]

In the acute phase of stroke, various regeneration processes occur due to angiogenesis, resolution of edema, decreased GABA function and axonal sprouting to facilitate cortical plasticity.[15] After cortical ischemia, GAP-43 immunoreactivity in the surrounding intact cortex increased, indicating axonal sprouting. GAP-43 increased significantly in the first days following ischemia (up to day 14).[16] The early post-stroke phase is crucial for enhancing neuroplasticity.[10,11] The most significant improvements occur within the first weeks after stroke, often reaching a plateau after 3-6 months with less significant recovery subsequently, especially concerning motor symptoms.[17] Early intervention during this phase can yield clinical benefits, allowing patients to be discharged earlier.[5,18] rTMS applied to the motor cortex can modulate cortical activity in the early phase of stroke, thereby improving motor function in patients suffering from acute ischemic stroke.[5,7,18]

In this study, improvements in motor strength started on the second or third day of rTMS procedure and reached their peak on the fourth day. Several previous studies reported similar results. Baumer T et al. demonstrated that repeated TMS sessions induced cumulative plastic changes of intrinsic motor cortex excitability if applied within 24 hours but not more than 1 week. This indicates that memory formation persists after TMS therapy.[19] Fregni et al. also reported that repeated TMS sessions increased the magnitude and/or duration of excitability changes in motor cortex. The magnitude of the rTMS action increases as sessions are repeated every day.[20]Neuroplasticityfacilitates neurons in the brain to adapt their functions to new situations by adding or removing synapses. Repeated stimulation leads to additional synapses and increased activity, while stopping the stimulation has the opposite effect.[21]Pulse TMS is a stimulus that affects depolarization of inhibitory or excitatory axons resulting in changes in cortical plasticity. When repeated, TMS pulses can either increase or decrease cortical excitability.[22]

We used a coupling protocol (a combination of high and low frequency rTMS). The rTMS group was given high frequency (HF) rTMS on the ipsilesional hemisphere followed by low frequency (LF) rTMS on the contralesional hemisphere. This coupling method provided synergistic benefits on motor performance in acute and subacute hemiplegic patients.[23] Recent evidence suggests that motor recovery following a stroke involves a hierarchical and dynamic framework of interacting mechanisms. Usually, after the loss of interhemispheric inhibition from the ipsilesional motor cortex to the contralesional hemisphere, when a stroke occurs, there is a tendency for overactivity to begin in the contralesional hemisphere. If this continues, transcalosal imbalance might occur and inhibits cortical reorganization within the ipsilesional hemispheres. This is a predictor of poor recovery after stroke. Inhibitory rTMS in the contralesional motor cortex has the potential to improve maladaptive transcalosal pathways, while excitatory rTMS in the ipsilesional motor cortex aims to increase cortical excitability.[24] This is the reason why we performed bilateral HF and LF rTMS which seems to be more beneficial than unilateral rTMS.

This study has some limitations. First, the outcome was only evaluated by clinical assessment without any objective parameters such as MEP (motor evoked potential). Second, the short follow-up period in which the assessment was only carried out after 5 sessions of rTMS, no data on the long-term efficacy of rTMS. Third, coil placement was based on manual measurement, and the coil was held by the operator, allowing for inaccurate or unequal coil placement throughout the session. Moreover, patient movement may cause variability in coil position.

5. Conclusion

rTMS can improve motor function in acute ischemic stroke patients and can be considered as an adjuvant therapy in assisting the recovery of post-stroke motor impairment.

6. References

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