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Original Article

Effectivity of Repetitive Transcranial Magnetic Stimulation Improving Depressive Symptoms and Motoric Strength Ischemic Stroke

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ABSTRACT

Introduction: *Post-stroke depression often causes problems. Depression can slow motor recovery. Giving antidepressants takes one month, and thus Transcranial Magnetic Stimulation (TMS) was developed, especially repetitive Transcranial Magnetic Stimulation (rTMS). This study aims to assess the effectiveness of rTMS in improving depressive symptoms and motor strength in ischemic stroke patients.* ***Methods:*** *An experimental study with a randomized pretest-posttest control group design was conducted at Wahidin Sudirohusodo Hospital and a network hospital in Makassar from August to October 2022. The treatment group received standard therapy for ischemic stroke, antidepressants, and rTMS; the control group received standard therapy for ischemic stroke and antidepressants for ten days. In this study, the Hamilton Depression Rating Scale (HDRS) and the Medical Research Council (MRC) scale were used and measured in the treatment and control groups on the first and tenth days.*
Results: *A total of 40 subjects met the criteria and were divided into a treatment group (n = 20) and a control group (n = 20). The HDRS score in the treatment group was smaller than in the control group. The value of left*

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extremity motor strength in the treatment group was greater than that of the control group using the Wilcoxon Test. The correlation of the HDRS score to motor strength in the treatment and control groups showed a negative correlation of the HDRS score to the left extremity using the Spearman Test.

Conclusions: *rTMS effectively improves depressive symptoms and motor strength in ischemic stroke, given standard ischemic stroke therapy, antidepressants, and rTMS.*

1. INTRODUCTION

Stroke is a worldwide health problem and a major cause of disability, including in Indonesia [(1)]. Based on data from the Global Burden of Disease Study (GBD), Indonesia has the highest disability rates in Southeast Asia. In 2013, it was reported that 113 million people experienced post-stroke disability [(2)]. Persistent motor weakness is a common condition. According to data at the University of Cambridge, 80-90% of ischemic stroke patients have motor weakness. Hemiparesis with concurrent hand, leg, shoulder, and hip weakness is the most common motor deficit in at least two-thirds of cases [(3)].

Another problem often encountered is post-stroke depression (PSD), which is estimated to affect 50 percent of stroke patients who survive. The problem that arises with PSD is that it can slow down motor repair [(4)]. Depression after a stroke negatively affects the recovery of motor power, exacerbates cognitive deficits, and increases the risk of stroke recurrence and death [(5)].

According to Lawson Wulsin, depression has been shown to slow post-stroke recovery and have a negative impact on motor repair. Studies from Neural Regeneration Research have confirmed clinical findings regarding the comorbidity between depression and stroke, indicating that depression can worsen the clinical outcome of ischemic stroke. This study shows that of 37 stroke patients, the mortality rate of stroke patients with depression was 70% in the tenth year after the stroke [(6)]. According to data from the Stroke Center and the Department of Neurology at Ulsan University in Seoul, Korea, the prevalence of depression in stroke ranges from 5 – 67% [(7)].

Several therapies for stroke patients with depression can reduce its severity. Psychotherapy and pharmacotherapy are the treatment options for depression. The pharmacotherapy often used is Selective Serotonin Reuptake Inhibitors (SSRIs) [(8), (9)]. For antidepressant therapy, it takes at least one month to produce a clinically significant response, and then its efficacy is only 50%, with a small proportion of remissions (30%) [(10)].

In the last decade, electromagnetic therapy has been developed to treat Neurological and Psychiatric diseases, namely Transcranial Magnetic Stimulation. This therapy is effective in cases of depression and has been approved by the Food and Drug Administration (FDA) in the USA. This stimulation was performed on the Dorsolateral Prefrontal Cortex (DLPFC), effectively improving depressive symptoms in

ischemic stroke patients. Several studies of Transcranial Magnetic Stimulation have also shown it is effective for motor repair in ischemic stroke[11]. This study was a research continuation from a previous study in 2017 examining the effectiveness of rTMS in improving depression after ischemic stroke. The novelty of this study is that the researchers linked the correlation of improvement in depression scores to motor strength in ischemic stroke patients, which had not been studied in earlier studies.

For this reason, researchers intend to determine the effectiveness of repetitive Transcranial Magnetic Stimulation in improving depressive symptoms and motor strength in ischemic stroke patients.

2. METHODS

Study Design

The research design used was experimental with a randomized pretest-posttest control group design. The research was conducted at Dr. Wahidin Sudirohusodo Hospital and Network Hospital in Makassar from August 2022-October 2022. The study population was all ischemic stroke patients. The research sample is part of the study population that meets the inclusion criteria. The research sample was obtained by consecutive sampling. In this study, using an unpaired numerical formula, the number of samples required is 40, divided into a treatment group (n=20) and a control group (n=20).

Inclusion Criteria

The inclusion criteria included ischemic stroke patients with depressive symptoms, aged 30-70 years, onset two weeks to 3 months, conscious, and expressed no objection to being included in the study by signing a letter asking for consent by the patient/guardian of the patient.

Exclusion Criteria

Following are the exclusion criteria: using a pacemaker and ringing the brain, having a history of seizures, having a history of disease or abnormalities in the brain, pregnant or lactating women, having a history of aphasia and severe cognitive impairment, history of previous use of antidepressant drugs, history of using Deep brain Stimulation, Vagal Nerve Stimulation, Cholear Infant. For various reasons, the criteria for dropping out were not being able to complete the rTMS intervention ten times in a row.

Procedures of Experiment

On the first day, the researcher explained the research procedure and recorded the patient's identity, patient or family history, and physical examination. Suppose the patient meets the inclusion and exclusion criteria requirements and is willing to be included in the study. In that case, the patient or guardian is asked to sign a consent letter to participate. The family and the hospital witnessed the research procedure. Assessment and recording of the HDRS score with the HDRS form, which contains 20 questions consisting of depressed mood, feelings of guilt, suicide self, insomnia-initials, insomnia-middle, insomnia-delayed, interests and work, retardation, agitation, anxiety-

psychological, anxiety-somatic, somatic-symptoms gastrointestinal, somatic-general symptoms, genital symptoms, hypochondriasis deprivation, body weight, and approach/understanding.

HDRS score 0 until seven are not depressed. Score 8 until 13 is mild depression, score 14 until 18 is moderate depression, score 19 until 23 is major depression and score > 23 is very severe depression. Motor strength was measured quantitatively using a Medical Research Council (MRC) scale. Zero: no contractions; 1: minimal contractions but unable to move joints; 2: able to move but unable to fight gravity; 3: able to defy gravity but unable to fight resistance; 4 -: able against gravity and light resistance; 4+: able to resist gravity and against strong resistance; and 5: normal strength. HDRS values and motor strength were measured on the first day and the tenth day before and after in the treatment and control groups.

The treatment group received standard ischemic stroke therapy, antidepressants, and rTMS for ten days. Before receiving the intervention, the HDRS score and motor strength scores were measured on the first day and the tenth day after the intervention was given.

The treatment group underwent rTMS with the following procedure: The study subjects sat with both arms placed on the thighs with the arms facing up, placed a figure eight coil in a divergent position in the precentral area of the hand area, performed a single pulse TMS in that area on the lesioned hemisphere and non-lesion bilateral to measure resting motor threshold (RMT), rTMS was performed on the left dorsolateral prefrontal cortex or 8 cm anterior to M1 given high-frequency rTMS (10 trains of the sec 5 Hz-rTMS) for ten days, rTMS was performed on the right dorsolateral prefrontal right cortex, or 8 cm anterior to M1 were given low-frequency rTMS (10 trains of the sec 5 Hz-rTMS) for ten days, rTMS was performed for ten consecutive days after all intervention sessions were completed and then analyzed. The rTMS procedure uses the Stroke protocol with depression, which will impact improving the HDRS score. By decreasing the HDRS value, there is expected to be an improvement in motor strength.

The control group received standard ischemic stroke therapy and antidepressants for ten days. On the first day, the HDRS score and motor strength values were measured, and on the tenth day, after being given standard ischemic stroke therapy and antidepressants.

Data Analysis

The data research will be processed using the SPSS version 25 program. Based on the normality test of Shapiro-Wilk (the number of research subjects is less than 50), the p-value < 0.05, it can be concluded that the distribution of variable data is not normal. Therefore, the statistical test used is the Wilcoxon test and the Mann-Whitney. This study used Spearmen's correlation test to assess the correlation between two variables.

Research Ethics

The Ethics Committee for Health Research, Faculty of Medicine, Hasanuddin University approved the study protocol with letter number 495/UN4.6.4.5.31/PP36/2022

and protocol number UH22080465. Written consent was obtained from each subject before carrying out the study protocol.

Researchers collected 45 subjects who met the inclusion criteria, and five subjects dropped out, so the number of samples that met the requirements for analysis was 40 subjects, divided into two groups, namely the treatment group (20 subjects) and the control group (20 subjects).

3. RESULTS

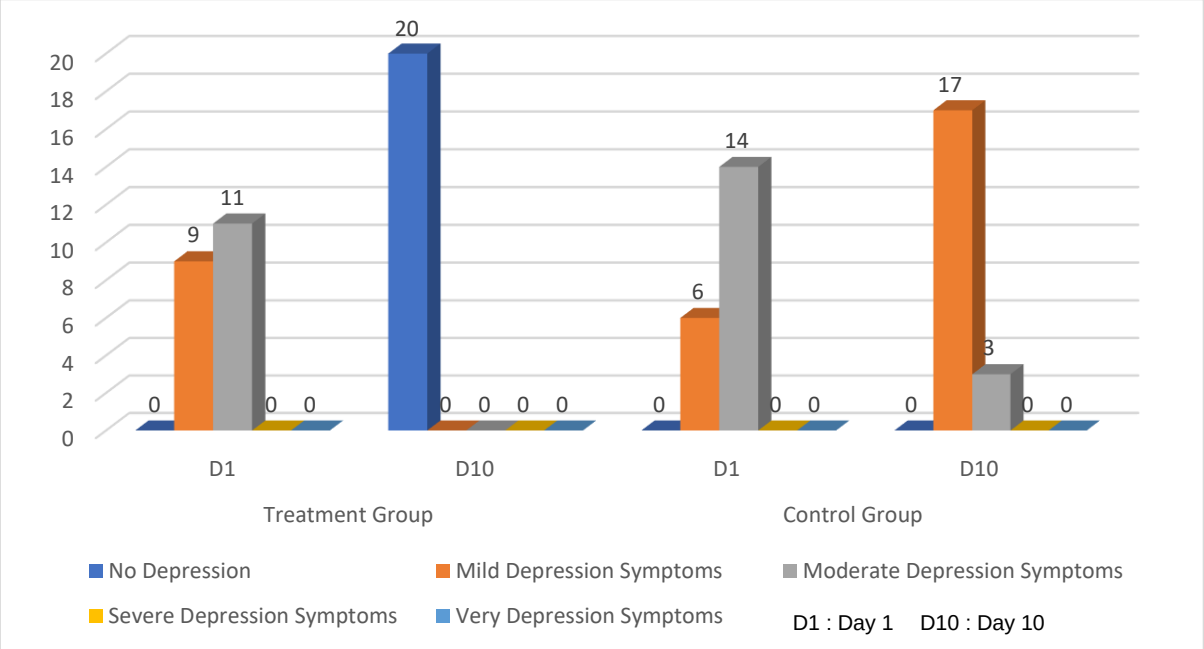
Researchers collected 45 subjects who met the inclusion criteria, and five subjects dropped out, so the number of samples that met the requirements for analysis was 40 subjects, divided into two groups, namely the treatment group (20 subjects) and the control group (20 subjects).

Table 1. Characteristics of Research Subjects

Variable		Group		p-value
		Treatment (n=20)	Control (n=20)	
Gender	Male	11 (55.0%)	11 (55.0%)	1.00
	Female	9 (45.0%)	9 (45.0%)	
Age (year)	30-40	2 (10.0%)	0 (0.0%)	0.088
	41-50	6 (30.0%)	3 (15.0%)	
	51-60	4 (20.0%)	11 (55.0%)	
	61-70	8 (40.0%)	6 (30.0%)	
Mean±SD		54.5 ± 11.49	58.15 ± 7.07	
Onset (month)	0.5	7 (35%)	3 (15%)	0.059
	1	11 (55%)	11 (55%)	
	2	2 (10%)	5 (25%)	
	3	0 (0 %)	1 (5%)	
Mean±SD		0.93 ± 0.44	1.28 ± 0.66	
Education	Elementary	4 (20%)	4 (20%)	0.321
	Senior High School	7 (35%)	11 (55%)	
	S1	8 (40%)	3 (15%)	
	S2	1 (5%)	2 (10%)	
Occupation	Housewife	3 (15%)	7 (35%)	0.035
	Retired	5 (25%)	0 (0%)	
	civil servant	1 (5%)	4 (20%)	
	Private	11 (55%)	9 (45%)	
Motor Power				
Hemiparesis	Right	11 (55%)	10 (52.5%)	1
	Left	9 (45%)	10 (50.0%)	

Source: Primary data, 2022

Table 1 shows the characteristics of research subjects based on gender and age. Overall, the subjects comprised 11 (55.0%) males and 9 (45.0%) females in the treatment and control groups. In the treatment group, most were aged 61-70 years old (40%), and in the control group, most were aged 51-60 years old (37.5%). The mean age in the treatment group was 54.5 ± 11.49 years, and the control group was 58.15 ± 7.07 years; the mean stroke onset in the treatment group was 0.93 ± 0.44 months, and the control group was 1.28 ± 0.66 months. In the treatment group, the highest number of subjects was undergraduate (40%), and the control group was high school (55%). In the treatment and control groups, most occupations were private. In the treatment group, the subjects who experienced the most right hemiparesis (55%) and the control group had the same ratio of right and left hemiparesis. Based on the normality test of Shapiro-Wilk (the number of research subjects is less than 50), the value of $p < 0.05$, it can be concluded that the distribution of variable data is not normal. Therefore, the statistical tests used are the Wilcoxon and Mann-Whitney tests.



Source: Primary data, 2022

Figure 1. Graph of the HDRS Score Based on the Degree of Depression Symptoms in the Treatment Group and Group Control

Data from **Figure 1** shows that in the treatment group, the most common on the first day was moderate depression, with an HDRS score of 17 in around 11 (55%) samples. On the tenth day, there was no depression, with an HDRS score of 3 in 20 (100%) samples. The control group showed that most on the first day were moderate depression, with an HDRS score of 17 around 14 (70%) samples. On the tenth day, most were mild depression with an HDRS score of 13 around 17 (85%) samples.

Table 2. HDRS Value in the Treatment Group and Control Group

HDRS value	Treatment Group			Control Group			p-value
	Median	Min	Max	Median	Min	Max	
D1	14.00	12.00	17.00	14.00	13.00	17.00	0.490*
D10	4.00	3.00	6.00	13.00	11.00	15.00	<0.001*
D1	14.00	12.00	17.00	14.00	13.00	17.00	<0.001**
D10	4.00	3.00	6.00	13.00	11.00	15.00	<0.001**

Source: Primary data, 2022 **Mann Whitney test* *** Wilcoxon test*

HDRS: *Hamilton Depression Rating Scale*
D1: Day 1
D10: Day 10

Table 2 shows the HDRS score in the treatment group before and after the intervention. The first day's HDRS score has a median value of 14.00 (min:12.00; max: 17.00). On the tenth day, the median value is 4.00 (min 3.00; max 6.00) with the Mann Whitney est. Statistical tests using the Mann-Whitney and Wilcoxon tests showed a significant value on the tenth day with a value of $p < 0.0001$. There is a control group of the first-day and tenth-day HDRS scores. The first day's HDRS score has a median value of 14.00 (min:13.00; max: 17.00). On the tenth day, the median value is 13.00 (min:11.00; max:15.00) with the Wilcoxon test. Statistical tests using the Mann-Whitney and Wilcoxon tests showed a significant value on the tenth day with a value of $p < 0.0001$.

Table 3. Motor Strength Values
Treatment Group and Control Group

Group		Motor Power						p-value
		H1			H10			
		Median	**Min**	**Max**	**Median**	**Min**	**Max**	
Treatment	**RUE**	3.50	0.00	5.00	4.50	3.00	5.00	**0.003***
	RLE	3.50	1.00	5.00	5.00	4.00	5.00	**0.003***
	LUE	5.00	0.00	5.00	5.00	2.00	5.00	**0.006***
	LLE	5.00	1.00	5.00	5.00	2.00	5.00	**0.004***
Control	**RUE**	4.00	0.00	5.00	4.00	1.00	5.00	0.083*
	RLE	4.00	0.00	5.00	4.50	1.00	5.00	0.083*
	LUE	5.00	0.00	5.00	5.00	0.00	5.00	1,000*
	LLE	5.00	0.00	5.00	5.00	0.00	5.00	0.317*

Primary data source, 2022 ** Wilcoxon test*

HDRS: *Hamilton Depression Rating Scale*
D1: Day 1
D10: Day 10
RUE: Right Upper extremity
RLE: Right Lower extremity
LUE: Left Upper extremity
LLE: Left Lower extremity

Table 3 shows the value of motor strength in the treatment group before and after the intervention. The treatment group had significant Wilcoxon test scores in the

right and left extremities (upper and lower) compared to the control group. The significant p-value in the right upper extremity is 0.003, the right lower extremity is 0.003, the left upper extremity is 0.006, and the lower left extremity is 0.004. The median value in the first-day treatment group for the right upper extremity was 3.50, on the tenth day 4.50; the lower right extremity first day 3.50, and on the tenth day 5.00; the upper left extremity first day 5.00, tenth day 5.00; lower left extremity first day 5.00, tenth day 5.00.

In the control group, the right and left extremities (upper and lower) of the control group had Wilcoxon test values that were not significant. The left and right extremities had Wilcoxon test values that were not significant (upper and lower extremities p=0.083; left upper extremity p=1.000; left lower extremity p=0.317). The median value in the control group on the first day for the right upper extremity was 4.00 (min: 0.00; max: 5.00), and on the tenth day was 4.00 (min: 1.00; max: 5.00), the right lower extremity first day 4.00 (min: 0.00; max: 5.00), the tenth day 4.50 (min: 1.00; max: 5.00); the left upper extremity first day 5.00 (min: 0.00; max: 5.00), the tenth day was on 5.00 (min: 0.00; max: 5.00), left lower extremity first day 5.00 (min: 0.00; max: 5.00), tenth day 5.00 (min: 0.00; max: 5.00).

Table 4. Comparison of Change (∆) Treatment Group and Control Group

Indicator	Treatment Group			Control Group			p-value
	Median	Min	Max	Median	Min	Max	
HDRS	-10.00	-13.00	-8.00	-1.50	-2.00	-1.00	**0.000***
Right Upper Extremity Motor Strength	1.00	0.00	4.00	0.00	0.00	1.00	**0.004***
Right Lower Extremity Motor Strength	1.00	0.00	3.00	0.00	0.00	1.00	**0.003***
Left Upper Extremity Motor Strength	0.00	0.00	3.00	0.00	0.00	0.00	**0.001***
Left Lower Extremity Motor Strength	0.00	0.00	2.00	0.00	0.00	1.00	**0.004***

Primary Data Source, 2022

HDRS: *Hamilton Depression Rating Scale*

Table 4 data compares changes (∆) in the treatment and control groups. The median HDRS value in the treatment group is -10.00 (min:-13.00; max:-8.00), and in the control group, -1.50 (min: -2.00; max: -1.00). The median value of motor strength in the treatment group was the right upper extremity 1.00 (min:0.00; max:4.00), the right lower extremity 1.00 (min:0.00; max:4.00), the left upper extremity 0.00 (min:0.00; max:3.00), and the left lower extremity 0.00 (min:0.00; max:2.00).

The median value of motor strength in the control group was the right upper extremity 0.00 (min:0.00; max:1.00), the right lower extremity 0.00 (min:0.00; max:1.00), the left upper extremity 0.00 (min:0.00; max:0.00), and the left lower

extremity 0.00 (min:0.00; max:1.00). Mann Whitney on the change ratio (∆) in the treatment and control groups had significant p values.

Table 5. Correlation of HDRS Scores on Motor Strength Treatment Group and Control Group

HDRS Value Treatment Group and Control Group		Right Upper Extremity	Right Lower Extremity	Left Upper Extremity	Left Lower Extremity
D1	r value	0.271	0.254	-0.347	-0.385
	p-value	0.091	0.113	**0.028**	**0.014**
D10	r value	0.255	0.170	-0.428	-0.368
	p-value	0.113	0.293	**0.006**	**0.019**
Delta	r value	-0.198	-0.181	0.068	0.142
	p-value	0.221	0.264	0.679	0.381

* Spearman Correlation Test

HDRS : *Hamilton Depression Rating Scale*
D1 : Day 1
D10 : Day 10

Table 5 shows the correlation between the HDRS and motor strength scores in the treatment and control groups using the Spearman correlation test shows that the upper and lower left extremities have a significant correlation value compared to the other extremities. The p-value for the left upper extremity (first day p=0.028; tenth day p=0.006). The p-value for the left lower extremity (first day p=0.014; tenth day p=0.019).

The HDRS score was negatively correlated with left upper and lower extremity motor strength. The negative correlation shows that the lower the HDRS score, the higher the motor strength value. The r value in the upper left extremity on the first day was -0.374; on the tenth day -0.428. The r value in the left lower extremity on the first day was -0.385; on the tenth day -0.368.

R-value change ratio (∆) for the right upper extremity -0.198, right lower extremity -0.181, left upper extremity 0.068, and left lower extremity 0.142. The p-value in the ratio of changes in change (∆) for the right upper extremity is 0.221. The right lower extremity is 0.264, the left upper extremity is 0.679, and the left lower extremity is 0.381. The comparison value of changes above shows a significant p-value with the HDRS score, negatively correlated in the upper and lower left extremities. The smaller the HDRS score, the greater the motor strength value.

4. DISCUSSIONS

This study demonstrated the effectiveness of repetitive transcranial magnetic stimulation (rTMS) in improving depressive symptoms by administering high-frequency 5 Hz in the left and right Dorsolateral Prefrontal Cortex. This study was divided into two groups, the treatment group, and the control group. This study showed an improvement in the HDRS score in the treatment and control groups. Based on the assessment of the degree of depressive symptoms in the treatment group on the first day, before the intervention showed nine (45%) subjects with mild depressive symptoms and 11 (55%) with moderate depressive symptoms, and on the tenth day, 20 (100%) subjects did not experience depression. In the control group, on the first day, six (30%) had mild

depressive symptoms. 14 (70%) had moderate depressive symptoms; on the tenth day, subjects with mild depressive symptoms were 17 (85%) and subjects with moderate depressive symptoms were three (15%). Based on statistical tests on the tenth day, the p-value was significant in the treatment and control groups. The decrease in the HDRS score in the treatment group was more significant than in the control group. Research by Frey et al. at the University of West Virginia, the United States, reported a significant decrease in the HDRS score with the Wilcoxon test (p=0.03) using rTMS for 20 sessions. rTMS is effective and safe for post-stroke depression patients [(12)]. rTMS can increase fractional anisotropy values, stimulate the left frontal lobe, increase the concentration of the brain-derived neurotrophic factor, and increase the reconstruction of damaged neural tissue, which ultimately restores its nerve structure. Da Silva Júnior et al. explains that rTMS is very effective in reducing depressive manifestations in stroke and it is proven in a clinical outcome better patient quality of life [(1)].

In this study, there was an improvement in motor strength in the treatment group after being given repetitive transcranial magnetic stimulation interventions. With the Wilcoxon test, the p-value is significant in the treatment group, and in the control group, the p-value is not significant. A study by Wang et al. reported that 17 out of 32 ischemic stroke patients with an onset of 2–6 months which were given contralesional LF-rTMS for ten days experienced significant motor improvements [(13)]. rTMS induces repetitive electrical responses in the cortex that result in long-term changes in cortical excitability that last beyond the time of stimulation. When low-frequency rTMS stimulation (1 Hz) causes reduced cortical excitation, while high-frequency rTMS stimulation (3-10Hz) causes increased excitation, high-frequency rTMS can decrease apoptosis after stroke [(13)].

This study demonstrated the effectiveness of rTMS in improving depressive symptoms and motor strength in ischemic stroke patients. There is a relationship between improved mood and better functional recovery [(14)]. Research by Da Silva Junior et al. reported a significant decrease in HDRS values after being given rTMS for 20 sessions (p=<.001); rTMS can improve depressive symptoms and quality of life after stroke [(15)].

This study uses a correlation test Spearman which showed a negative correlation of the HDRS score to the left upper and lower extremity motor strength. The lower the HDRS score, the higher the motor strength value. There is a negative correlation between the HDRS score on left extremity motor strength with cerebral lesions in the right hemisphere. The right hemisphere is responsible for emotions, plays a role in cognitive and language functions, and maintains attention on the bilateral side of the environment, perception, imagination, and motor skills of the left extremity [(16), (17)]. Right hemisphere lesions are associated with depressive symptoms [(18)(19)]. Bindawas et al. at King Saud University, Saudi Arabia, in 2017 reported that of 383 stroke patients, 157 patients with left hemiparesis experienced more significant motor functional improvement than patients with right hemiparesis [(20)]. Research by Yoshida et al. in 2018 at the University of Estadual de Campinas, Brazil, reported that depressive symptoms were negatively correlated with all motor skill variables, and high motor skills were associated with low depressive symptoms. In line with the research, Herman et

al. reported a correlation between depressive symptoms and low motor skills and vice versa [21].

Bewernick et al., in 2017, at the University of Mannheim, Germany, reported reduced motor activity correlated with depression. Elevation of mood increases motor activity (Bewernick et al. 2017) [22].

The limitation of this research is that it is still subjective at the time anamnesis was carried out to measure the HDRS score on the first and tenth days in the treatment and control groups. The author's suggestion for further research is to examine depression biomarkers (5-HT, BDNF, CRP, IL-6, TNFά, etc.) as an additional parameter in measuring the effectiveness of rTMS in improving depressive symptoms in ischemic stroke patients, and conduct further research by comparing the effectiveness of rTMS in improving depressive symptoms and motor strength in acute and chronic onset.

CONCLUSION

Repetitive Transcranial Magnetic Stimulation effectively improved depressive symptoms and motor strength in ischemic stroke. There is a negative correlation between the HDRS value on left upper and lower extremity motor strength in ischemic stroke patients with depressive symptoms.

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Conflict of Interest Statement:

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