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Effect of Repetitive Transcranial Magnetic Stimulation on Change in Delta Theta Alfa Beta Ratio (DTABR) and Motor Function in Ischemic Stroke Patients

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Abstract

Background: Stroke is the leading cause of long-term disability worldwide. The electroencephalography (EEG) of ischemic stroke patients is a slow background and the quantitative electroencephalogram (qEEG) shows an increased delta+theta/alpha+beta ratio (DTABR). Disability can be assessed using a Fugl Mayer Motor Assessment (FMA). In this study, we will examine the effect of Repetitive transcranial magnetic stimulation (rTMS) on changes in DTABR and assess motor function improvement in ischemic stroke patients with unilateral brain lesions. *Methods:* Thirty patients were divided into 2 groups. The first group received standard stroke therapy and gave rTMS intervention. The second group received only standard stroke therapy. All patients recorded using a EEG recorder and the results will be converted into qEEG. All samples will also be assessed for motor function using FMA before and after the intervention. The qEEG results obtained the absolute value of the power of each brain wave which we then calculated DTABR before and after treatment. *Results:* There was a greater decrease in DTABR in the treatment group when compared to the control group on the EEG electrodes Cz ($p=0.029$), C3 ($p=0.048$), C4 ($p=0.004$), Pz ($p=0.015$) and total DTABR ($p=0.011$) and greater motor improvement in the treatment group when compared to the control group $p<0.001$. In the Spearman's test there is a relationship between changes in DTABR and FMA with p value = 0.001. *Conclusion:* There is an increase in motor function associated with a decrease in DTABR in patients with ischemic stroke with unilateral lesions after rTMS intervention

Keywords: Stroke Ischemic, Repetitive Transcranial Magnetic Stimulation, Fugl Mayer Assesment, Quantitative Electrocephalogram

1. Introduction

Stroke is the second leading cause of death after ischemic heart disease and is the leading cause of long-term disability worldwide (Coupland et al., 2017; Benjamin et al., 2019). In 2019, the worldwide incidence of stroke was around 12.2 million new cases with 7.63 million of whom were people with ischemic stroke (GBD, 2020). In

Indonesia alone, the prevalence of stroke is quite high, namely 10.9% per 1000 population. This figure increased when compared to the Basic Health Research (Riskesdas) in 2013 which was 7%. The prevalence of stroke in 2018 was highest in East Kalimantan (14.7%) and the lowest in Papua Province (4.1%) (Kemenkes, 2018).

In 2016, 60% of new cases of ischemic stroke patients were people aged <60 years and about 7% were under 44 years of age (Lindsay et al., 2019). According to the American Heart Association, nearly 75% of stroke patients experience disability and 15-30% of stroke survivors have a severe and permanent level of disability (Go et al., 2014). Disability in stroke patients can be in the form of motor weakness, sensory disturbances, language disorders, memory disorders and emotional disturbances depending on the area where the vascularization disorder occurs (NINDS, 2020). Motor weakness causes many problems, including causing difficulty in walking. or activity and may cause the patient to become immobilized. Immobilization can cause joint pain, limited range of movement (ROM), joint stiffness, muscle atrophy, muscle spasm, shoulder pain, knee flexion contractures, muscle weakness and footdrop (Elmasry et al., 2015). in stroke patients. Management of stroke patients can be in the form of preventive, promotive, curative and rehabilitative. Preventive and promotive efforts are usually carried out at first-level health facilities in the form of discovery, early detection and control of stroke risk factors (Kemenkes, 2013). Curative management is generally carried out in hospitals, acute ischemic stroke management can be in the form of recanalization of blood vessels such as recombinant tissue plasminogen activator (rTPA). with thrombolytics and mechanical thrombectomy (Powers et al., 2019). Therapy using rTPA and mechanical thrombectomy gave excellent clinical outcomes (Prawiroharjo, 2017), but this procedure also has limitations including the limited time of administration, limited infrastructure such as the availability of medical personnel and imaging equipment is lacking, geographical conditions, and community factors such as low levels of knowledge cause the management of acute ischemic stroke not to be maximal (Tangkudung, 2020). Post-acute stroke patients with motor weakness are generally given repetitive physical exercise, physical activity with the help of technology such as the use of robots and virtual reality, as well as noninvasive brain stimulation in this case the use of Transcranial Magnetic Stimulation (TMS) which is intended to stimulate neuroplasticity (Edwards, 2008).

rTMS affects synaptic plasticity in several ways, by inducing increased release of neurotransmitters such as dopamine, stimulating the growth of glial cells and preventing neuronal cell death. Stimulation of the motor cortex using rTMS can increase the release of the neurotransmitter dopamine in the nucleus accumbens (Strafella, 2003). rTMS can activate the glutamate system, activation of the glutamate system will activate N-methyl-D-aspartate (NMDA) receptors which will affect brain neuroplasticity (Moretti et al., 2020). Stimulation produced by rTMS also helps in the reperfusion process by increasing adenosine triphosphate. ATP) in the striatum of ischemic cerebral hemispheres (Kim & Yim, 2018). The combination of physical exercise and rTMS when performed simultaneously can induce neuroplasticity well and provide better motor improvement results than when administered alone (Yang et al., 2020). The rTMS intervention has also been shown to affect wave activity. brain associated with changes in neuroplasticity, nerve transmission, and blood flow to the brain (Zhong et al., 2021).

Electoencephalography (EEG) can record the electrical activity of the brain which is described with brain waves. When cerebral blood flow (CBF) decreases, brain tissue ischemia occurs and an abnormal EEG picture is obtained in the form of an increase in slow wave activity (delta and theta) and a decrease in fast waves (alpha and beta) (Hirsch et al., 2021; Jordan, 2004). Abnormalities that appear can be an increase in the delta/alpha ratio (DAR), an increase in (delta+theta)/(alpfa+beta) ratio (DTABR) and changes in brain symmetric index (BSI) are common in stroke patients (Finnigan et al., 2016; Sheorajpanday et al., 2011). DTABR and alpha relative power are quantitative indices. Quantitative Electroencephalography (qEEG) is the best in determining stroke outcome. DTABR is said to be associated with cerebral perfusion and oxygen metabolism. Motor outcomes were assessed using the modified Ranking Score (mRS) and a unidirectional relationship was found between low mRS and low DTABR (Bentes et al., 2018). In general, the DTABR value is said to be normal if it has a value < 1 (Finnigan & Putten, 2013).

The protocol of administering rTMS stimulation with a combination of high frequency on the ipsilateral lesion and low frequency on the contralateral lesion is a common protocol (Zhong et al., 2021). Administration of rTMS with a frequency of excitation in the area of the motor cortex ipsilateral to the lesion and a frequency of inhibition in the contralateral lesion can increase cerebral blood flow (CBF). High-frequency stimulation (>5 Hz) leads to increased alpha and beta wave activity (Thut et al., 2011) and can decrease delta activity in patients with schizophrenia (Kamp et al., 2016). Administration of rTMS with a frequency of 10 Hz at the Cz EEG electrode area can reduce delta activity at the lesion site which may play a role in clinical improvement (Zhong et al., 2019). Administration of rTMS with a frequency of 1 Hz to the motor cortex, increased the absolute power of delta waves in normal subjects (Qiu et al., 2019). In this study, the researcher wanted to see the effect of giving rTMS on DTABR and motor function of ischemic stroke patients with unilateral lesions.

2. Method

2.1 Research Design

This study is an experimental study with a pre-test post-test control group design that aims to compare changes in DTABR using quantitative EEG and changes in motor function of post-ischemic stroke patients in the group receiving standard ischemic stroke therapy with a combination group between standard ischemic stroke therapy and repetitive transcranial magnetic stimulation (rTMS).

2.2 Research Location and Time

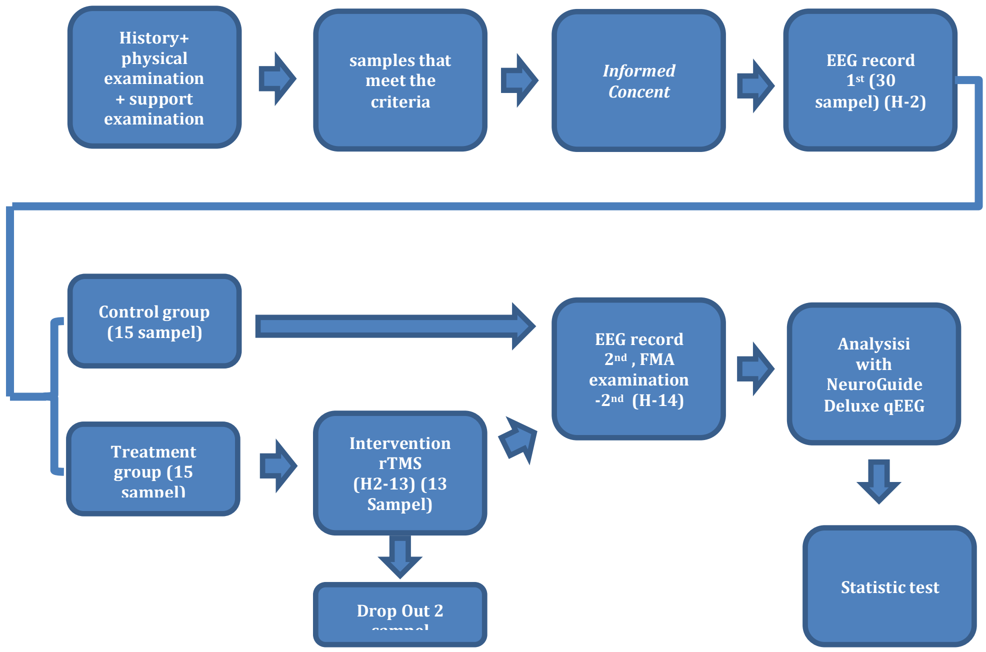
The research was conducted at the Neurology Polyclinic of Dr. Central General Hospital. Wahidin Soedirohusodo, from October 2021 to January 2022, Makassar. Population and Sample. The study population was post-ischemic stroke patients who visited the Neurology Polyclinic Iof Wahidin Sudirohusodo Hospital from October 2021 to January 2022. The study sample was determined by consecutive sampling, i.e. all subjects who came and met the research criteria were included in the study until the required number of subjects was met. Samples were taken from the study population based on the order of admission to the hospital (Consecutive sampling).

2.3 Population and Sample

Inclusion criteria in this study were post-ischemic stroke patients diagnosed based on history, physical examination and CT scan results without contrast, age 35-65 years, first attack, onset of more than 14 days and less than 3 months, supratentorial lesions, weakness moderate - very severe motor skills based on the FMA score, aware, cooperative and willing to be included in this study by signing an informed consent. The exclusion criteria were having received rTMS therapy, patients with contraindications to the use of TMS; use of cardiac pacemakers, cochlear implants and use of metal artifacts and patients at risk or history of seizures. The criteria for drop-out patients in this study were patients who did not participate in the electroencephalography recording session, the patient did not participate in the entire repetitive Transcranial Magnetic Stimulation session, the patient died, the patient withdrew as a sample, due to certain reasons.

2.4 Data Collection

All subjects were given an explanation about the study, if they agreed they were asked to sign an informed consent. Subjects were divided into two groups, namely treatment and control which were determined based on the time of arrival. Subjects who came in the order of 1-15 were the treatment group and 16-30 were the treatment group. All subjects received standard therapy, namely medication and rehabilitation (according to the ischemic stroke management protocol at Dr. Wahidin Sudirohusodo Hospital) and the treatment group was added to rTMS stimulation. On the first day of the visit, all selected subjects were assessed using the FMA, which can check the motor strength of the upper and lower extremities. On day 2, all subjects were recorded for 5 minutes of EEG. Furthermore, rTMS stimulation was given with a combination of high frequency (HF) of 10 Hz on the ipsilateral lesion and low frequency (LF) of 1 Hz on the contralateral lesion. The rTMS was given 10 times, 5 times consecutively every day, then 2 days apart and then 5 days in a row. On the 14th day, all subjects were again assessed using FMA and EEG recordings. The results of the EEG recording will be processed using NeuroGuide Deluxe qEEG software and converted into quantitative electroencephalogram (qEEG) data. Then, the ratio (delta+theta)/(alpha+beta) (DTABR) was calculated on the EEG electrodes Cz, C3, C4, Pz, P3 and P4, and DTABR total. The total DTABR is the total absolute power value of each wave on all electrodes installed (19 electrodes). In this study, the Fugl-Mayer Assessment Test was used to assess the level of motor recovery in ischemic stroke patients. There are five domains that are assessed by the Fugl-Meyer scale, namely, 1) Motor function (maximum score in the upper extremity is 66, for the lower extremity 34), 2) Sensory function (maximum score is 24), 3) Balance (maximum score is 14), 4) Joint range of motion (maximum score is 44), 5) Joint pain (maximum score is 44). In the application of FMA, each of these five FMA domains can be separated according to the purpose of the assessment. Motor domain assessment includes assessment of shoulder, elbow, forearm, wrist, hand, hip, knee and ankle movement, coordination and reflexes. The FMA reliability value for stroke patients is quite high with an intraater value of r=0.98-0.99 and a retest r=0.97. For the upper extremities, the intraater value r = 0.995-0.996 and for the lower extremities the intraater value r = 0.96. The maximum value for upper and lower extremity FMA examination is 100, then divided into 4 criteria. Very severe criteria if the FMA score is 0-35, severe 36-55, moderate 56-79 and mild >79. During data collection there were 2 samples in the treatment group that had to be excluded because they met the drop-out criteria. The sample collection method can be seen in Figure 1.



2.5 Repetitive TMS

The rTMS intervention was given in 2 cycles. Each cycle consists of 5 consecutive days, then a pause of 2 days, followed by a second cycle for 5 consecutive days. rTMS was performed in the M1 area, which is the primary motor area. On the ipsilateral lesion was given rTMS with a frequency of 10 Hz while on the contralateral lesion was given rTMS with a frequency of 1 Hz

2.6 Analysis Data

All data will be analyzed using IBM© SPSS© 25 (New York, United States). To assess the distribution of data, the Shapiro-Wilk test is used. For normal data distribution, Paired T test and Independent T test were used, while for abnormal data distribution, Wilcoxon test and Mann Whitney U test were used. The hypothesis is said to be significant if the p value <0.05 is obtained. The correlation test used Spearman's test.

2.6.1. Research permit and Ethical Eligibility

In carrying out this research, all research subjects were given an explanation of the aims, objectives and uses of the research, including the risks that could occur. After receiving an explanation, the subject signed the Research Participant Approval Letter and every action was carried out with the permission and knowledge of the subject through an informed consent form. This research has also been approved by the health research ethics committee of the Hasanuddin University RSPTN RSUP Dr. Wahidin Sudirohusodo Makassar with number 712/UN4.6.4.5.31/PP36/2021.

2.7 Results

This research was conducted on 30 subjects which were divided into 2 groups. The first group consisting of 15 samples was the treatment group that received rTMS intervention while the second group of 15 subjects was the control group who only received standard stroke therapy. Demographic data and patient characteristics can be seen in Table 1. Table 1 shows there is no significant difference between the two groups based on the FMA category.

Table 1: Demographic data of research sample

Charasterictis		**Treatment**			**Control**			**P**
		(n)	**%**	**Mean**	**(n)**	**%**	**Mean**	
Age	36-45 years old	3	20	52.26 (SD ±8.05)	3	20	51.93 (SD ±6.91)	0.904[a]
	46-55 years old	6	40		9	60		
	56-65 years old	6	40		3	20		
Onset Stroke (day)		15	-	30.86 (SD ±23.75)	15	-	22.46 (SD ±11.03)	0.526[b]
Gender	Man	11	73.3	-	11	73.3	-	1.00[c]
	women	4	26.7	-	4	26.7	-	
Risk Factor	HT	9	60	-	11	73.3	-	0.141[c]
	DM	0	0	-	0	0	-	-
	HT+DM	6	40	-	4	26.7	-	0.699[c]
Lesion location	Right Hemisfer	10	66.7	-	9	60	-	0,705[c]
	Left Hemisfer	5	33.3	-	6	40	-	
FMA Category	Very severe	6	40	-	5	33,3	-	0,264[c]
	Severe	8	53,3	-	8	53,3	-	1.00[c]
	Moderate	1	6,7	-	2	13,4	-	0,685[c]

Source: Primary Data a) independent T test, b) Mann-Whitney test, c) Chi-Square test. FMA: Fugl Mayer

2.8 Assesment Test

Table 2 shows the changes in DTABR before and after therapy in the control and treatment groups. In the treatment group, all EEG electrodes were Cz (p=0.019), C3 (p=0.012), C4 (p=0.007), Pz (p=0.004), P3 (p=0.032), P4 (p=0.003) and total DTABR. (p=0.003) experienced a significant decrease in DTABR between before and after treatment. Meanwhile, in the control group, only the EEG electrodes Pz (p=0.017) and P4 (p=0.001) experienced a significant decrease in DTABR.

Table 2: DTABR Score Before and After Therapy

EEG Electrode	**Treatment**						**Control**					
	Mean	**SD**	**Median**	**Min**	**Max**	**P**	**Mean**	**SD**	**Median**	**Min**	**Max**	**P**
Cz_Pre	2.21	1,52	1,98	0,33	5,87	0,019**	1.35	0.80	1,11	0,4	3,04	0,681**
Cz_Post	1.45	0.81	1,34	0,27	2,71		1.18	0.66	1,05	0,35	2,34	
C3_Pre	2,25	1,55	1,89	0,30	6,17	0,012**	1.49	1.37	1,04	0,5	5,18	0,109*
C3_Post	1.4	0.8	1,39	0,24	2,76		1.18	0.83	0,7	0,46	3,15	
C4_Pre	2.07	1.5	1,83	0,30	5,88	0,007**	1.43	0.90	1,1	0,31	3,18	0,154**
C4_Post	1.22	0.76	1,21	0,19	2,59		1.31	0.83	1,17	0,31	2,82	
Pz_Pre	2.15	1,33	1,83	0,29	5,38	0,004**	1.44	0.92	1,15	0,37	3,22	0,017*
Pz_Post	1.25	0.62	1,22	0,29	2,21		1.18	0.77	0,93	0,34	2,61	
P3_Pre	1,92	1,17	1,86	0,29	4,46	0,032**	1.32	1.14	1	0,26	4,29	0,069*
P3_Post	1.37	0.84	1,14	0,26	2,75		1.06	0.71	0,72	0,24	2,62	

P4_Pre	1,96	1.55	1,34	0,28	5,61	0,003*	1.48	1.15	1,08	0,12	3,69	0,001*
P4_Post	1.25	0.79	1,31	0,26	2,74		1.10	1.05	0,73	0,06	2,56	
DTABRtpre	2,11	1,12	2,17	0,54	4,59	0,003**	1,47	0,93	1,22	0,43	3,9	0,054**
DTABRtpost	1,39	0,7	1,16	0,34	2,54		1,21	0,66	0,96	0,39	2,36	

*Source: Primary Data, *Wilcoxon test, **Paired t test*

Table 3 shows the comparison of changes in DTABR in the treatment group and the control group. There was a significant difference in DTABR scores on the electrodes Cz (p=0.029), C3 (p=0.048), C4 (p=0.004), Pz (p=0.015) and total DTABR (p=0.011) when compared between the treatment and control groups. The decrease in the treatment group was greater than the control group. This may reflect the effect of rTMS on changes in DTABR where the changes were greater in the treatment group compared to the control group at the Cz, C3, C4, Pz and DTABR total EEG electrodes.

Table 3: Comparison of DTABR Scores of Treatment and Control Group

Variable	**Group**	**Δ Mean (SD)**	**Median**	**Min**	**Max**	**Significant**
delta_Cz	Treatment	0,76 (±1,02)	0,35	-0,06	3,41	0,029*
	Control	0,17 (±0,33)	0,04	-0,32	0,8	
delta_C3	Treatment	0,85 (±1,03)	0,82	-0,15	3,46	0,048*
	Control	0,32 (±0,72)	0,05	-0,43	2,58	
delta_C4	Treatment	0,85 (±0,95)	0,7	-0,08	3,46	0,004*
	Control	0,11 (±0,28)	0,02	-0,2	0,7	
delta_Pz	Treatment	0,90 (±0,90)	0,57	0	3,17	0,015*
	Control	0,25 (±0,37)	0,07	-0,1	1,05	
delta_P3	Treatment	0,54 (±0,81)	0,4	-0,59	2,26	0,279*
	Control	0,26 (±0,51)	0,13	-0,46	1,67	
delta_P4	Treatment	0,71 (±1,03)	0,33	0	3,34	0,489*
	Control	0,38 (±0,49)	0,25	0,01	1,68	
Total delta_DTABR	Treatment	0,72 (±0,69)	0,54	0,14	2,36	0,011*
	Control	0,26 (±0,47)	0,04	-0,12	1,54	

*Source: Primary Data, *mann Whitney U test*

Table 4 shows changes in FMA scores before and after therapy. In the control and treatment groups, there were significant differences in motor function after therapy. This is indicated by the significance value of motor function before and after therapy in the treatment group and the control group having a p value = 0.001 (<0.05).

Table 4: FMA Score Before and After Therapy

	Treatment					**Control**				
	Mean (SD)	**Median**	**Min**	**Max**	**p**	**Mean (SD)**	**Median**	**Min**	**Max**	**p**
FMA_pre	36,23 (±19,23)	39	8	63	0,001*	39,4 (±22,87)	41	8	79	0,001*
FMA_post	62,92 (±19,37)	65	29	88		53,2 (±21,89)	56	15	84	

*Source: Primary Data, *Paired t test,**Wilcoxon test* ***description :****FMA : Fugl Mayer Assesment Test, FMA_UE : Fugl Meyer Assesment Test Upper Extremitiy. FMA_LE : Fugl Meyer Assesment Test Lower Extremitiy.*

Table 5 shows a comparison of changes in motor function between the treatment group and the control group. There was an increase in the difference in FMA scores almost two times greater in the treatment group with an average value of 26.69 (±5.48) compared to the control group with an average value of 13.8 (±6.88). There was a significant difference between the treatment and control groups with p value < 0.001 where the change was greater in the treatment group than the control group.

Table 5: Comparison of FMA Scores in the Treatment and Control Groups

Group	Δ Score (mean±SD)	Median	Min	Max	p
Treatment	26,69 (±5,48)	24	19	35	
Control	13,8 (±6,88)	16	7	29	<0,001*

*Source: Primary data, *independent t test*

Table 6 shows the relationship between changes in total DTABR and an increase in motor function. Total DTABR and motor function were tested using Spearman's correlation test, it was found that there was a significant relationship between changes in total DTABR and changes in motor function with p value = 0.001. The correlation is strong positive which is indicated by the value of .584. This means that the greater the decrease in DTABR, the greater the increase in motor function (FMA score).

Table 6: Analysis of the relationship between total DTABR and the improvement of motor function in the treatment and control groups

Spearman's rho		delta DTABRtotal	delta FMA
delta DTABRtotal	Correlation Coefficient	1.000	.584**
	Sig. (2-tailed)	.	.001
	N	28	28
delta FMA	Correlation Coefficient	.584**	1.000
	Sig. (2-tailed)	.001	.
	N	28	28

*Source: Primary Data, *Spearman's correlation test*

3. Discussion

This study aims to determine the effectiveness of Repetitive Transcranial Magnetic Stimulation (rTMS) with high frequency (10 Hz) on the ipsilateral lesion and low frequency (1 Hz) on the contralateral lesion to changes in the Delta+Theta/Alfa+Beta (DTABR) ratio and motor function improvement. in ischemic stroke patients with motor impairment.

In this study initially there were 30 samples divided into 2 groups, namely the treatment group (n=15) and the control group (n=15). The treatment group was the group that received 2 cycles of rTMS intervention. The control group was the group that received standard stroke therapy in the form of drugs and physiotherapy. In its development in the treatment group there were 2 samples that dropped out because the patient resigned, so that the total number of samples at the end of the study was 28 samples where the treatment group (n = 13 samples) and the control group (n = 15 samples).

Various previous studies have shown that the incidence of stroke will increase with age (Schwamm et al., 2017). Age is the strongest risk factor for stroke and this stroke risk will double every decade over age 55 (Caplan, 2016). In this study, the highest age group was 46-55 followed by 56-65 years. The most important predictors of outcome in the acute phase of stroke were stroke severity and patient age. Stroke severity can be assessed clinically, based on various parameters of neurological impairment (eg, mental changes, motor deficits, language, visual field deficits, behavior) and the size and location of the infarct on neuroimaging by MRI or CT scan (Konig et al., 2008). In old age, patients experience improvement. but at a slower pace and overall age has a relatively small impact on motor improvement in stroke patients (Teasell & Hussein, 2020).

The incidence of stroke in men is higher than in women (Perdossi, 2011). As the age increases, the incidence of stroke in women increases. A population-based study in Sweden found that the incidence of stroke in women was 60% lower than that of men at the age of 55-64 years, but at the age of 75 women had a 50% higher incidence than men (Lofmark & Hammarstrom, 2007). In this study the number of male subjects as many as 22 people (73.3%) and 8 women (26.7%).

Hypertension is the second strongest risk factor after age and people with hypertension are about 3 or 4 times more likely to have a stroke (Chobanian et al., 2003). A strong association between hypertension and stroke has been associated with a strong effect of hypertension on the cerebral circulation. In cerebral vessels, hypertension is known to cause hypertrophy of the vessel walls and a reduction in the diameter of the external lumen of the vessels. In addition, hypertension alters the ability of endothelial cells to release vasoactive factors and increases systemic and cerebral arterial constrictor tone (Iadecola & Gorelick, 2004). All samples in this study had hypertension risk factors and 10 of them had hypertension and diabetes mellitus. In the demographic data, there were no significant differences between the treatment group and the control group in age, gender, risk factors and lesion location.

Brain waves are associated with neuronal activity in the brain that reflects the process of excitation and inhibition of nerve cells (Rabiller et al., 2015). The increase in excitability of nerve cells is described by an increase in the neuronal population as well as when the nerve cell is inhibited, which occurs is a decrease in the neuronal population (Jensen & Mazaheri, 2010). The main factor that inhibits functional recovery after stroke is a change in synaptic function, namely a decrease in excitability or a decrease in excitability in the part of the brain affected by stroke and interhemispheric imbalance. Poststroke recovery is promoted by reducing transcallosal inhibition in the affected hemisphere and inhibition of excitability from the normal hemisphere. rTMS as noninvasive brain stimulation can be used as an additional therapeutic option for motor function recovery after stroke because it can regulate cerebral cortex excitability and nerve plasticity depending on the stimulation parameters used. rTMS can also induce synaptic plasticity and alter interhemispheric interactions (Fisicaro et al., 2019).

The working principle of TMS is to produce an induced current that can affect brain metabolism and nerve electrical activity. Administration of rTMS with a frequency of 1 Hz can inhibit the cortex while >1 Hz can excite the cerebral cortex (Lewis et al., 2016). Based on this principle, the treatment group in our study apart from drug therapy was also given rTMS stimulation with a combination of high frequency (10 Hz) on the ipsilateral lesion and low frequency (1 Hz) contralateral to the lesion. With this combination, we expect that on the side of the lesion will experience cortex excitation, while on the contralateral side of the lesion will occur cortical inhibition. The excitation process can induce synaptic plasticity in the infarct area and the inhibitory process can reduce healthy brain activity and provide interhemispheric balance that plays a role in stroke functional recovery (Fisicaro et al., 2019). In the control group only received standard stroke therapy in the form of drugs and medical rehabilitation 3 times a week for 2 weeks. week. Previous research conducted by Long et al (2018) used 3 treatment groups, the first group consisting of 20 people was the control group, the second group consisted of 21 people from the lower frequency (LF-rTMS) group and the third group consisted of 21 people from the group. combination of high frequency (HF-rTMS) 10 Hz with LF-rTMS (1 Hz). In this study, an increase in upper extremity motor function was found using the Fugl-Meyer Assessment (FMA) after being given a combination of low and high frequencies for 2 weeks when compared to other groups. In the control group, there was an insignificant improvement in motor function on examination 15 days after the onset but the results changed to be significant after the follow-up 3 months later (Long et al., 2018). These results are different from the results of our study where there were significant motor changes in the first 2 weeks either in the control and treatment groups where the motoric increase in the treatment group was greater than in the control group. Our results are supported by the study conducted by Du Juan et al, they divided into 3 groups where the group received high-frequency rTMS (10 Hz) intervention on the ipsilateral lesion, low-frequency rTMS (1 Hz) on the contralateral lesion, and the control group had there was a significant difference in the improvement of motor function using FMA after 2 weeks of therapy, but when compared between the treatment group compared to the control group there was a significant difference where the improvement in the treatment group was better than the control group (Du et al. 2019). Similar results were also obtained in a study conducted by Bintang, A.K et al who got the results that there were significant differences in the improvement of motor function using the Stroke Rehabilitation Assessment of Movement (STREAM) in both treatment and control patients, the treatment group in this study received a combination of high frequency and low frequency rTMS while in the control group only received standard stroke therapy (Bintang et al., 2020).

Motor improvement in patients with central nervous system injuries may occur due to the spontaneous healing process. This depends on the remaining activity of the neurons in the penumbra area (the area around the lesion). There are three mechanisms that the brain uses to promote spontaneous recovery after a stroke. The three are reperfusion, edema management, and diaschisis reversal. Reperfusion refers to restoring blood flow to the damaged area. The brain can achieve this in a number of ways, one of which is by increasing blood pressure. For this reason, the researchers recommend caution when trying to lower blood pressure in stroke patients. While very high blood pressure can be dangerous, lowering it too low can hinder spontaneous recovery. Management of edema, decreased oxygen in the brain causes increased swelling (edema), which blocks the blood supply and causes further damage. Therefore, a major part of spontaneous recovery involves reducing edema. This can occur naturally but sometimes requires medication or oxygen therapy. Once the swelling is reduced, blood flow can return, and function is usually restored. Diaschisis reversal, also known as neuroshock, refers to suppressed nerve activity due to loss of input from damaged areas of the brain. This will resolve on its own within a few weeks or by improving blood flow and treating edema (Maher, 2020).

Medical rehabilitation also plays a role in the functional recovery process of post-stroke patients. Plasticity in medical rehabilitation depends on experiential exposure through certain training that can activate neural plasticity mechanisms (Maher, 2020). Training that can activate neural plasticity is training that has repetitive, specific, intensity and long-term nature (Kleim & Jones, 2008). Specific training can increase cortical activity in the brain. ipsilesi brain hemispheres (Lage et al., 2015) and training that has the intensity of spaced practice can increase neuronal activity (Gerbier & Toppino, 2015). The duration of therapy and repeated exercises also affect plasticity, the longer and more frequent the therapy, the better the functional improvement (Thomas et al., 2017; Kwakkel, 2009). With the spontaneous healing process and a successful rehabilitation process. well then in patients who only get drug therapy and physiotherapy can also experience improvements in motor function as we get in the control group of our study.

In stroke patients, EEG recordings were obtained in the form of an increase in slow waves, namely delta and theta. The absolute power of this delta wave is related to the infarct volume. An increase in absolute power in the slow wave frequency band (delta and theta) and a decrease in absolute power in the fast wave frequency band (alpha and beta) are seen in people with decreased brain metabolism such as in stroke (Jordan, 2004). In previous studies, the mean value of DTABR scores in normal people is <1 (Finnigan & Putten, 2013), this is in accordance with our study where the initial DTABR mean value >1 on the six EEG electrodes (Cz, C3, C4, Pz, P3 and P4) and the total DTABR in the control and treatment groups.

In this study we assessed the absolute ratio of delta+theta/alpha+beta wave power (DTABR) at the C3, C4, Cz, P3, P4, Pz and total DTABR electrodes. The reason for taking it at this location is because C3, Cz and C4 are responsible for the motor function of the body. In addition, electrodes located at parietal locations, such as P3, Pz and P4, can also be used to classify motor movement signals as they relate to cognitive processes in the brain (Yahya et al., 2019). Total DTABR represents the overall strength of both slow and fast brain waves on the 19 attached EEG electrodes.

Administration of high-frequency (10 Hz) rTMS stimulation in patients with unilateral lesions can also reduce delta activity on the side of the lesion which may play a role in clinical improvement (Zhong et al., 2021). Administration of rTMS with a frequency of 1 Hz in the motor cortex, increases the absolute power of delta waves in normal subjects (Qiu et al., 2019). Administration of rTMS with a frequency of 10 Hz at point Cz got an absolute decrease in delta wave power on the ipsilateral lesion (Zhong et al., 2021). Based on this we gave 10 Hz stimulation on the ipsilateral lesion and 1 Hz on the contralateral lesion. effect in lowering the value of DTABR. In our results, there was a significant decrease in DTABR consisting of Cz, C3, C4, Pz, P3, P4 and total DTABR in the treatment group with $p < 0.05$.

In the control group there was a significant decrease in DTABR scores with $p < 0.05$ on the Pz and P4 EEG electrodes. The decrease in DTABR in the control group may occur because the control group also experienced a significant improvement in motor function which was assessed after 2 weeks. This can happen because there is a relationship between improved motor function and changes in brain waves shown in previous studies, including an increase in cortical activation marked by an increase in alpha wave activity in the treatment group receiving Constraint-induced Movement Therapy (CIMT) compared to the control group (Ahmed et al., 2018). This explanation agrees with Carrion et al, who carried out the medical rehabilitation process on 21 patients and found that delta and alpha waves were signs of the recovery process; the higher the alpha power, the better the patient's recovery outcome. They also stated that the relative power of alpha waves has a tendency to increase with increasing motor performance and activities of daily living (Leon et al., 2009). Ingemanson et al 2019, conducted a study on the effect of robotic-assisted medical rehabilitation on 30 chronic stroke patients with upper extremity motor disorders, it was found in 8 out of 9 patients who did not improve had somatosensory disturbances (Ingemanson et al., 2019). Motor improvement depends on the extent of the injury to the sensory system, cortical sensorimotor connectivity and good proprioception. The fewer disturbances in the sensory and proprioceptive systems will give better motor improvement results, this happens because in the medical rehabilitation process, the part of the brain that is stimulated first is the sensory cortex (gyrus post centralis) which is represented by EEG electrodes Pz, P3 and the new P4 will stimulate the motor area (gyrus precentralis). Based on this, a significant decrease in DTABR in the control group can occur in the Pz and P4 areas because these areas are sensory areas plus none of our study samples had proprioceptive disturbances.

Here is a relationship between changes in DTABR and improvements in motor function using the FMA score after the Spearman's test. The relationship is positive, namely the higher the decrease in DTABR the better the motor function as assessed using the FMA. DTABR has a unidirectional relationship with motor clinical outcomes assessed using the modified Ranking Score (mRS) where the lower the DTABR the lower the mRS (Bentes et al., 2018). High delta wave activity is also associated with poor outcome and is associated with loss of consciousness (Leon et al., 2008).

The limitation of this study is the EEG recording process, because at the time of recording the patient was awake, we could not control his mood. An agitated patient can affect the EEG recording by making it predominant for fast waves.

4. Conclusion

Repetitive Transcranial Magnetic Stimulation (rTMS) is effective in improving motor function in ischemic stroke patients. rTMS was also effective in reducing DTABR at the Cz, C3, C4, Pz and DTABR total EEG electrodes. The decrease in DTABR is associated with improvement in motor function, where the higher the decrease in DTABR, the better the motor function.

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ABBREVIATIONS

Abbreviations	Meanings
rTMS	*repetitive Transcranial Magnetic Stimulation*
HF-rTMS	*High Frequency- repetitive Transcranial Magnetic Stimulation*
LF-rTMS	*Low Frequency- repetitive Transcranial Magnetic Stimulation*
DTABR	Rasio (Delta+Teta)/(Alfa+Beta)
FMA	*Fugl Mayer Assesment Test*
FMA-UE	*Fugl Mayer Assesment Test-Upper Extremity*
FMA-LE	*Fugl Mayer Assesment Test-Lower Extremity*
EEG	*Electroencephalogram*
qEEG	*Quantitative Electroencephalogram*