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The Effect of High- and Low-Frequency Repetitive Transcranial Magnetic Stimulation Therapy on Serum Brain-Derived Neurotropic Factor Level and Motor Ability in Ischemic Stroke Patients: A Single-Center Study

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Abstract

BACKGROUND: Repetitive transcranial magnetic stimulation (rTMS) is widely used in various neurological cases. rTMS is an effective method of restoration in patients with disability due to central nervous system disorder.

AIM: This study aimed to determine the effect of high and low frequency of rTMS on serum brain-derived neurotropic factor (BDNF) levels and motoric abilities in ischemic stroke patients.

METHODS: The study design was an experiment with a purposive sampling consecutive on 27 samples with the onset of ischemic stroke 6 months. The study was conducted from February to October 2018; samples were recruited from Neurology Ward of Wahidin Sudirohusodo hospital and its affiliating centers. The serial of rTMS intervention was delivered in "Brain" Clinic center. After fulfilling the inclusion criteria and the initial examination of serum BDNF and motor ability, samples were randomly divided into two groups, intervention group who received standard therapy with rTMS therapy (n = 14) and the control group who only received standard therapy (n = 13). rTMS was given for 2 min frequency of 1 Hertz (Hz) contralesion and 5 Hz ipsilesion every day for 10 days. Assessment of serum BDNF levels and motor skills was conducted on days 1 and 10 of the study. Serum BDNF levels were measured by the monoclonal antibody ELISA technique while motor skills were measured based on the score of the Stroke Rehabilitation Assessment of Movement (STREAM). Serum BDNF values and the STREAM delta score were compared between the two groups of samples.

RESULTS: The results showed significant changes only occurred in motor abilities in both groups of samples after 10 days of rTMS therapy with the Wilcoxon test ($p < 0.5$). The Mann–Whitney U-test showed a more significant change ($p < 0.5$) in the treatment group than in the control ($p = 0.5$).

CONCLUSION: rTMS has an effect on improving motor ability in ischemic stroke patients. This change in motor abilities is not related to serum BDNF levels in this study.

Introduction

Stroke is a health problem the whole world, the incidence rate is increasing and is the leading cause of disability. It was reported that, in 2013, globally, there were 2.57 million people stroke survivors worldwide, 6.5 million people died from stroke, 113 million people have disability-adjusted life years due to stroke, and 10.3 million have new cases of stroke [1]. In Indonesia, the incidence of stroke also increases sharply. Data from the 2018 *Riset Kesehatan Dasar* (Riskesdas) on population aged ≥15 years by province stated that the prevalence of stroke increased from 7/1000 in 2013 to 10.9/1000 in 2018. At Dr. Wahidin Sudirohusodo Hospital in Makassar, South Sulawesi, Indonesia, stroke ranks highest in the number of hospitalized patients [2]. Ischemic stroke incidence is higher at 89.9% compared to 10.1% hemorrhagic stroke.

In general, the affected blood vessels are the media and anterior cerebral arteries which give blood supply to the area of the brain that regulates motor skills and speech, so neurological deficits are more often motoric disorders, such as difficulty moving the hands and feet. This condition will certainly lead to limitations in carrying out daily activities, ranging from simple activities, such as holding, raising hands, to more complex motor activities, such as eating, changing clothes, brushing teeth, and walking. Functional stimulation of the cerebral cortex, both magnetic and electrical, is considered as one of the restoration techniques that can improve functional ability in patients, especially if accompanied by intensive motor exercises [3].

Transcranial magnetic stimulation (TMS) is a non-invasive method that uses magnetic fields to stimulate neuron cells in the brain and record stimulus responses using electromyography. The effect of repetitive TMS (rTMS) on modulating brain plasticity is followed by increased levels of BDNF which plays an important role in neurogenesis, migration, and differentiation of neuron cells, synaptogenesis, and angiogenesis, such as nerve growth factor and vascular endothelial growth factor. Excitatory stimulation in the ipsilesion region is associated with changes in neurotransmitters and neurotropic factors [4]. However, whether changes in BDNF levels independently after rTMS therapy are directly related to changes in motor functional ability after ischemic stroke is still unclear. Therefore, this study aims to see whether there is a relationship between BDNF levels and motor functional abilities after high- and low-frequency rTMS therapy in ischemic stroke patients.

Materials and Methods

Study location and time

This study was conducted from February to October 2018. The study samples were collected at the Inpatient Neurology Unit of Dr. Wahidin Sudirohusodo Hospital. Repetitive TMS therapy was carried out in "Brain" TMS Clinic and blood specimen analyzing was carried out in Laboratorium of Universitas Hasanuddin Hospital, Makassar City, South Sulawesi, Indonesia.

Study design and variables

This study was a randomized, controlled, pre-posttest experiment in a single center comparing the effect of standard ischemic stroke therapy in combination with rTMS intervention. The study protocol was approved by the Ethics Committees of Medical Faculty, Universitas Hasanuddin. All study samples were provided written informed consent and approval prior participating. Detail study flows are described in Figure 1.

Population and samples

The population of this study were all ischemic stroke patients who were hospitalized at Wahidin Sudirohusodo Hospital, Makassar, Indonesia. The study samples were patients with first attack stroke with onset time of 1–6 months and were obtained by consecutive sampling until the number of patients needed was fulfilled.

Inclusion and exclusion criteria

Patients were included in the study if fulfilled the inclusion criteria of having a diagnosis of ischemic stroke based on clinical symptoms and CT head scan results without contrast. Patients with hemiparesis with mild-moderate clinical disorder (mRS ≤ 4) due to damage to the unilateral brain hemisphere associated with ischemic stroke. Stroke onset was more than 1 month. The age of the patient ranges from 35 to 80 years and willing to participate by signing an informed consent. Samples were exclude if they have a history of using implantable pacemakers; hemorrhagic stroke or transient ischemic attack (TIA); ischemic stroke with severe clinical disorders; epilepsy; history of heart, lung, and liver; kidney failure; and cognitive impairment.

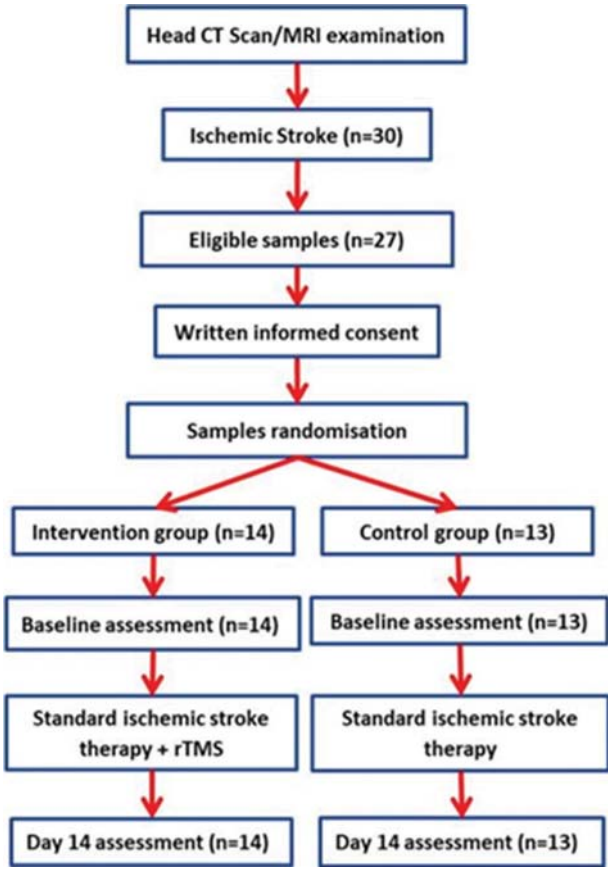

Figure 1: Study flow

Randomization

The study samples were recruited from the inpatient unit of stroke ward in one hospital. Randomization was performed with random pick-up from the samples name list after the confirmation of patient eligibility before the study begun. Samples were randomly assigned into one of two groups, i.e., intervention group (standard ischemic stroke therapy + rTMS) and control group (standard ischemic stroke therapy alone). Samples were identified by sequential numbers assigned at randomization. The sample assignment notice was sent only to physician who performed the rTMS intervention. The patients were blinded to group assignment until the study was completed.

Data collection methods

Data are obtained in the primary way. Samples were given an explanation of the study. If they agreed, they have been asked to sign an informed consent following the study. History taking of the study sample was carried out, a physical examination was performed to diagnose ischemic stroke and a definitive diagnosis was established based on a non-contrast head CT scan image assessed by a radiologist. Indonesian version of the Montreal cognitive assessment was performed to exclude severe cognitive impairment and examination of functional motor skills with the Stroke Rehabilitation Assessment of Movement (STREAM) score for motor impairment grading.

Repetitive TMS

The treated samples were treated with rTMS intervention after they were hospitalized, in 2 cycles. Each cycle is carried out for 5 consecutive days with a delay of 2 days and then followed by the 2nd cycle for 5 consecutive days. rTMS targets stimulation in the primary motor area (M1). In the hemisphere area of the ipsilesion cerebral, rTMS is carried out with a high frequency of 5 Hz while in the contralesion hemisphere a low-frequency stimulus of 1 Hz is given. Stimulation is given 3 beats (pulse) per 1 s burst (stimulus). Each hemisphere received 20 series of stimulus for 10 s followed by a resting interval of 2 s between stimulations so that each hemisphere cortex received 600 stimulus. The intensity of the ipsilesion hemisphere stimulus is 75% and the contralesion is 90% motor threshold (MT).

Data analysis technique

The data obtained were analyzed using the SPSS 21 statistical test that uses Pearson's statistical test. Assessment of hypothesis testing was stated as significant if $p \leq 0.05$.

Ethics statement

The study was performed following the principles of the Declaration of Helsinki. Participation in the study was fully voluntary and anonymous and was approved by the Ethics Commission for Medical Research of Faculty of Medicine, Universitas Hasanuddin.

Results

Demographic data and patient characteristics

Table 1 shows the distribution of subjects by sex, age, time of onset of stroke, degree of motor impairment, the STREAM score with a description of several domains, and BDNF serum levels. The study subjects consisted of 14 (54.16%) males and 13 (45.84%) females with an overall age average of 58.87 (±8.43) which there was no significant difference in mean age in the treatment and control groups (p = 0.332). The mean onset of stroke in the treatment and control groups was 40.43 (±37.502) and 45.62 (±33.604) days and this difference was not significant (p = 0357). The mean BDNF serum levels did not differ in the two groups (p = 0.409), which were 3.0170 (±1.313) in the treatment group and 3.688 (±1.019) in the control group. There was no significant difference between the treatment group and control group for the first measurement value on the paresis side variable, STREAM EU score, STREAM LE score, and STREAM mobility score.

Table 1: Characteristics of the study sample

Variables	Treatment (n=14)	Control (n=13)	p-value
Gender			
Male (n=14; %)	6 (42.85)	8 (61.53)	0.332
Female (n=13; %)	8 (57.15)	5 (38.47)	
Age (year; mean ± SD)	54.50 (± 8.591)	62.15 (± 6.530)	0.357
Onset (day; mean ± SD)	40.43 (± 37.502)	45.62 (± 33.604)	0.706
STREAM score			
UE (mean ± SD)	9.50 (± 3.156)	6.69 (± 4.785)	0.179
LE (mean ± SD)	11.00 (± 2.882)	8.23 (± 3.833)	0.379
Mobility (mean ± SD)	11.50 (± 4.911)	10.08 (± 5.361)	0.550
Total score (mean ± SD)	32.14 (± 10.007)	25.00 (± 13.080)	0.386
Degree of motor impairment			
Severe (n; %)	4 (28.57)	8 (61.54)	0.98
Moderate (n; %)	9 (64.28)	3 (23.08)	
Mild (n; %)	1 (7.15)	2 (15.38)	
BDNF serum levels (mean ± SD)	3.0170 (± 1.313)	3.688 (± 1.019)	0.409

mRS: Modified Rankin Scale, UE: Upper extremity, LE: Lower extremity, STREAM: Stroke Rehabilitation Assessment of Movement, BDNF: Brain-derived neurotropic factor, SD: Standard deviation.

Comparison of the STREAM scores on the basic motor skills of upper extremity (UE) and Lower extremity (LE) between the treatment and control groups

Table 2 shows that the mean score of the basic UE motor skills in the treatment group (9.50 [± 3.156]) and controls (6.69 [±4.78]) in the measurement I. There was an increase in mean motor score measurement II in the two study groups, but the difference in measurements I and II for the basic UE motor skills score in the treatment group (3.07 [± 1.33]) and controls (2.77 ± 2.28) did not show significant differences (p = 0.204) and the mean score of LE basic motor skills in the treatment group (11.00 [± 2.88]) and controls (8.23 [± 3.83]) in measurement I. It also showed an average increase in motor score measurement II in both the study groups, but the difference in measurements I and II for the score of LE basic motor skills in the treatment group (3.86 [±2.41]) and controls (2.54 [± 2.18]) did not show a significant difference (p = 0.325).

Comparison of mobility scores between the treatment and control groups

Table 3 shows an analysis of the comparison of changes in the STREAM score in the component

Table 2: Analysis of the comparison of the STREAM scores on the basic motor skills of UE and LE in the treatment and control groups

Basic motor skills	Treatment (n=14)			Control (n=13)			p-value
	Measurement I	Measurement II	Δ score	Measurement I	Measurement II	Δ score	
UE (mean ± SD)	9.50(± 3.156)	12.57(± 3.20)	3.07(± 1.33)	6.69(± 4.78)	9.46(± 4.61)	2.77(± 2.28)	0.204
LE (mean ± SD)	11.00(± 2.88)	14.86(± 2.35)	3.86(± 2.41)	8.23(± 3.83)	10.77(± 3.61)	2.54(± 2.18)	0.325

Source: Primary data; statistical analysis was carried out by Chi-square test. LE: Lower extremity, UE: Upper extremity.

Table 3: Comparison analysis of the treatment and control groups mobility ability scores

Mobility skills	Treatment (n=14)			Control (n=13)			p-value
	Measurement I	Measurement II	Δ score	Measurement I	Measurement II	Δ score	
Mobility (mean ± SD)	11.50 (± 4.91)	17.07 (± 5.41)	5.57 (± 1.74)	10.08 (± 5.36)	12.08 (± 4.77)	2.00 (± 1.53)	0.014

Source: Primary data; statistical analysis was carried out by Chi-square test.

mobility of ability in the treatment and control groups. There was an increase in mobility ability scores in both groups, with an average difference of increase (5.57 [±1.74]) in the treatment group and (2.00 [± 1.53]) controls, cross-tabulation test on the two difference values showed a significant difference (p = 0.014).

Comparison of degree motor impairment between the treatment and control groups

Table 4 shows that there was a tendency for changes in the degree of motor impairment scores in the two groups with the average score difference (12.93 [±4.73]) in the treatment group and (7.31 [± 5.67]) in the control group. After the significance test of cross-tabulation on the two difference values showed a significant difference (p = 0.05).

Comparison of serum BDNF level in the treatment and control groups

Table 5 shows an analysis of the comparison of BDNF serum levels in the treatment and control groups in measurements I and II. From Table 5, the mean serum BDNF level in measurement I in the treatment group was 3.017 ng/ml (±1.313), while in the control group ranged 3.688 ng/ml (±1.019) with the cross-tabulation test did not show significant differences between the two groups. The mean difference in serum BDNF levels was (0.12 ng/ml [±1.072]) in the treatment group and (0.09 ng/ml [±0.837]) in the control group. Cross-tabulation test on the difference between the two study groups did not show a significant difference (p = 0.409).

Significance of serum BDNF levels on improving motor skills in the treatment and control groups

Table 6 shows the relationship between changes in serum BDNF levels in improving motor skills in the study group. From Table 6, the results of the Spearmen correlation test on the study data did not show a significant relationship between changes in serum BDNF levels and improvement in motor skills in the two study groups.

Discussion

Functional stimulation of the cerebral cortex, both magnetically, is one of the restoration techniques that can improve patient's motor abilities, especially if accompanied by intensive motor exercises [3]. The principle of cortical facilitation with this stimulus follows the Hebbian neural network theory that activation of certain nerve cells will affect the connection of surrounding neural networks. Excitatory stimulation in the primary motor cortex region of the ipsilesion brain can increase functional synaptic connections with neurons in the pre-motor and secondary motoric regions. Otherwise, inhibitory stimulation in the primary motor area of the contralesion brain will reduce contralesion motor neuron activity and give ipsilesion nerve tissue the opportunity to strengthen synaptic bonds. Furthermore, ipsilesion stimulation in areas other than the primary motor area is also thought to induce changes in synaptic connections between brain regions.

A total of 27 samples met the inclusion criteria to be the samples of the study. Furthermore, the samples were divided according to the order of visits to the brain clinic in two groups, namely, the treatment group (n = 14) and control (n = 13) until the total sample fulfilled. Samples in the treatment group received rTMS intervention in 2 cycles. In the ipsilesion cerebral hemisphere area, rTMS is carried out with a high frequency of 5 Hz while in the contralesion hemisphere is given a low-frequency stimulus of 1 Hz, which refers to the interhemispheric balance theory [5], [6]. The intensity of ipsilesion stimulation is 75% and contralesion 90% MT.

The samples in the control group only received standard therapy, namely, medical and physiotherapy. Two methods of sham rTMS for the control group often used in the rTMS study are as follows: (1) Control samples were given rTMS with a frequency of <1 Hz with intensity below the MT (sub-MT) [7] and (2) the control sample received rTMS with the location of the coil plate vertical to the scalp or did not touch the scalp but the sample still heard the sound "ta..ta.ta" when stimulation was carried out [6], [8]. One rTMS study in subacute ischemic stroke patients suggested that even repeated stimulation from low-frequency rTMS <1 Hz can still have an inhibitory effect on stimulated areas [9], [10].

Table 4: Comparative analysis of the degree motor impairment in the treatment and control groups

Motor skills disorder (Mean±SD)	Treatment (n=14)			Control (n=13)			p-value
	Measurement I	Measurement II	Δ score	Measurement I	Measurement II	Δ score	
Motoric impairment degree	32.4 (±10.07)	45.07 (±9.27)	12.93 (±4.7)	25.0 (±13.08)	32.31 (±11.89)	7.31 (±5.6)	0.05

Source: Primary data; statistical analysis was carried out by Chi-square test.

Table 5: Comparative analysis of serum BDNF levels in the treatment and control groups

BDNF serum level, ng/ml	Treatment (n=14)			Control (n=13)			p-value
	Measurement I	Measurement II	Δ score	Measurement I	Measurement II	Δ score	
BDNF serum (mean±SD)	3.017 (±1.313)	3.136 (±1.41)	0.12 (±1.072)	3.688 (±1.02)	3.781 (±2.13)	0.09 (±0.837)	0.409

Source: Primary data; statistical analysis was carried out by Chi-square test. BDNF: Brain-derived neurotropic factor.

Age and gender are often associated with the prevalence of ischemic stroke. In this study, the variable control was carried out in the age group, risk factors, and other factors, such as therapy obtained by the sample. Statistical analysis on demographic data obtained $p > 0.05$, which concluded that the demographic variables did not differ significantly in the two groups. These results also show similar things about demographic data in the previous study. Data on the 2011 stroke guidelines from Pokdi Perdossi showed that the highest incidence of stroke was in the age range of 45–64 years (54.2%) and the incidence in male was higher than in female and also similar to the previous stroke and rTMS studies conducted by Hosomi *et al*. which showed that the average age of the study samples was 62.4 (±15.5) [7].

Table 6: Analysis of the significance of serum BDNF levels on improving motor skills in the treatment and control groups

Spearman's rho		Delta BDNF serum	Delta KMF
Delta BDNF serum	Correlation coefficient	1.000	−0.063
	Sig. (two tailed)	-	0.756
	n	27	27
Delta KMF	Correlation coefficient	−0.063	1.000
	Sig. (two tailed)	0.756	-
	n	27	27

Source: Primary data; statistical analysis was carried out by Chi-square test. BDNF: Brain-derived neurotropic factor.

Ischemia in the brain triggers a change in the organ structure of brain tissue that influences the mechanism of recovery motor skills after a stroke. The current hypothesis states that local reorganization occurs due to takeover of functions or vicarization [11], tissue damaged by intact tissue in peri-infarct regions, this mechanism is also known as peri-regional organization. The stages of local reorganization in brain tissue take place in the acute-subacute phase for approximately 1–12 weeks and facilitate spontaneous functional recovery [4]. Until the end of the 12th week, neuron in the ipsilesion area continued to show a decrease in excitation ability and survival indicating the possibility of other mechanisms involved in restoring motor abilities after stroke that could potentially involve the secondary motor cortex [12].

This study uses an assessment instrument of the Stroke Rehabilitation Assessment of Movement (STREAM) to assess the degree of motor impairment after stroke [13]. The STREAM instrument has three assessment subscales, namely, voluntary movement of superior extremities, voluntary movements of inferior extremities, and basic mobilities, such as clenching, grasping, lying down, sitting, and walking. The maximum total score for all subscales is 70. The basic motor ability of the samples was seen in the STREAM subscale scores of the superior and inferior extremities. In general, the data of this study showed an increase in all scores of the STREAM subscales in both groups, but the results of statistical analysis of these data showed significant differences only in the components of motor mobility and not in basic motor abilities. The mean score of the inferior extremity STREAM measured on the 1st day and day 10 was higher than the superior extremities in both groups. This is parallel with the study conducted by Li *et al*. who assessed the effect of rTMS on improving motor function in subacute ischemic stroke. In his study, Li reported that improvement in motor dysfunction in the superior extremities tended to be slower than recovery in the inferior extremities [6]. A different matter was suggested by Chang *et al*. in a study conducted to assess the long-term effect of rTMS on recovery of motor function in 28 subacute ischemic stroke patients. From the study data, Chang concluded that there was no significant difference found in the hand and foot motor skills after being given rTMS therapy. The difference in results obtained by Chang *et al*. with this study can be explained because of the different stimulation methods used. Chang *et al*. used rTMS with a high frequency of 10 Hz and 90% MT intensity only in ipsilesion [8]. The balance theory of interhemispheric suggests that stimulation on one side of the hemisphere can interfere with transcallosal mutual inhibition-excitation in both of brain hemispheres [6]. Motor deficits after ischemic stroke result from a loss of inhibitory effect on the contralesion hemisphere cortex [5]. rTMS facilitates reorganization of the motor cortex through regulation of neuron and synaptic excitability [3].

A systematic review study of the Cochrane data base regarding the efficacy of rTMS and improvement in functional ability after stroke suggested that administration of rTMS interventions did not show a significant increase in clinical outcome improvement as measured by the Barthel index in stroke patients [14]. This systematic review study further concludes that existing scientific evidence does not suggest the use of rTMS as a routine therapy after stroke, although this study still provides recommendations for further research on the therapeutic effects of rTMS on improving motor skills in ischemic stroke patients. However, the data obtained from the results of this study showed that repeated

TMS interventions for 10 consecutive days with 5 Hz ipsilesion stimulation frequency and 1 Hz contralesion and 75% intensity affected the motor skills of the first attack ischemic stroke patients with onset <6 months.

Efforts were made to reduce the bias toward the results of the study obtained, namely, by "matching" the demographic variables of age, gender, onset, risk factors, and standard therapy including the use of drugs. The limitation of this study is the difficulty of controlling physiotherapy after outpatient care. The assessment of the STREAM score is only carried out by one person so that the scores obtained can be overestimated or underestimated.

In the studies of Schmolesky et al and Cho et al that involves measuring and validating the basal serum of BDNF values stated that the levels of basal BDNF values were ranged from 22.94 ± 9.12 ng / mL - 24.95 ± 7.28 ng / ml in healthy male and female populations [15]. Low serum BDNF levels are found in people with a tendency toward behavioral mental disorders, such as anxiety, panic attacks, depression, memory disorders, and schizophrenia. The other studies have also linked low serum BDNF levels with Alzheimer's and diseases associated with vascular disorders.

BDNF is a factor that plays an important role in the mechanism of neurogenesis and synaptogenesis, especially after brain tissue injury, such as ischemic stroke. BDNF levels are found in serum and peripheral plasma circulation. Research on serum BDNF levels in stroke patients has also been carried out [7], [16]. In general, from these studies, it was concluded that the factors that influence serum BDNF levels are gene BDNF polymorphism so that changes in serum BDNF levels after rTMS therapy will be affected in a way by BDNF gene polymorphism [16], [17].

The plasticity character of the brain is used in the principle of remodeling and recruitment in the area after ischemia. There are three main forms of reorganization that have been described: (1) Increase cortical excitability in the remote cortex, but still connected to the core of the stroke; (2) reduce lateralization activity; and (3) somatotopic modification in intact cortex regions [3]. Hoping that stimulation with different frequencies in both brain hemispheres can trigger rebalancing of brain excitation-inhibition and affect motor improvement. Changes in serum BDNF levels are also expected to affect neurogenesis and synaptogenesis so that cortical somatotopic remodeling in both hemispheres can occur. The results of statistical tests conducted on this study data indicate that there is an improvement in the degree of motor impairment after repeated TMS in the treatment group, but this improvement does not related to changes in serum BDNF levels. The results of the same study were also shown in the previous studies [18]. This may be due to many factors that contribute to post-stroke motoric improvement.

A study was carried out in Japan to evaluate the effect of BDNF level in improving superior extremities skills after rTMS therapy. The study was conducted on a total of 62 samples with low-frequency stimulation of 1 Hz in the somatotopic region of the interosseous dorsalis contralesion muscle for 14 days. In another study group, rTMS therapy was combined with standard physical rehabilitation therapy. The clinical outcome of motor ability is measured using the Fugl-Meyer scale and Wolf Motor Function. The peripheral blood samples of the study samples were collected and measurements were taken on polymorphism BDNF, pro-BDNF, and Matrix metalloproteinase (MMP-9) levels. The results of the study concluded that the combination of standard rTMS therapy and physical rehabilitation increased serum BDNF levels and MMP-9 but were not related to improvement in motor skills of the study samples. The researcher also concluded that standard rTMS interventions did not affect BDNF gene polymorphism [7]. In this study, the administration of rTMS therapy was carried out with the same protocol toward all treated samples and did not based on the reference of BDNF gene polymorphism. Another study by Hwang *et al*. also showed that BDNF genotype differences could influence differences in response to rTMS [18]. In future, it may be necessary to take an individual dose of rTMS therapy refer to this BDNF gene diversity.

Conclusion

rTMS has an effect on improving motor ability in ischemic stroke patients on the first attack on ≤6 months which this change is greater in the treatment group than in the control group. Improvement in motor skills does not related to serum BDNF levels in this study. rTMS does not affect serum BDNF levels in ischemic stroke patients. The practical benefit of this study is to support the existence of literature that states the contribution of rTMS intervention as adjuvant therapy in patients with motor stroke impairment after ischemic stroke.

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