The Effectiveness of the Home Rehabilitation Program (HRP) after the Application of Transcranial Magnetic Stimulation (TMS) Post-Stroke

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Abstract. Transcranial Magnetic Stimulation (TMS) for post-stroke patients has been shown to improve motor function in a short period, but no one has yet investigated how post-stroke rehabilitation will provide an optimal effect after additional patient Home Rehabilitation Programs (HRP) is applied. The objective of this study was to determine the efficacy of an additional HRP following TMS application in influencing plasticity and upper motor function post-stroke. RCT's study involved 10 post-ischemic strokes divided into two groups, 5 as a treatment group who received an HRP after TMS 1 Hz and 5 as a control group who received only TMS 1 Hz. Investigate plasticity using BDNF human marker and upper motor function using the Action Research Arm Test (ARAT) and the Wolf Motor Function Test (WMFT) before and after the program was run for 7 days in a row. An independent t-test result showed that there was a significant difference in the effect of upper motor function (ARAT and WMFT) between the treatment compared to the control group with a p-value < 0.05. Increased levels average of BDNF also occurred in the treatment group. The combination of HRP after the TMS indicates a plasticity process that was in line with improved finger motor skills and hand motor function. A strong correlation between increased levels of BDNF with ARAT and WMFT. A HRP after TMS 1 Hz application was more effective in improving the level of BDNF and motor function post- ischemic stroke.

Keywords: Home Rehabilitation Program, Transcranial Magnetic Stimulation, Post-Stroke

1 Introduction

The impact of rising ischemic stroke incidence leads to an increase in health issues, one of which is motor function limitation. It may cause upper extremity weakness, making it

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difficult for a person to carry out daily activities [1]. Transcranial Magnetic Stimulation (TMS) at 1 Hz has been shown to increase brain plasticity and intracortical inhibition in non-lesional brains, as well as improve finger motor skills and hand function [2]. The post-stroke rehabilitation process, which is gradual and takes a long time, necessitates additional rehabilitation efforts from the patient, which can be done at home. A home rehabilitation program (HRP) is a type of home self-training with some specific exercises based on activity principles, focusing on distractions, specific tasks, intense, interesting, collaborative, self-directed, and patient-centered [3]. Exercising for 7 days continuously and on a regular basis can increase the blood supply that carries oxygen to the brain, activating neuronal cells in the brain [4].

The human cerebral cortex contains several highly specialized motor regions that control specific motor functions. There is an area important for hand skills in the pre-motor area (M1) just above the Broca area, which is anterior to the primary motor cortex, which is used for hand and finger movements. Hand movements will become uncoordinated and uncontrolled if this area is damaged by the lesion [5]. Neuronal plasticity in this area can be modulated by a variety of stimuli.

TMS is a treatment that improves neuronal plasticity and motor function by sending electromagnetic waves from the brain to the injured body part and stimulating the cortical part [6]. While the HRP works to increase the stimulation of motor areas in the brain via a patient-performed activity, this then stimulates the restoration of motor control [7]. HRP seeks to identify the best functional movement control strategy to improve efficiency and effectiveness in the rehabilitation of stroke patients. HRP also has a function to optimize learning and encourage daily activities [8]. HRP exercises designed to practice eating skills and three upper extremity motor functions (writing exercises, manipulating cards, and handyman) after application of TMS 1 Hz will optimize plasticity by increasing the level of BDNF and rehabilitation of upper extremity motor functions, as observed with the action. Research Arm Test (ARAT) for motor function and the Wolf Motor Function Test (WMFT) for upper extremity functional ability.

2 Methods

The feasibility of a randomized controlled trial in two groups was assessed using the human marker BDNF and the ARAT for upper extremity motor function, which consists of four elements: grasp, grip, pinch, and gross motor [9] and the WMFT for upper extremity functional ability on 10 respondents who were recruited based on the inclusion criteria. Respondents who signed informed consent in accordance with the ethics committee's requirements. The convenience sampling method was used in this study to randomly divide respondents into two groups: the treatment group (which received HRP for 60 minutes after receiving TMS 1 Hz for 20 minutes in the hospital) and the control group (which received only TMS) for 7 consecutive days (Table 1).

Table 1. The Application of treatment and control groups after ischemic stroke

Group	Intervention	Focus
Treatment group	HRP for 60 minutes after TMS 1 Hz for 20 minutes	Stimulation of movement strategies and stimulation in the M1 motor area, interhemispheric balance, triggering MEP to increase upper extremity motor function
Control group	TMS 1 Hz for 20 minutes	Stimulation in the M1 motor area, interhemispheric balance, triggers MEP to increase upper extremity motor function

An independent t-test using SPSS 23 version software was used to compare the differences in upper extremity motor function between the control and treatment groups. In this study, the statistical significance was set at 5%. Fig. 1 shows the flow chart of participants.

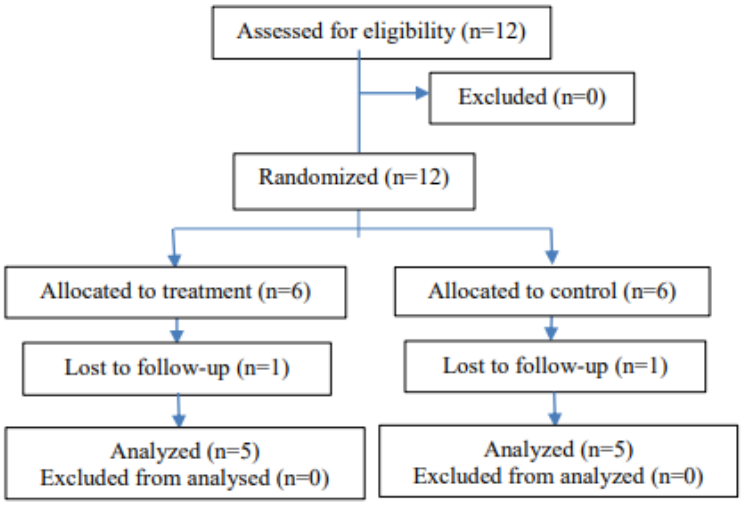

Fig. 1. Participant Flow Chart

2.1 Eligibility Criteria

Post-ischemic stroke patients with upper extremity motor function disorders participated in this study. The Mini-Mental State Examination (MMSE) screening test was tested to respondents with normal vision and hearing, muscle strength of 3 or higher, and the ability to understand commands easily.

2.2 Home Rehabilitation Program (HRP)

The program is based on principles: distraction-focused, task-specific, intense, engaging, collaborative, self- directed, and patient-centered. Patient-centered HRP that include elements of skills, capacities, and motivation that support in motor learning and are consistent with new knowledge [3]. Activities include eating skills, writing exercises, card manipulation, and handyman.

2.3 TMS 1 Hz

TMS at a low frequency of 1 Hz was applied to the contralesionally side's M1 area (1 Hz, 90 percent [rMT], 1,200 pulses). In the motor cortex, a figure-eight coil with a rapid 2 magnetic stimulator delivered the TMS stimulatory signal.

2.4 Research Tools

ELISA (enzyme-linked immunosorbent assay) kit to measure the concentration of BDNF in blood serum, washing buffer (PBS or TBS). The examination uses Human BDNF Immunoassay with DBNT 00 catalog number packaged and distributed by R&D System, Inc. 680 Minneapolis, P253762 United States America.

The ARAT is a valid and reliable measuring tool for assessing upper extremity motor function, which consists of four elements (grasp, grip, pinch, and gross motor) used to measure motor function [9]. A score of zero (0) indicated no movement, while a score of three (3) indicated normal movement. The sum of one item score resulted in four subscale scores: grasp (18 points), grip (12 points), pinch (18 points), and gross motor (9 points). A total scale score of 57, indicates normal performance [10].

The WMFT is a measuring tool that has an excellent ICC (Intraclass Correlation Coefficients) value for evaluating extremity functional activity after an ischemic stroke [11]. The WMFT consists of 15 tasks, and the time spent on each task was measured and added up to determine upper extremity disorders and activity limitations [10]. Average execution time expressed in seconds, calculated by adding the execution times of each task (with a maximum of 120 seconds each) and dividing by the number of tasks. The total score, expressed as a functional ability score (WMFT), is the sum of the 15 items' scores (with an ordinal score of 6 points from 0 to 5). The highest possible total score is 75, with lower scores indicating lower functional levels [12].

2.5 Data Evaluation

All respondents completed a pre-test prior to the treatment and a post-test was conducted with the human marker BDNF, ARAT and WMFT measuring instruments after the treatment was completed for 7 days. To investigate plasticity using observe pre and post-test

level of BDNF, while to describe motor function variables, univariate analysis was used. SPSS 23 was used to analyze all of the collected data. The normality test was measured using the Shapiro Wilk test. The parametric independent t-test was used to compare the influence differences between the control and treatment groups.

2.6 Research Ethical Dimension

The study was carried out in accordance with scientific and ethical principles using no. 3080/b.1/KEPK- FKUMS/XI/2020. Before beginning the research, the researcher explained the research objectives to the respondents and obtained their approval, as evidenced by a signed informed consent form as a participant without coercion.

3 Results

This study was conducted at Pura Raharja Kulon Progo Yogyakarta Hospital, Indonesia with 10 participants who met the inclusion criteria, 5 of whom were assigned to the treatment group and 5 to the control group. Overview of characteristics of respondents as shown in Table 2.

Table 2. Characteristics of the subjects

Characteristics	Treatment group		Control group		p-value
	n = 5	%	n = 5	%	
Age					
45 – 60 years	3	60.0%	1	20%	
60 – 70 years	2	40.0 %	4	80%	0.516
Mean ± SD	56.20 ± 6.419		65.00 ± 4,583		
Gender					
Male	3	60.0 %	3	60%	1.000
Female	2	40.0 %	2	40%	
Lesion point					
Right	5	100 %	2	40%	
Left	-		3	60%	
Characteristics	Mean ± SD	p-value	Mean ± SD	p-value	
Motor function (Pre-ARAT value)	17.80 ± 1.924	0.928	17.00 ± 4.183	0.167	
Upper extremity functional ability	21.00 ± 2.550	0.692	18.00 ± 3.391	0.564	
Plasticity (pre-BDNF)	48468.20 ± 21379.120	0.856	54537.80 ± 20438.093	0.534	

The effectiveness of the home rehabilitation program after the application of Transcranial Magnetic Stimulation post stroke to determine BDNF levels as an indicator of plasticity, motor function and upper extremity functional ability showed significant influences as shown in Table 3. While the strong correlation between increasing levels of BDNF and improving motor function and upper extremity functional ability is indicated by the increase in ARAT and WMFT values can be seen in Table 4.

Table 3. Effectivity treatment in plasticity, motor function, and functional ability upper extremity post-stroke between the control group and the treatment group

Groups	Pre-post mean	Mean difference ± SD	p-value
BDNF (mg/dl)*			
Treatment group	48468.20 – 65730.20	17262.00 ±10418.808	0.005
Control group	54537.80 – 51179.80	-3358.00 ± 5781.060	
Upper extremity motor function (ARAT)			
Treatment group	17.50 – 39.33	21.83 ± 1.906	0.0001
Control group	17.00 – 20.20	3.2 ± 0.619	
Upper extremity functional ability (WMFT)			
Treatment group	20.83 - 41.50	20.67 ± 6.947	0.001
Control group	18.00 - 22.00	4.00 ± 1.581	

*BDNF in healthy people of 9042 – 57830 pg/ml.

Table 4. Correlation between plasticity and motor function and functional ability upper extremity post-stroke

Correlation between variables	p-value	Correlation
Correlation between plasticity and motor function	0.042	0.650
Correlation between plasticity and upper extremity functional ability	0.006	0.792

4 Discussion

Many studies showed the importance of home rehabilitation programs (HRP) after hospital treatment as an effort to optimize the restoration of function. In addition, various post-stroke interventions in hospitals are widely carried out, including the application of TMS. TMS uses electromagnetic induction to create small electrical currents in the brain [13]. TMS at 1 Hz was used to stimulate ipsilesional M1 and inhibit M1 contralesions. It has been demonstrated that both approaches improve motor function. The contralesional area of M1 plays a compensatory role in motor recovery, particularly in the early post-stroke period [14]. The combination of HRP after TMS showed good effects, not only improving

the plasticity process but also being shown to improve motor function and upper extremity functional ability.

Home rehabilitation to optimize the post-stroke restoration process have been shown to be effective in influencing plasticity and clinical outcomes in the function abilities. The analysis showed that the effect of motor function and upper extremity motor function obtained a value of 0.0001 and 0.001, respectively. That are indicating that there was a different effect on the average value of motor function and upper extremity motor function in post- ischemic stroke patients. The difference in the effect test was calculated using the average difference between the pre and post-test data, the difference means in the motor function and upper extremity functional ability of the treatment and control groups was 21.83 points/57 points and 20.67 points/75 points, respectively (the MCID value was obtained 3 points). There is a different effect on the average value of motor function in the treatment group (added by HPR after applied TMS 1 Hz) that is significantly more effective than in the control group (TMS 1 Hz only), both statistically and clinically.

The home rehabilitation program's repetitive and focused movements are capable of forming new connections between motor systems and activating spinal motor neurons, which are the foundation of stroke recovery. Exercises that use specific movements and are repeated can activate the peri-infarct cortex, which can improve upper extremity motor function in patients who have had a stroke. A simple motor task training in M1 excitability changes caused the MEP amplitude to increase in focus (specifically for the trained muscle) demonstrating that motor training can affect direction coding at the M1 level [15]. HRP has an effect on the level of daily activity [16]. The addition of HRP has also been shown to significant effects on the study. Rehabilitation programs are able to increase the stimulation of motor areas in the brain that can stimulate motor control recovery [7], integrate the motivational component with skill and capacity through impairment improvement, and confidence through the liveliness involved in task selection, problem solving, and decision making [17]. Patients adapt in a variety of activities thus giving to try to solve problems during functional tasks more effective in improving upper extremity function and performance of daily activities [18].

According to the theory of interhemispheric competition, some of the motor function deficits in post-stroke patients are caused by a loss of inhibition to the contralateral cortex as a result of injury. TMS at 1 Hz can aid in the reorganization of regional cortical functions by regulating cortical excitability, which affects neural function. In general, TMS 1 Hz can inhibit cortical hemisphere excitability stimulation, facilitate interhemispheric excitability balance, increase contralateral hemisphere excitability, or decrease contralateral hemisphere excitability to promote motor function restoration [19]. TMS 1 Hz can improve brain plasticity and inhibition intracortical in a brain that does not have lesions, also having a positive effect on finger motor skills and hand function [2]. The results of these studies also showed an increase in BNDF levels as one of the markers of the plasticity process. The statistical tests showed a significant influence (p-value < 0.05) with an average increase in

BDNF levels of 17262.00 mg/dl in the treatment group compared to the control group which tended to remain even lower in BDNF levels.

The combination of HRP after the TMS indicates a plasticity process that was in line with improved motor function and upper extremity functional ability. The correlation test showed significant and a strong correlation between increased levels of BDNF with ARAT (motor function) values by 0.650 and WMFT (upper extremity functional ability) by 0.792. The plasticity process has optimized motoric performance. TMS 1 Hz can improve brain plasticity and intracortical inhibition in non-lesion brains, also having a positive effect on finger motor skills and hand function [2]. Stimulation through exercises to do daily activities at home (writing exercises, manipulating cards, and handyman) becomes a learning to improve their functional abilities easily. Increased activity in the lesioned hemisphere's primary sensorimotor and motor areas is important for increasing functional activity. Task-oriented training causes cortical reorganization based on motor control and motor learning, which contributes to improved upper extremity motor function in patients with post-ischemic stroke [20].

Related to the correlation between the value of BDNF as an indicator of plasticity was also strongly related to the value of ARAT which indicates an increased in motor function and WMFT which indicates an increased in upper extremity functional ability. One marker is BDNF, a protein that has a central role in cortical plasticity that influences post-stroke behavioral improvements. BDNF has important functions in neurodevelopmental differentiation, axon growth, synapse plasticity and nerve repair [21], decreased infarct volume, improvement of motor function, and increased levels of MK and BDNF, increased proliferation of astrocytes, increased angiogenesis and reduction of nerve apoptosis and oxidative stress [22]. BDNF acts by binding to the tropomiosin kinase receptors (TrkB) in the MAPK and PI3K-Akt pathways, which have positive effects for neuronal proliferation, differentiation, development of synapses of nerve cells, inhibiting inflammation, neurotoxicity as well as neural apoptosis [18],[23] and further contribute to promoting synaptic plasticity in learning and memory [24].

Following an evaluation that included a combination a home rehabilitation program and transcranial magnetic stimulation at 1 Hz for 7 consecutive days, the results revealed an increase in plasticity and upper extremity motor function from the patient's initial difficulty carrying out activities independently that required HRP to train voluntary movements so that they could in still synergistic patterns in the brain. Grasping and raising the hand necessitates strength and cooperation between the flexor and extensor muscle components obtained from the HRP so that they can carry out activities independently.

Meanwhile, patients who received only TMS 1 Hz intervention saw an improvement in upper extremity motor function. However, because the patient's motor skills were not trained to produce movement, the patient still has difficulty performing activities independently, where neuroplasticity should be stimulated through HRP to improve motor function abilities in post-ischemic stroke patients.

Practical Implications. Stroke risk can be influenced by age and gender. An imbalance in the interhemisphere occurred during a stroke, impairing motor function. The combination of home rehabilitation programs (eating skills, writing exercises, card manipulation, and handyman) and TMS has been shown to have a good effect in improving post-stroke function. Both statistically and clinically that the addition of 1 Hz TMS and HRP can significantly improve plasticity, upper extremity motor function and functional ability in post-ischemic stroke patients (the effect will be felt by the patient directly). TMS at 1 Hz provided stimulation to improve motor function by facilitating interhemispheric balance.

The use of HRP as a task or exercise involving holding, grasping, pinching, and gross motor skills caused movement in the fingers and hands (stimulating the M1 area). The resulting movement may have increased muscle contraction and strength, resulting in improved upper extremity motor activities.

Research Limitations. Even though the time intensity had been determined and decided, the researchers could not control the respondent's compliance, whether all the respondents did the exercise for the same duration of time at the time HRP was used.

5 Conclusion

Combination of home rehabilitation program and TMS 1 Hz was a significant difference in the effect of plasticity, motor function and upper extremity functional ability post ischemic stroke compared to the control group with p-value < 0.05. Increased levels of BDNF also have a strong correlation in motor function and upper extremity functional ability.

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