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Research Article

Corticomotor excitability after two different repetitive transcranial magnetic stimulation protocols in haemorrhagic stroke patients

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ABSTRACT

Intracerebral haemorrhage (ICH) or haemorrhagic stroke can be managed medically or by surgical evacuation of the hematoma. However, several authors have reported no significant difference when compared between both interventions in haemorrhagic stroke patients. We aimed to assess the use of Transcranial Magnetic Simulation (TMS) as supportive of medical and surgical interventions to assist the rehabilitation process in haemorrhagic stroke patient. A randomized control trial was performed on twenty nine patients and randomized into three groups; (1)Facilitatory, (2)Inhibitory and (3)Sham group. Patient underwent two weeks of TMS Stimulation protocol for total of 10 sessions. The pre and post Motor Evoked Potential (MEP) reading between groups were compared and analyzed. Our result indicated that regardless of patient's age and ICH clot size, the improvement in MEP score after TMS facilitatory protocol was significantly higher compared to the Sham protocol group ($p = 0.02$). Such correlation however, was not observed in the inhibitory protocol group ($p = 0.175$). Collectively, our finding had demonstrates TMS potential as a safe and non-invasive tool for supportive management of ICH stroke as patients and that patient with stable ICH will have better motor function recovery post rTMS facilitatory protocol regardless of their age and clot size.

1. Introduction

Transcranial magnetic stimulation (TMS) has recently attracted attention as a new non-invasive neural tissue simulation method for the rehabilitation of stroke patient [1]. Recovery from hemiparesis post stroke likely to involve the motor learning processes [2]. At the cellular or molecular level, learning motor skills is associated with neural plasticity mediated in part by long- term potentiation (LTP) and long-term depression (LTD) [3]. LTP is defined as long lasting synaptic enhancement, whereas LTD by the decrease of synaptic activity, both mediated by AMPA and/or NMDA receptors [4]. LTP and LTD like changes can be induced in healthy and stroke patients using various TMS protocols through application of low frequency trains of repetitive transcranial magnetic stimulation (rTMS) (inhibitory protocols) or high frequency rTMS stimulation (facilitatory protocols). Inhibitory rTMS can lead to a significant decrease in cortical excitability that lasts beyond the time of stimulation [5]. In comparison, high frequency stimulation of rTMS can lead to significant facilitation of cortical excitability [6]. Interestingly, rTMS may also exert long-lasting effects through gene induction linked to neuroplastic changes [7]. Thus, in the context of post-stroke reorganization, modulation of motor networks with TMS may serve a complementary role to traditional therapies in enhancing post stroke motor recovery.

Repetitive stimulations can change the excitability of the cerebral cortex at the stimulated site and also at the remote areas along the functional anatomical pathway [8]. Motor Evoked Potential (MEP) has been shown to be useful as a quantitative physiologic measurement for both diagnostic and therapeutic in the stroke population. For the diagnostic purposes, it has been published in many studies that presence of MEP in the early phase of stroke is a good indication of motor recovery in a stroke patient, suggesting a valuable marker of for prognostication of stroke recovery [9]. It was also suggested that the MEP is a sensitive investigation marker for quantitative evaluation of motor recovery in stroke patient [10]. In one of the largest group of study examining MEP in 118 S patient following the progression of stroke survivor up to 12 months, the presence of MEP in a post-stroke patient

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was associated with better survival and functional recovery [11]. Likewise, an absence of MEP will indicates poor recovery and higher rate of mortality. Therapeutically, according to a systematic review done to evaluate the effectiveness of rTMS in stroke population, an encouraging evidence suggested that rTMS helps to improve short-term upper extremity function and mortality in chronic stroke. The systematic review however, did not suggest which setting of rTMS (between facilitatory and inhibitory) will benefit stroke patient better.

The disruption of the higher brain function is in direct proportion with the amplitude and frequency given during the therapy. If the stimulation is too low (less than 5 Hertz), inhibition will be dominant, while if stimulation is higher (5–20 Hz), facilitations will be more prominent. (18–22) Suzanne et al. mentioned that in healthy adults, motor cortex excitability is symmetrical between both brain hemispheres and the amount of inhibition from one area of primary motor cortex (M1 area) to the other side of primary motor cortex area is similar [12]. Following a stroke, this M1 area activity will be reduced in the lesion site and increased on the contralateral M1 area. This increase of activity in the contralesional site can increase the transcallosal inhibition signal given to the lesion site which may impair the stroke recovery process in the lesioned hemisphere [13].

Transcranial magnetic stimulation causes changes in neuronal activity via rapidly changing magnetic field at the cortical area stimulated. This leads to immediate and long-lasting effect depending on the frequency given. However, during the process, various factors involved that may influence neuronal changes. These include somato-sensory effect and distinct clicking sound that was produced as the current flow through the coils and causing vibration [14]. To ensure the neuronal changes effects are directly related to magnetic field instead of being produced by indirect effects of TMS, Sham protocol was recommended. This refers to the placebo effect of TMS as patient perceived that TMS pulses were applied to their head with the presence of auditory and somato-sensory perception but without magnetic field frequency given/involved [15].

The aim of this inhibition rTMS (low frequency) is to improve recovery process of the lesion brain side by suppressing the inhibition signal from the non-lesion brain side. On the other hand, facilitatory rTMS (high frequency) to the affected hemisphere will be aiming at increasing the brain activity and thus, also will aid in modulating neuroplasticity and motor recovery. Many literatures study the effect of TMS in ischaemic patient and very few have documented the effect of TMS in haemorrhagic patient. Therefore, the role of TMS in haemorrhagic patient is poorly understood and the mechanism remains to be elucidated. Study by Jang, SH, patient with the presence of MEP or a preserved corticospinal tract showed a better motor outcome than without preservation of descending corticospinal tract [16].

Therefore, this study intended to investigate the corticomotor excitability between the two rTMS settings in haemorrhagic stroke patients. The facilitation protocol was given to the injured brain hemisphere and the inhibition protocol to the contralesional hemisphere and comparison was made on the basis of which modality resulted in better improvement in corticomotor excitability. There is no pain or need of pain relieving method during the procedure and no hospital stay is needed during the procedure. Finding from this study provides informative and communicating evidence on how TMS can help haemorrhagic stroke patient in the rehabilitation process. It can also provide an alternative means to the pharmacological treatment by promoting recovery of motor function and improve quality of life. The hypothesis made are patient who underwent TMS intervention will show better motor function recovery and there will be no different between excitatory and inhibitory protocol compared to Sham or control group.

2. Methods

2.1. Participants

Twenty nine participants were recruited from patients that was admitted in the Hospital University Sains Malaysia due to haemorrhagic stroke and from Neurosurgery Clinic Hospital University Sains Malaysia. After passing through patient's inclusion and exclusion criteria, patients were randomized into three groups. Facillitatory group which underwent facilitation protocol to the injured brain hemisphere, inhibitory group which received inhibitory protocol to the contralesional hemisphere and sham/control group which received sham stimulation on the dominant side. Inclusion criteria include age > 18 years old with stabilized first haemorrhagic stroke at least one month duration. Patient must be able to demonstrate at least 10 degrees of active extension at the paretic index finger (metacarpophalangeal joint) and not involved in other ongoing research for stroke. Exclusion criteria include patients which medically unstable, deformity or disease related the upper or lower limbs other than stroke, inability to sit still for at least 30 min (during preparation and stimulation period), patient who got pacemaker, spinal or bladder stimulator, previous skull opening or trauma, history of epilepsy , and presence of metallic foreign body. The study procedures were approved by the ethics committee of University Sains Malaysia and conducted in accordance with the Declaration of Helsinki. All participants provided informed consent before the experiment

2.2. Study process

Patient safety was assessed based on "screening questionnaire before rTMS form" by the International Federation of Clinical Neurophysiology, the safety and ethical guidelines for the use of Transcranial Magnetic Stimulation (TMS) in clinical practice and research [17]. All patients need to fill out and signed all appropriate consent forms prior to their test. Once patients have consented to participate in this study, an envelope assigning into one of the three protocols were given. The envelope was given by trained hospital staffs responsible to perform the TMS protocol.

2.3. Clot volume identification and calculation

Plain CT brain scan was used as the modality of choice to detect ICH due to fast availability and able to identify acute ICH with great sensitivity and specificity. CT brain scan was performed using the Philips CT scanner. Axial slices of 9 mm (Philip scanner) or 10 mm were done parallel to the orbitomeatal line from the base of the skull up to the vertex. Classification of each hematoma location was based on the location of the epicenter of the hematoma, i.e. lobar (frontal, parietal, temporal, occipital), thalamic, basal ganglia/internal capsule, cerebellar, or brain stem. The presence of an associated intracranial hematoma on the CT scan was noted and classified further into deep or lobar ICH. On the basis of CT classification, developed by Kanaya and Kuroda [18], basal ganglionic hemorrhage was used. ICH volume was calculated based on CT brain image using the ABC/2 method, where A is the maximal hematoma diameter on the axial CT brain with the largest hematoma, B is the maximal hematoma diameter perpendicular to A and C is the number of CT slice with hematoma and multiplied by slice thickness (ignoring slices with less than 25% of hematoma area compared with the reference slice) [19,20].

2.4. Assessment of cortical excitability:

Intervention using rTMS were done using a Double 70 mm Cooled Coil System attached to the rTMS machine. The cooled coil is available in the double 70 mm configuration and can be run for extended periods of time without overheating thus removing the need to replace coils during protocols of stimulation. Effect of the both lesion and non-lesion cortical side were measured using the Motor evoked potential. The optimal site of stimulation (motor hot spot) on the skull was defined as the location where the largest recorded motor evoked potentials (MEP) in the surface electromyography of the first dorsal interosseous (FDI) muscle of the tested upper limb. Surface anatomy for the motor cortex was identified using one of the two methods. First method we measure the distance from nasion to the inion, then we divide into half. 2 cm posterior to the midposition of the arc is the position of central sulcus. Anterior to this point the the primary motor cortex. Second method, by measure 5 cm posterior to the coronal suture is the location of motor cortex.

From there, Rest Motor Threshold (RMT) was established, which was defined as the lowest intensity of stimulation that can produce MEP > 50 ÂμV peak to peak amplitude of the muscle 5 times out of 10 tries with the patient at rest. The process was repeated for 10 times, and the mean of the 10 MEP amplitude was taken as the mean MEP for the FDI on the paretic side. Absent MEP was defined as failing to get MEP > 50 ÂμV peak to peak amplitude of the muscle after 10 tries with the patient at rest. Domains of interest in this study are the changes in physiological neuronal excitability (motor evoked potential) in the paretic hand first dorsal interosseous (FDI). For each subject, mean MEP from 10 MEP recordings was calculated for the side which contralateral to the side of TMS stimulation.

2.5. rTMS protocols

One of the three following protocols was randomly applied for the duration of 2 weeks with total of 10 sessions. 1) Facilitatory to the ipsilesional area: A series of 10 Hz rTMS at 80% RMT to lesional hemisphere M1 primary motor cortex with 50 pulses per train(5 sec) for 20 trains with a 25sec intertrain interval. (10 Hz × 5 s × 20 trains = 1000 pulses) [21]. 2) Inhibitory setting to the contralesional area: A series of focal 1 HZ rTMS to non-lesional hemisphere over the M1 primary motor cortex at 90% RMT intensity for 20 min. (1 Hz × 60 s x20min = 1200 pulses) [22]. or 3) As for the control group or Sham group, patient was given simulated TMS sound without any stimulation or inhibition current given. After each protocol, mean MEP from 10 MEP recordings was recalculated using the same method as above and any new changes in amplitude were recorded. Measurement taken was the changes in physiological neuronal excitability (motor evoked potential) in the paretic hand first dorsal interosseous (FDI).

2.6. Statistical analysis:

The data was analysed by using SPSS version 22. Data was checked for the distributions and outliers. Pre and post mean difference of MEP score was analysed by using ANOVA test analysis to know the effect of the facilitatory and inhibitory stimulation to the lesion and non-lesion side of the brain. The data was further analyzed to compare with the Sham group. Post Hoc analysis was performed using bonferroni.

3. Results

3.1. Demographic

Thirty two participants were recruited during the period from 1 August 2016 till August 2018. Patient who comply with the inclusion and exclusion criteria and consented to the study randomized into three groups. However, only 29 participants completed the TMS protocol intervention. Another three patients were not included in the study due to logistic reason and participants decided to withdrawn from the study. The rTMS protocols were performed by neurological rehabilitation team, department of neuroscience, Hospital Universiti Sains Malaysia. The clinical characteristics of the participants are shown in Table 1. The mean (SD) age of the study sample was 51.86 (1.91) years, and the mean (SD) of the ICH clot size was 22.95 (0.79) cm^3. The mean for the intervention time was 5.76 (0.55) months. From these 29 participants, 16 subjects were male and the other 13 were female. Data was collected for MEP reading pre and post TMS protocol intervention. Mean for the pre TMS MEP reading was 63.71(1.54) and the mean for post TMS MEP reading was 69.71(1.83).

3.2. Cortical excitability

In the Facilitatory protocol, stimulation was given to the lesioned hemisphere of the brain and the inhibitory protocol, stimulation was given to the nonlesional side. The aimed was to investigate the effect or improvement in the MEP reading pre and post TMS intervention. Data statistical analysis, ANOVA Univariate analysis was conducted to determine the mean difference between pre and post of fascilatory, inhibitory and Sham protocols. Results were summarize in Table 2. It was found that MEP score after TMS facilitatory protocol was significantly higher compared to the Sham protocol group ($p = 0.02$). However, post TMS MEP reading for patients underwent facilitatory protocol showed no significant difference compared to the inhibitory protocol ($p = 0.257$). No significant difference was also noted in the inhibitory group when compared to the Sham group for the post TMS MEP reading ($p = 0.175$).

Further analysis of other variables, we interested to know if age, ICH clot size and intervention time has any effect or influence for the motor recovery in patient who underwent TMS stimulation either facilitatory or inhibitory protocol. There was no significant difference for patients with different age, ICH clot size and different time period for intervention time for TMS protocol. Comparing with all three group (facilitatory group, inhibitory group and Sham group), the result showed no significant improvement in the MEP reading post TMS protocol stimulation.

4. Discussion

Transcranial magnetic Stimulation is a non invasive tool and can be performed safely without any risk involved. The utilization of both facilitatory and inhibitory repetitive Transcranial Magnetic Stimulation (rTMS) protocols was successfully done without any unwanted detrimental side effects in all subjects and all recording of MEP were accomplished successfully. The present study compared three different groups which underwent three different protocols. MEP reading pre and post stimulation was evaluated to identify which group of patient may benefit from rTMS protocols. Many studies have proven that facilitatory protocol will improves motor functional status post rTMS [23]. Finding from this study produced similar result in a way that patient showed an improved functional outcome following rTMS stimulation. Significant improvement was observed in patient receiving facilitory protocols compared to the control group especially if the procedure was performed at the early stage of the disease process. This is due to the reserve neuronal capacity to regenerate and promote better motor function recovery. However, overall data analysis showed no significant difference in the change or improvement in MEP reading when compared across three groups. Kim et al [24] successfully showed that a single session facilitatory rTMS to the affected hemisphere can enhance the MEP of that side with a larger improvement in MEP amplitude compared to a sham rTMS. A similar finding was reported in this study.

Inhibitory protocol involved stimulation to the contralesional site of the cerebral hemisphere. This stimulation is to decrease the inhibitory connection from the non-lesional hemisphere to the lesional cerebral hemisphere. Therefore, motor functional recovery can take place and muscle power will improve. In this study, there was no significant improvement in the muscle power in the inhibitory protocol group. MEP reading post TMS stimulation in ICH patient has limited improvement and not statistically significant compared to the control group. Studies

Table 1
Demographic and clinical data for patients in the Transcranial Magnetic Stimulation (TMS) group Variables.

	Facilitatory Group, Mean (SD)	Inhibitory Group, Mean (SD)	Sham Group Mean (SD)	Total,	P Value
Patients, N (%)	12 (41.4%)	9(31%)	8(27.6%)	29	
Gender, N (%) Male Female	6 6	5 4	5 3	16 (55.2%) 13 (44.8%)	
Age (years), Mean (SD)	52.16 (3.32)	52.7 (3.3)	50.7(3.59)	51.86 (1.91)	0.931
Clot Size (cm3), Mean (SD)	23.27 (1.25)	22.93 (1.59)	22.51 (1.49)	22.95 (0.79)	0.957
Intervention time, (months), Mean (SD)	5.58 (0.92)	5.78 (1.01)	6.0 (1.07)	5.76 (0.55)	0.940

SD: standard deviation

Table 2
MEP values for three different groups and changes in the MEP values post rTMS protocol.

Group	Pre rTMS MEP, mean (SD)	Post rTMS MEP, mean (SD)	Mean (95% CI)	Mean Different (95% CI)	P value
Facilitory Protocol	65.27 (2.52)	74.68 (2.98)	73.16 (70.39,75.93)	1 vs 2: 3.75 (-1.63,9.13)	0.257
				1 vs 3: 8.28 (2.67,13.7)	0.02
Inhibitory Protocol	60.71 (2.81)	66.50 (2.76)	69.41 (66.17,72.65)	2 vs 1: −3.75 (−9.13,1.63)	0.26
				2 vs 3: 4.53 (-1.332,10.4)	0.175
Sham Protocol	64.75 (2.65)	65.88 (3.02)	64.88 (61.50,68.25)	3 vs 1: −8.286 (−13.7,-2.88)	0.02
				3 vs 2: −4.53 (−10.4,1.33)	0.175

rTMS: repetitive Transcranial Magnetic Stimulation.
SD: standard deviation.
Vs: versus.
*analysis using ANOVA test, post hoc analysis using bonferroni.

have proven that in the ICH patients, corticospinal tract was disrupted or destroyed once the bleeds occur [25]. Therefore, most likely, connection that involved with the inhibitory pathway also was affected. Limited inhibition from the non lesional cerebral hemisphere results in the minimal effect of rTMS in ICH patient. Previous studies showed better recovery in ICH stroke patient compared to the ischaemic patient [26].

In theory, younger patient will has better motor recovery due to the better adaptive neural capacity post stroke insult [27]. Correlate with our findings, age and gender showed no significant influence when comparing across three different groups. However, younger patient tend to be more motivated and more compliant to the treatment protocol. Similar findings were found for effect of ICH clot size and intervention time. There are studies investigate the effect of rTMS even after 11 years post stroke insult. Studies showed that recovery could take place for extended time period and rTMS can be considered for therapy of chronic stroke [28]. Intracerebral heamatoma clot size smaller than 30 cm^3, without evidence of midline shift and mass effect can be safely managed medically. Within first three hours of symptoms onset, about 73% of patients will have some degree of hematoma enlargement and ICH clot size enlargement can occur up to 12 h after onset [29]. Bigger ICH clot size is correlated with poor outcome and worse neurological symptoms. Investigating the effect of rTMS in ICH patients, regardless the ICH clot size, our data showed no significant different in the MEP values pre and post TMS protocol. This study demonstrated that smaller ICH clot size will not produce any better post TMS MEP reading compared to the control or Sham group. Patients with bigger ICH clot size noted to have more prominent hemiparesis and significant muscle weakness. Therefore, we found in facilitatory protocol, patient with larger ICH clot size produced bigger MEP reading difference or improvement compared to the patients with smaller ICH clot size.

Cortical stimulation in stroke patients can be achieved by both invasive and non-invasive method. Both methods have shown a promising result in improving motor recovery in the stroke population. The non-invasive method is much preferred as it has proven to be useful tool to safely and painlessly examine cortical and corticospinal physiology. Subsequently, non invasive tool will improve compliant. Neuronavigation rTMS system is a method of applying rTMS with real-time visualisation and feedback of coil position to improve targeting and stimulus delivery with better precision [30]. We implemented superficial surface marking to identify the motor area and subsequently location for rTMS protocol. However, no studies have clearly explained or prove whether neuronavigation rTMS is superior to the superficial surface marking.

Some researchers argued that low-frequency rTMS can decrease the excitability of the non-lesional area, this will lead to poor hand function to the non-paretic side [31]. However, a recent meta-analysis in May 2014 found contradicting evidence to this theory and stated that no side effects found in the healthy hand after rTMS [32]. On the other hand, the meta-analysis also noted increased risk of seizure in facilitatory setting of 20 Hz or 25 Hz with set at 120–130% of resting motor potential. Luckily, the risk of developing seizure in rTMS had been reduced to very minimal since the introduction of the rTMS guideline, safety limit and safety questionnaire.

Our finding suggests that although the MEP post rTMS facilitatory protocol and inhibitory protocol showed numerical improvement, only the facilitatory protocol shows a significant improvent and the gain in the inhibitory group is not enough to be statistically significant. There were many studies using both facilitatory and inhibitory settings of rTMS showing a promising result in recovering upper extremity motor function in patients with acute stroke, but there are limited study which investigate the motor recovery in ICH patient post rTMS protocol. Furthermore, study that compares the effectiveness of each setting for ICH patient was well investigated. This study was designed to analyze any statistically significant changes in MEP after subjects underwent different rTMS protocol. In the clinical setting, the result of this study showed that there is statistically significant difference in using fascilitatory rTMS setting but not for inhibitory rTMS setting. This will provide information for physicians when wanted to decide which rTMS protocols to be used in ICH patient.

5. Conclusion

In conclusion, rTMS is safe non invasive tool which can be used for ICH stroke patient. Patient who underwent facilitatory rTMS protocol has significantly improved MEP post intervention. However, other factors such as age, gender, clot size, and intervention time showed no significant difference across three different protocols. Therefore, patient with stable intracerebral haemorrhage will have better motor function recovery post rTMS facilitatory protocol regardless of their age, clot size and time for the intervention. Nonetheless, more patients can be benefited from the rTMS intervention in the near future as rTMS can be a useful tools as an additional non-surgical treatment to treat ICH stroke patient.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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