The Egyptian Journal of Hospital Medicine (April 2023) Vol. 91, Page 4692-4696

Clinical and Neurophysiological Evaluation of Recovery after Ipsilesional High-Frequency Repetitive Transcranial Magnetic Stimulation in Patients with Acute Ischemic Stroke: Experience in Minia University Hospital

Muhammad M. Ismail*, Wael T. Soliman, Mohamed M. Abdelkader, Hadeer K. Mohamed, Rasha N. Saleh

Department of Neurology, Faculty of Medicine, Minia University, Egypt

***Corresponding author:** Muhammad Mamdouh Ismail, **Mobile:** (+20)1010648246, **Email:** Mohamed.Mamdouh@mu.edu.eg

ABSTRACT

Background: The role of repetitive transcranial magnetic stimulation (rTMS) in improving post-stroke recovery has been suggested due to its known modulatory effect on the cortical excitability. It might be therapeutically used either by high-frequency stimulation (>1 Hz) to the motor cortex of the affected cerebral hemisphere, or by low-frequency stimulation (≤1 Hz) to the motor cortex of the nonlesional hemisphere.

Objective: This study was aimed to evaluate the clinical and neurophysiological improvement after ipsilesional high-frequency rTMS in patients with acute ischemic stroke.

Patients and methods: Fifty patients of both sexes were included in this randomized double-blind sham-controlled study in the period between July, 2021 and March, 2022. Patients included were admitted to the Stroke Unit, Department of Neurology, Minia University Hospital. TMS sessions were delivered for 7 consecutive days. All patients were both clinically and neurophysiologically evaluated just before the beginning of the 1st rTMS session and after the end of the 7th session. Patients were clinically evaluated by Medical Research Council (MRC) scale, National Institutes of Health Stroke Scale (NIHSS) and Modified Rankin scale (mRS). Neurophysiologically, patients were evaluated by measuring the resting motor threshold (RMT) to ipsilesional and contralesional abductor pollicis brevis (APB) muscles and the central motor conduction time (CMCT) in lesion side.

Results: Twenty-five patients were subjected to real rTMS and twenty-five to sham stimulation. After the end of sessions, there was significant clinical and neurophysiological improvement in outcome in the favor of real rTMS group.

Conclusion: It could be concluded that ipsilesional high-frequency rTMS improves recovery in patients with acute ischemic stroke.

Keywords: Stroke, Recovery, Ipsilesional high-frequency, rTMS.

INTRODUCTION

Worldwide, stroke represents the second most common cause of death and disability. Burden increases in low- and middle-income countries [(1)]. Traditional methods, such as physical therapy and occupational therapy usually applied to facilitate recovery after stroke. Repetitive transcranial magnetic stimulation (rTMS) has been increasingly used for the treatment of post-stroke motor weakness, aphasia and depression [(2)].

The role of rTMS in improving post-stroke motor recovery and rehabilitation has been suggested due to its known modulatory effect on the cortical excitability. Stroke affects the balance of inhibitory transcallosal pathways between both primary motor areas. The affected hemisphere disrupts by the infarction itself and also by inhibitory impulses from the contralateral hemisphere. So, rTMS might be therapeutically used either by high-frequency stimulation (>1 Hz) to the motor cortex of the affected cerebral hemisphere, or by low-frequency stimulation (≤1 Hz) to the motor cortex of the nonlesional hemisphere [(3)].

This study aims at studying the clinical and neurophysiological improvement after ipsilesional high-frequency rTMS in patients with acute ischemic stroke.

PATIENTS AND METHODS

Fifty patients of both sexes were included in this randomized double-blind sham-controlled study in the period between July, 2021 and March, 2022. Patients included were admitted to the stroke unit of the Neurology Department in Minia University Hospital, presented with acute stroke (within 72 hours from onset) with motor deficit, due to subcortical ischemia in the territory of middle cerebral artery (MCA) as diagnosed by brain diffusion weighted magnetic resonance imaging (DW-MRI).

We excluded patients younger than 18 years old, patients with hemorrhagic strokes, brain tumors, dementia, aphasia, mental retardation, history of seizures and patients with magnetic sensitive metal implants in head, neck or close to the TMS coil field. We also excluded patients with residual weakness from previous strokes, pregnant patients and patients with severe systemic illness and organ failure. All patients were subjected to complete history taking including stroke risk factors, general examination and neurological examination.

Received: 27/11/2022
Accepted: 29/01/2023

All patients had routine laboratory investigations and brain imaging emphasizing diffusion weighted magnetic resonance imaging (DW-MRI). TMS sessions were delivered through a figure-of-eight coil connected to Neurosoft TMS system (TeleEMG, LLC, Los Angeles, California; 510k number: K160309) for 7 consecutive days (except weekends).

All patients were both clinically and neurophysiologically evaluated just before the beginning of the 1st rTMS session and after the end of the 7th session. Regarding the clinical evaluation, patients were evaluated by Medical Research Council (MRC) scale to determine improvement in the degree of muscle weakness, National Institutes of Health Stroke Scale (NIHSS) to a assess improvement in stroke severity and by Modified Rankin scale (mRS) to estimate patients' functional improvement **(4, 5, 6)**. In the other hand, neurophysiological evaluation was done by measuring the resting motor threshold (RMT) to ipsilesional and contralesional abductor pollicis brevis (APB) muscles and the central motor conduction time (CMCT) in lesion side. RMT was obtained by either detecting the lowest stimulus intensity needed to elicit motor evoked potentials (MEPs) > 50 μV peak-to-peak amplitude in at least 5 of 10 consecutive trials; or by detecting the minimal intensity needed to induce at least 1 visible muscle fasciculation in APB **(7, 8)**. CMCT was obtained by subtracting the peripheral conduction time from the MEP latency elicited after motor cortical TMS **(9)**.

For the real rTMS group, high frequency (5 Hz) stimulation to the ipsilesional primary motor cortex (M1) was applied with an intensity of 120% of the RMT, when it could be detected; in case RMT of the ipsilesional M1 couldn't be detected the stimulation intensity was set to the maximum output. 500 pulses per session were delivered (10 trains of 5Hz for 10 seconds with a 50-second intertrain interval). While in sham rTMS group we applied stimulation with the same parameters as real stimulations, but the coil was placed at a 90° angle to the scalp using two-wing 90-degree method, by tilting the coil 90 degree off the scalp in double wing tilting position. In our study, we followed the safety guidelines by **Rossi *et al.* (10)**.

Ethical Approval:

This study was ethically approved by the Institutional Review Board of Faculty of Medicine, Minia University (Approval No. 619:2020). Written informed consent of all the participants was obtained after explaining the advantages, disadvantages, and risk of possible complications. The study protocol conformed to the Helsinki Declaration, the ethical norm of the World Medical Association for human testing.

Statistical Analysis

Data were collected, revised, coded and entered to the SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 20 for Microsoft Windows. The non-parametric quantitative data were presented as median and interquartile range. The comparison between the two groups was done by using *Mann-Whitney test.* The p-value was interpreted as the following: P> 0.05 = non-significant (NS), P < 0.05 = significant (S), P < 0.01 = highly significant (HS).

RESULTS

Fifty patients of both sexes were included in this randomized double-blind sham-controlled study in the period between July, 2021 and March, 2022. Twenty-five patients were subjected to real rTMS and twenty-five to sham stimulation. All patients tolerated the procedures well without any reported adverse effects. In real rTMS group, age was 55.60 ± 11.47; while in sham group, was 57.84 ± 8.39. In real rTMS group, 66.0% of patients were males and 34.0% were females; while in the sham group, 48.0% were males and 52.0% were females. There was no statistically significant difference between the two groups regarding age or sex. There was also no statistically significant difference between the two groups regarding stroke risk factors (e.g. HTN, DM, smoking, and cardiac disease).

The comparison between real rTMS and sham groups before starting sessions showed no significant difference both clinically and neurophysiologically (Table 1).

Table (1): Clinical and neurophysiological scores of studied groups before receiving rTMS sessions

Before	Real rTMS Group	Sham Group	P-value	Sig.
	No. = 25	No. = 25		
NIHSS				
NIHSS (Total)	8 (7-9.5)	9 (6-10)	0.589	NS
MRC				
MRC scale (Total)	10 (7-12)	9 (7-14)	0.740	NS
MRS				
MRS	4 (3-4)	4 (3-4)	0.587	NS
RMT				
RMT (Healthy Side)	35 (30-40)	35 (30-40)	0.847	NS
RMT (Lesion Side)	50 (45-51)	52.17 (50-60)	0.158	NS
CMCT				
CMCT (Lesion Side)	9.65 (8.537-11.435)	10.44 (8.736-12.1)	0.662	NS

NIHSS: National Institutes of Health Stroke Scale, MRC: Medical Research Council, MRS: Modified Rankin scale, RMT: resting motor threshold, CMCT: central motor conduction time.

After the end of sessions, there was significant improvement in outcome in the favor of real rTMS group. Improvement has been measured clinically by NIHSS, MRC scale and MRS; and neurophysiologically by RMT and CMCT (Table 2).

Table (2): Clinical and neurophysiological scores of studied groups after receiving rTMS sessions

After	Real rTMS Group	Sham Group	P-value	Sig.
	No. = 25	No. = 25		
NIHSS				
NIHSS (Total)	6 (2.5-7)	9 (5.5-10)	**<0.001**	**HS**
MRC				
MRC scale (Total)	15 (11-20)	9 (6-16.5)	**0.004**	**S**
MRS				
MRS	3 (1-3)	4 (3-4)	**0.005**	**S**
RMT				
RMT (Healthy Side)	35 (30-40)	35 (30-40)	0.792	NS
RMT (Lesion Side)	45 (40-50)	51.59 (47.5-62.5)	**0.005**	**S**
CMCT				
CMCT (Lesion Side)	8.265 (6.935-10.112)	10.56 (8.9-12)	**0.010**	**S**

DISCUSSION

In this study, we aimed to evaluate the clinical and neurophysiological improvement after ipsilesional high-frequency rTMS in patients with acute ischemic stroke. Fifty patients of both sexes were included in this randomized double-blind sham-controlled study. Patients included were admitted to the stroke unit of the Neurology Department in Minia University Hospital, presented with acute stroke within 72 hours from onset. We applied rTMS within 72 hours of onset, during initial hospital admission, to maximize patients' recruitment and compliance to antiplatelet treatment and physiotherapy sessions and also to minimize their dropout. We included patients with motor deficit due to subcortical ischemia in the territory of MCA, as previous studies showed poor therapeutic effect of rTMS in patients with cortical ischemic strokes [11, 12].

In our study, we choosed to apply ipsilesional high frequency rTMS rather than contralesional low frequency stimulation. Our choice followed results by **Sasaki *et al.*** [13] who found that ipsilesional high frequency rTMS in the early phase of stroke was more beneficial for motor recovery of the affected upper limb than contralesional low frequency stimulation.

High frequency (5 Hz) stimulation to the ipsilesional M1 was applied to our patients for 7 consecutive days with an intensity of 120% of the RMT, 500 pulses per session were delivered. These parameters were chosen in agreement with the meta-analysis done by **Xiang *et al.*** [14] who collected all studies published between January, 2005 and May, 2018 investigating rTMS in post stroke recovery with exclusion of low quality studies

They discussed the optimal parameters of rTMS in post stroke patients. Their analysis showed that the effect of rTMS was better when applied relatively early, within 30 days of stroke onset, than when applied after 30 days. The analysis showed that the effect was strongest in studies that used 1–7 sessions, while rTMS became less effective when number of sessions increased after 7. There was no significant difference in improvement when using stimulation frequencies between (1–10) Hz. Regarding the stimulation intensity and number of pulses, no significant recommendation has been reached [14]. So, regarding stimulation intensity, we followed **Khedr *et al.*** [15] **and Noh *et al.*** [16]; and regarding number of pulses we followed **Hosomi *et al.*** [17].

Assessment of our patients just before the beginning of rTMS sessions showed no significant difference neither clinically nor neurophysiologically between the real rTMS group and the sham group. But after the end of sessions, there was significant improvement in outcome in the favor of real rTMS group. Improvement has been measured clinically by NIHSS, MRS and MRC scale; and neurophysiologically by RMT and CMCT.

NIHSS has been frequently used in many studies as an important tool for assessment of the clinical improvement in stroke severity after rTMS sessions [18, 19, 20, 17, 21, 22].

Regarding the MRS, it has an agreement with other stroke scales and has a strong correlation with the infarct volume. It has been used as a valid tool to demarcate effective and ineffective stroke therapeutic interventions, with one-point change on the MRS is a clinically significant [23]. MRS has been used to evaluate patients' functional improvement after different rTMS therapeutic trials using different stimulation parameters [19, 24, 21, 25].

Our results were also in agreement with **Du *et al.*** [21, 25]; they used MRC scale to measure improvement in the degree of muscle weakness after both ipsilesional high-frequency rTMS and low-frequency stimulation to the healthy side in patients with acute ischemic stroke.

Moreover, our patients showed significant improvement in the ipsilesional cortical excitability after real rTMS sessions. This neurophysiological improvement was measured by the significant decrease in RMT of the affected hemisphere, as what has been reported by **Khedr *et al.*** [18, 19] **and Du *et al.*** [21, 25]. There was also significant decrease in CMCT of the affected hemisphere. That was also in agreement with **Du *et al.*** [25].

In the other hand, in our sample, there was no significant change in the contralesional cortical excitability as measured by RMT of the healthy hemisphere. That could be explained by the studies that compared the use of ipsilesional high-frequency rTMS with contralesional low-frequency stimulation; they showed that suppression of cortical excitability of the healthy hemisphere was seen only when used low-frequency stimulation to the healthy side [18, 21, 25].

CONCLUSION

Ipsilesional high-frequency rTMS improves recovery in patients with acute ischemic stroke.

Supporting and sponsoring financially: Nil.
Competing interests: Nil.

REFERENCES

1. **Saini V, Guada L, Yavagal D (2021):** Global Epidemiology of Stroke and Access to Acute Ischemic Stroke Interventions. Neurology, 97 (20): 6-16.
2. **Lefaucheur J, Aleman A, Baeken C *et al.* (2020):** Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014-2018). Clin Neurophysiol., 131(2): 474-528.
3. **Corti M, Patten C, Triggs W (2012):** Repetitive transcranial magnetic stimulation of motor cortex after stroke: a focused review. Am J Phys Med Rehabil., 91(3): 254-70.
4. **Compston A (2010):** Aids to the investigation of peripheral nerve injuries. Medical Research Council:

Nerve Injuries Research Committee. His Majesty's Stationery Office: 1942; pp. 48 (iii) and 74 figures and 7 diagrams; with aids to the examination of the peripheral nervous system. By Michael O'Brien for the Guarantors of Brain. Saunders Elsevier: 2010; pp. [8] 64 and 94 Figures. Brain, 133(10):2838-44. doi: 10.1093/brain/awq270.

5. **Brott T, Adams H, Olinger C *et al.* (1989):** Measurements of acute cerebral infarction: a clinical examination scale. Stroke, 20(7): 864-70.
6. **van Swieten J, Koudstaal P, Visser M *et al.* (1988):** Interobserver agreement for the assessment of handicap in stroke patients. Stroke, 19(5): 604-7.
7. **Rothwell J, Hallett M, Berardelli A *et al.* (1999):** Magnetic stimulation: motor evoked potentials. The International Federation of Clinical Neurophysiology. Electroencephalogr Clin Neurophysiol., 52: 97-103.
8. **Hanajima R, Wang R, Nakatani-Enomoto S *et al.* (2007):** Comparison of different methods for estimating motor threshold with transcranial magnetic stimulation. Clin Neurophysiol., 118(9): 2120-22.
9. **Udupa K, Chen R (2013):** Central motor conduction time. Handb Clin Neurol., 116: 375-86.
10. **Rossi S, Hallett M, Rossini P *et al.* (2009):** Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol., 120(12): 2008-2039.
11. **Ameli M, Grefkes C, Kemper F *et al.* (2009):** Differential effects of high-frequency repetitive transcranial magnetic stimulation over ipsilesional primary motor cortex in cortical and subcortical middle cerebral artery stroke. Ann Neurol., 66(3): 298-309.
12. **Emara T, El Nahas N, Abd Elkader H *et al.* (2009):** MRI can Predict the Response to Therapeutic Repetitive Transcranial Magnetic Stimulation (rTMS): in Stroke Patients. J Vasc Interv Neurol., 2(2): 163-8.
13. **Sasaki N, Mizutani S, Kakuda W *et al.* (2013):** Comparison of the effects of high-and low-frequency repetitive transcranial magnetic stimulation on upper limb hemiparesis in the early phase of stroke. J Stroke Cerebrovasc Dis., 22: 413-418.
14. **Xiang H, Sun J, Tang X *et al.* (2019):** The effect and optimal parameters of repetitive transcranial magnetic stimulation on motor recovery in stroke patients: a systematic review and meta-analysis of randomized controlled trials. Clin Rehabil., 33(5): 847-864.
15. **Khedr E, Ahmed M, Fathy N *et al.* (2005):** Therapeutic trial of repetitive transcranial magnetic stimulation after acute ischemic stroke. Neurology, 65(3): 466-468.
16. **Noh J, Lim J, Choi T *et al.* (2019):** Effects and safety of combined rTMS and action observation for recovery of function in the upper extremities in stroke patients: A randomized controlled trial. Restor Neurol neurosci., 37(3): 219-230.
17. **Hosomi K, Morris S, Sakamoto T *et al.* (2016):** Daily repetitive transcranial magnetic stimulation for poststroke upper limb paresis in the subacute period. J Stroke Cerebrovasc Dis., 25(7): 1655-1664.
18. **Khedr E, Abdel-Fadeil M, Farghali A *et al.* (2009):** Role of 1 and 3 Hz repetitive transcranial magnetic stimulation on motor function recovery after acute ischaemic stroke. Eur J Neurol., 16(12): 1323-30.
19. **Khedr E, Etraby A, Hemeda M *et al.* (2010):** Long-term effect of repetitive transcranial magnetic stimulation on motor function recovery after acute ischemic stroke. Acta Neurol Scand., 121(1): 30-7.
20. **Sasaki N, Mizutani S, Kakuda W *et al.* (2013):** Comparison of the effects of high- and low-frequency repetitive transcranial magnetic stimulation on upper limb hemiparesis in the early phase of stroke. J Stroke Cerebrovasc Dis., 22(4): 413-8.
21. **Du J, Tian L, Liu W *et al.* (2016):** Effects of repetitive transcranial magnetic stimulation on motor recovery and motor cortex excitability in patients with stroke: a randomized controlled trial. Eur J Neurol., 23(11): 1666-1672.
22. **Guan Y, Li J, Zhang X *et al.* (2017):** Effectiveness of repetitive transcranial magnetic stimulation (rTMS): after acute stroke: A one-year longitudinal randomized trial. CNS Neurosci Ther., 23(12): 940-946.
23. **Broderick J, Adeoye O, Elm J (2017):** Evolution of the Modified Rankin Scale and Its Use in Future Stroke Trials. Stroke, 48(7): 2007-2012.
24. **Emara T, Moustafa R, ElNahas N *et al.* (2010):** Repetitive transcranial magnetic stimulation at 1Hz and 5Hz produces sustained improvement in motor function and disability after ischaemic stroke. Eur J Neurol., 17(9): 1203-1209.
25. **Du J, Yang F, Hu J *et al.* (2019):** Effects of high- and low-frequency repetitive transcranial magnetic stimulation on motor recovery in early stroke patients: Evidence from a randomized controlled trial with clinical, neurophysiological and functional imaging assessments. Neuroimage Clin., 21: 101620.