The Egyptian Journal of Hospital Medicine (July 2023) Vol. 92, Page 6232- 6238

Therapeutic Effect of Ipsilesional High-Frequency Repetitive Transcranial Magnetic Stimulation Following Local Botulinum Toxin Injection in Post-Stroke Upper Limb Spasticity

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ABSTRACT

Background: One of the most prominently apparent stroke consequences is spasticity. By preventing acetylcholine release at the neuromuscular junction, intramuscular injection of botulinum toxin can reduce post-stroke stiffness. Additionally, repetitive transcranial magnetic stimulation (rTMS), a type of noninvasive brain stimulation (NIBS), is well recognised to impact neuroplastic changes and control the healing of injured brain areas. **Objective:** The aim of the current study was to evaluate the combined effect of local botulinum toxin injection and ipsilesional high-frequency rTMS (HF-rTMS) on spastic UL in post-stroke patients, and if this effect could add together to the other treatment modalities available to these patients. **Patients and Methods:** 45 patients with post-stroke spastic upper limb (UL) were injected with botulinum toxin type-A (BoNT-A), then randomly designated to treatment with 20 Hz rTMS (Real rTMS group), N= 22 and SHAM rTMS group, N=23, applied over the ipsilesional cortex over 4 weeks. Spasticity was assessed with Modified Ashworth scale (MAS), the motor function of the affected upper limb was evaluated serially by Wolf Motor Function Tests (WMFT) and motor power was assessed by Medical Research Council (MRC) just before administration, 1.5 months and 3 months after administration of BoNT-A. **Results:** The real rTMS group showed significant improvement of spastic muscles as evident by reduction of their MAS score with significant improvement of motor function and motor power as shown by WMFT and MRC. **Conclusion:** These findings suggested that, the application of HF-rTMS over the ipsilesional cortex following local BoNT-A injection contributes in reduction of spasticity and improves motor power and function in post-stroke patients.

Keywords: Spasticity, Botulinum toxin, Repetitive Transcranial Magnetic Stimulation, Post-Stroke.

INTRODUCTION

One of the most significant impairments linked to upper motor neuron injuries is frequently thought to be spasticity. In the chronic period following a stroke, 20% of individuals experience limb spasticity [(1)]. Contractures may occur as a result of other issues such as motor weakness, sluggish movement of the afflicted limb, discomfort, and deformity brought on by spasticity. As a result, post-stroke spasticity significantly lowers quality of life [(2, 3)]. Treatment options for post-stroke spastic disorders include intramuscular injections of botulinum toxin, selective peripheral nerve block with phenol, and oral anti-spastic medicines [(4, 5)]. The neuromuscular junction is inhibited by the local injection of botulinum toxin type A (BoNT-A), which also lessens the spasticity of the injected muscle. However, not all spasticity patients or with all grades may show improvement in active motor function on the spastic limb after botulinum toxin injection [(6–10)]. In contrast, several studies demonstrated the therapeutic efficacy of repetitive transcranial magnetic stimulation (rTMS) administered to the ipsilesional or non-lesional hemisphere for post-stroke patients with upper limb spastic weakness [(11-13)]. In stroke patients with spasticity, rTMS significantly reduced it, according to **Wang *et al.*** [(14)]. This practical outcome of rTMS may be accounted for by increased neuronal activity in the lesional hemisphere brought on by decreased interhemispheric inhibition towards the lesional hemisphere [(11–14)]. As a result, numerous institutions safely employ the use of rTMS and occupational therapy (OT) as a therapeutic technique for the treatment of spastic upper limb (UL) weakness [(15)]. The effectiveness of rTMS/OT appears to be impacted by the degree of the afflicted upper limb's motor functional impairment, which is mostly dependent on the presence or absence of spasticity [(16)].

The aim of our current study was to evaluate the combined effect of local botulinum toxin injection and ipsilesional HF-rTMS on spastic UL in post-stroke patients, and if this effect could add together to the other treatment modalities available to these patients.

PATIENTS AND METHODS

Our study participants were 45 post-stroke patients of both sexes. All patients were enlisted from Neurology Outpatients Clinic of Minia University Hospital with age ranged 18-90.

Inclusion criteria: Time after onset of stroke of 12 months or more, past history of a sole manifested stroke only, no cognitive disability with a pre-treatment Mini Mental State Examination score ≥ 26, Modified Ashworth scale (MAS) ≥ 1 for finger flexor and/or wrist flexor muscles and Medical Research Council (MRC) ≥ 2.

Botulinum Toxin Injection:

All patients were injected by botulinum toxin type-A (BoNT-A) in the spastic UL muscles guided by Ultrasonography (US) by using EUROMUSCULUS spasticity approach. BoNT-A (BOTOX, GlaxoSmithKline, Tokyo, Japan) is sold in vials that include 100 units of the BoNT-A formulation that is vacuum-dried powder, 0.5 mg of human serum albumin, and 0.9 mg of sodium chloride that must be reconstituted with sterile normal saline (0.9%) to a total volume of 2 ml. The US equipment used was (SAMSUNG ULTRASOUND SYSTEM HS60) to assess the accurate site for spastic muscles injection.

Received: 16/02/2023
Accepted: 18/04/2023

We have selected some of the proximal and distal UL muscles for BoNT-A injection as (pronator teres (PT), pronator quadratus (PQ), flexor carpi radialis (FCR), flexor carpi ulnaris (FCU), flexor pollicis brevis (FPB), flexor pollicis longus (FPL), flexor digitorum superficialis (FDS), flexor digitorum brevis (FDB) and biceps brachii). The dose of BoNT-A administered for each patient was calculated according to degree of spasticity and size of the targeted muscle. Then all patients were simply randomized into 2 groups; one received real high-frequency rTMS (N= 22 patients) on the ipsilesional cortex and the other group was subjected to SHAM-rTMS (N= 23 patients).

The number of received sessions were 3 sessions weekly for 4 weeks. Full history was obtained from all patients and they were subjected to full general examination to exclude any contraindication for BoNT-A injection or rTMS application. In addition, to assess motor tone and power, so decide whether the patient is suitable for the procedure or not. The Modified Ashworth scale (MAS) was used to assess spasticity, Wolf Motor Function Tests (WMFT), which is a functional ability scale with 15 timed activities was used for assessing the afflicted upper limb motor function, the average performance time for 15 timed tests was calculated and Medical Research Council (MRC) was used to estimate the motor power. Patients were subjected to complete neurological examination to assess the degree of spasticity, motor power and motor function by means of the previously mentioned scales just before the injection day (1st visit), 1.5 months later (2nd visit), 3 months later (3rd visit) after injection with BoNT-A.

Repetitive Transcranial Magnetic stimulation:

The magnetic stimulation was delivered through 8-figured shaped coil connected to Neuro-MS/D magnetic stimulator (Neurosoft LLC, Ivanovo, Russia). The patients were randomly divided into 2 groups, real rTMS group (A) and SHAM rTMS group (B). All participants received 12 rTMS sessions over 4 weeks (3 sessions per week). We caught electromyogram (EMG) from abductor pollicis brevis (APB) in the primary motor area situated by moving the coil until we obtained maximal amplitude motor evoked potentials (MEPs). Once the best position was obtained, we have detected the motor threshold. Motor threshold of the hand was ascertained by providing single TMS pulse over the optimal location and by minimizing the stimulus intensity in steps of 1% stimulator output. The lowest TMS stimulus strength used to induce small motor evoked potential (usually 50 μV) while the recorded muscle was at rest, is the resting motor threshold (RMT).

The following HF-rTMS settings were employed in this study: 20 Hz, 2-s stimulation, 1200 pulses, 110% RMT intensity at the stimulation site, 28-s inter-train interval, and 15 minutes each session. The ipsilesional hemisphere was used for all real rTMS sessions. The magnetic coil was attached to the hotspot of the Abductor Pollicis Brevis (APB) cortical representative region in the afflicted side of the brain for the sham group, but no magnetic stimulation was administered. Following each rTMS session, all subjects were advised to get 30 minutes of UL traditional physical therapy (infrared rays, ultrasound rays, and active & passive motor exercises).

No patients with conditions known to be contraindications for rTMS as implantation of cardiac pacemaker, recent history of seizures, marked cognitive impairment, pregnancy or patients with recognised contraindications for intramuscular injection of BoNT-A, such as preexisting neuromuscular illnesses, bleeding disorders, allergy or hypersensitivity to the product, or who had undergone BoNT-A injections in the previous 3 months, were included in our present study.

Ethical Approval: The Institutional Review Board of the School of Medicine at Minia University gave the present research its stamp of approval (No 10:1/2021). All participants provided signed informed permissions after having the benefits, risks, and potential consequences explained to them. All procedures used in this research followed the guidelines laid forth in the Helsinki Declaration by the World Medical Association.

Statistical Analysis

The data were analysed using the IBM SPSS version 25 statistical package software. For quantitative data, mean, SD and lowest and maximum range were used, as well as number and percentage for qualitative data. The Independent Samples t-test was used to analyse parametric quantitative data between the two groups, while the Paired Samples T-test was used to analyse temporal differences within each group. The Chi-square test, on the other hand, was employed to compare categorical variables. A P-value of 0.05 or less was judged statistically significant.

RESULTS

Forty-Five (45) patients of both sexes were involved in this prospective randomized double-blinded SHAM-controlled study. Twenty-two (22) patients were subjected to real HF-rTMS while twenty-three (23) patients were subjected to SHAM rTMS. The procedures done were tolerated by all patients without any reported complications or side effects. In the real rTMS group, age was 50.4 ± 8.8, while in SHAM group, age was 50.4 ± 8.2 without any significant statistical difference between the 2 groups. In the real rTMS group, 63.6% were males and 36.4% were females, while in SHAM group, 60.9% were males and 39.1% were females. As regards handedness, in the real rTMS group, all patients were right handed, while in the SHAM group, 95.7% were right handed and 4.3% were left handed without any statistically significant difference. There was also no statistically significant difference between the two mentioned groups regarding risk factors or other values as shown in table (1).

Table (1) Demographic Data

		Real rTMS	SHAM rTMS	P value
		N=22	N=23	
Age	Range Mean ± SD	(37-65) 50.4±8.8	(38-65) 50.4±8.2	0.978
Sex	Male Female	14(63.6%) 8(36.4%)	14(60.9%) 9(39.1%)	0.848
Handedness	Rt Lt	22(100%) 0(0%)	22(95.7%) 1(4.3%)	0.323
Smoking	Non-smoker Current smoker Ex-smoker	16(72.7%) 3(13.6%) 3(13.6%)	11(47.8%) 9(39.1%) 3(13%)	0.142
Diabetes	Non-diabetic Diabetic	14(63.6%) 8(36.4%)	9(39.1%) 14(60.9%)	0.100
Hypertension	Non hypertensive Hypertensive	10(45.5%) 12(54.5%)	8(34.8%) 15(65.2%)	0.465
CAD	No Yes	16(72.7%) 6(27.3%)	13(56.5%) 10(43.5%)	0.256
Dyslipidemia	No Yes	13(59.1%) 9(40.9%)	8(34.8%) 15(65.2%)	0.102
Previous stroke	No Yes	22(100%) 0(0%)	23(100%) 0(0%)	1
Stroke type	Ischemic Hemorrhagic	20(90.9%) 2(9.1%)	19(82.6%) 4(17.4%)	0.413
Side	Rt Lt	8(36.4%) 14(63.6%)	9(39.1%) 14(60.9%)	0.848
Complications	No Yes	22(100%) 0(0%)	23(100%) 0(0%)	1
Affected area	Parietal Parietal & Temporal	17(77.3%) 5(22.7%)	17(73.9%) 6(26.1%)	0.793
Total dose	Range Mean ± SD	(300-400) 329.5±42.4	(200-400) 347.8±57.4	0.234

CAD: Coronary Artery Disease

As regard clinical assessment of motor function by WMFT, results showed statistically significant difference in the real rTMS group in the 2nd visit (after 1.5 months) and 3rd visit (after 3 months) in comparison with assessment at base-line. Meanwhile, there was no significant difference if we compared assessment between 2nd and 3rd visit. While, in SHAM rTMS group, there was significant difference at 2nd visit only in comparison with 1st visit with significant difference between the 2 groups (real rTMS and SHAM rTMS group) at the 2nd and 3rd visit in favor of the real rTMS group (Table 2).

Table (2) WMFT

WMFT		Real rTMS	SHAM r TMS	P value
		N=22	N=23	
Baseline	Range Mean ± SD	(21-51) 32.6±7.6	(21-40) 30.9±6.3	0.412
After 1.5 months	Range Mean ± SD	(40-74) 52±7.1	(35-53) 43.9±5.9	**<0.001***
After 3 months	Range Mean ± SD	(31-57) 47.8±6.3	(22-40) 31.4±6.2	**<0.001***
P value between times				
Baseline vs 1.5-months		**<0.001***	**<0.001***	
Baseline vs 3-months		**<0.001***	0.178	
1.5-months vs 3-months		**0.003***	**<0.001***	

WMFT: Wolf Motor Function Tests, N= 22: total No. of patients in the real rTMS group, N= 23: total No. of patients in the SHAM rTMS group.

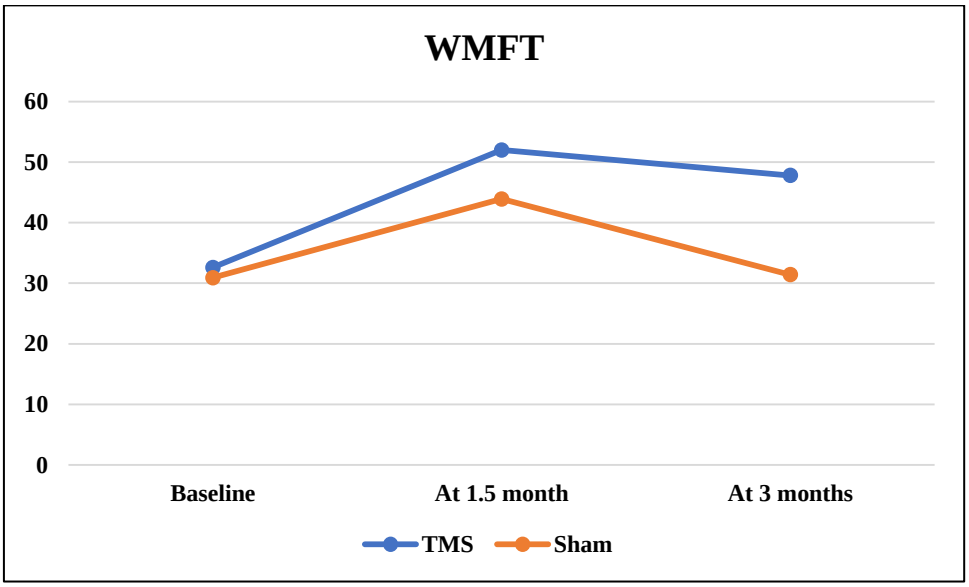

Figure (1): WMFT**:** Wolf Motor Function Tests.

As regards assessment of motor power by MRC through the number of injected muscles in each group, in real rTMS group, results showed statistically significant difference at 2nd (3.7 ± 0.4) and 3rd visit (3.5 ± 0.6) in comparison with the 1st visit (2.8 ± 0.5). While, in the SHAM rTMS group, results showed significant difference only at 2nd visit (3.5±0.5) in comparison to the 1st visit (2.8 ± 0.8) with significant difference between the two compared group at 2nd and 3rd visit in favor of the real rTMS group (Table 3).

Table (3) MRC

MRC		**Real rTMS**	**SHAM rTMS**	**P value**
		N=198	**N=207**	
Baseline	Range Mean ± SD	(2-4) 2.8±0.5	(2-4) 2.8±0.8	0.836
After 1.5 months	Range Mean ± SD	(3-5) 3.7±0.4	(2-4) 3.5±0.5	**<0.001***
After 3 months	Range Mean ± SD	(2-4) 3.5±0.6	(2-4) 2.8±0.6	**<0.001***
P value between times				
Baseline vs 1.5-months		**<0.001***	**<0.001***	
Baseline vs 3-months		**<0.001***	0.447	
1.5-months vs 3-months		**<0.001***	**<0.001***	

MRC: Medical Research Council, N= 198: total No of assessed UL muscles in real rTMS group, N= 207: total No of assessed UL muscles in SHAM rTMS group.

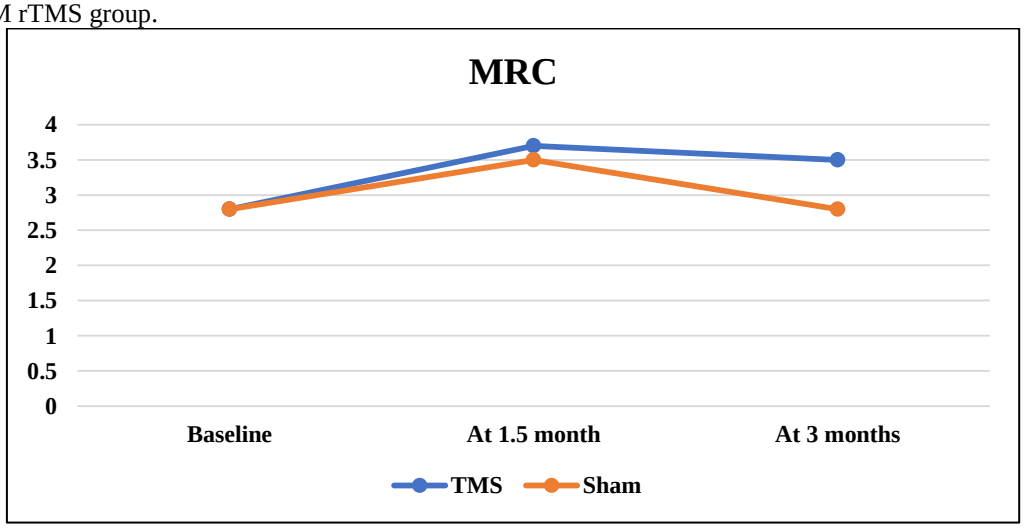

Figure (2): MRC: Medical Research Council.

Concerning assessment of spasticity in the affected UL muscles by MAS, results showed in the real rTMS group that, there was significant reduction of MAS score as regards comparison of 2nd visit (1.4 ± 0.5) to 1st visit (3.4 ± 0.5) and also in comparison, of 3rd visit (1.5 ± 0.6) to 1st visit without any significant difference between 3rd and 2nd visit. While, in the SHAM rTMS group, results showed significant reduction of MAS score in comparison of 2nd visit (2.1 ± 0.6) to 1st visit (3.4 ± 0.5) with statistically significant difference between the two groups at the 2nd and 3rd visit in favor of the real rTMS group (Table 4).

Table (4) MAS

MAS		**Real rTMS**	**SHAM rTMS**	**P value**
		N=198	**N=207**	
Baseline	Range Mean ± SD	(2-4) 3.4±0.5	(2-4) 3.4±0.5	0.142
After 1.5 months	Range Mean ± SD	(1-3) 1.4±0.5	(1-4) 2.1±0.6	**<0.001***
After 3 months	Range Mean ± SD	(1-3) 1.5±0.6	(1-4) 3.1±0.6	**<0.001***
P value between times				
Baseline vs 1.5-months		**<0.001***	**<0.001***	
Baseline vs 3-months		**<0.001***	**<0.001***	
1.5-months vs 3-months		**0.037***	**<0.001***	

MAS: Modified Ashworth scale, N= 198 total No. of the assessed UL muscles in the real TMS group, N=207 total No. of the assessed UL muscles in the SHAM group.

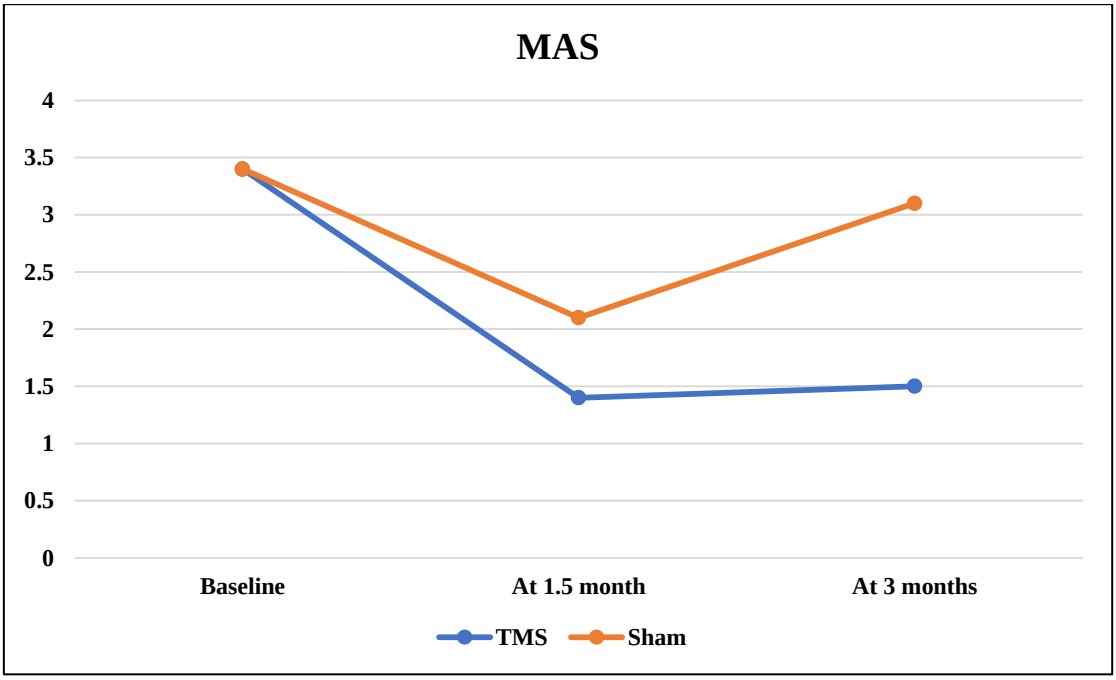

Figure (3): MAS (Modified Ashworth scale).

DISCUSSION

The purpose of our current prospective double-blinded SHAM- controlled study was to evaluate the combined effect of local botulinum toxin injection and HF-rTMS on spastic UL in post-stroke patients. We studied this effect in 45 post-stroke patients with spastic UL after they were blindly divided into 2 groups, one subjected to HF-rTMS and the other to SHAM-rTMS after local BoNT-A injection. The use of BoNT-A injection as a therapeutic tool for the upper limb spasticity after stroke was evident by many randomized controlled trials and has shown significant effectiveness to diminish the resistance to passive limb movement [3, 6-8], that effect was most evident for 4-8 weeks after the injection, and gradually subside after that period as was shown in a previous study by **Kaji *et al.*** [17].

The main basis for the theory supporting the use of rTMS in post-stroke rehabilitation is the neuroplastic effects it has on altered electrophysiological mechanisms involving increased transcallosal inhibition and decreased intracortical inhibition of the healthy hemisphere over the impaired side [18]. The therapeutic perspective of rTMS is therefore consistent with the interhemispheric competition concept and aims to regulate the imbalance between the healthy and damaged hemispheres [19, 20]. As was done in the current study, this can be targeted either by applying high-frequency rTMS to the ipsilesional hemisphere to increase cortical excitability or by applying low-frequency rTMS to the contra-lesional hemisphere to lessen the effects on the ipsilesional cortex [21]. Consequently, a broader effect produced by rTMS, involving the stimulation of certain structural changes within the cortex, in addition to changing functional connections between various and distant parts of the brain, network oscillations are eventually adjusted [22, 23]. In addition, the discharge of different neuromodulators (such as acetylcholine, dopamine, norepinephrine, and serotonin) can be activated by rTMS [24, 25]. Thus, contributing to the production of certain neurotrophic factors that may contribute to accelerate the recovery process [26, 27, 28].

In our current study significant reduction of spasticity (reduction of MAS score) was noted in the group that received real rTMS combined with intra-muscular BoNT-A injection as compared to the group that was injected with BoNT-A but received SHAM rTMS only and this may reflect the possible therapeutic role of HF-rTMS in reduction of spasticity and consequently improving of the motor function as was assessed by WMFT. In a previous study by **Mally and Dinya** [29] that used low frequency consecutive rTMS (1 HZ) for 1 week on the non-lesional hemisphere, proved to significantly diminish limb spasticity in post-stroke patients. On the other hand, **Centonze *et al.*** [30] have shown that with the use of HF-rTMS (5HZ) spasticity is dramatically reduced in spastic limbs of multiple sclerosis patients when administered to the lesional hemisphere for two weeks in a row.

Because using both excitatory 5 Hz rTMS over the lesional hemisphere and inhibitory 1 Hz rTMS over the non-lesional hemisphere can help the lesional hemisphere's neuronal activity [31, 32], it can be theorized that, alleviation of spasticity in the affected limb could be explained by increase of the neural activation in the lesional hemisphere. Following that, an increase in descending inhibitory input through the corticospinal tracts due to increased neuronal activity in the motor cortex in the lesional hemisphere leading to decreased excitability of gamma and alpha neurons [33, 34]. This also is in agreement with **Naro *et al.*** [35], who has proved that, high-frequency stimulation of the cortex can exacerbate spasticity in patients. In a word, reduction of the contra-lesional brain activity has no apparent impact on spasticity management. Consequently, the treatable effect of low- versus high-frequency stimulation and the means by which TMS alleviates spasticity stand to be clarified in the future work.

STUDY LIMITATIONS

This study has some limitations, attributable to limitations of the hospital's practical conditions and financial factors, follow-up done for 3 months duration is proportionally short and could not assess the long-term effects so, it is better to maintain follow-up for a longer period to study the long-lasting effects in the future. Moreover, the used tools are almost entirely functional scoring indicators that depend mainly on clinical assessment only and there is a paucity of electrophysiological indicators such as MEPs or imaging as functional magnetic resonance imaging (fMRI). All of these limitations should be taken into consideration in the future work up.

CONCLUSION

In conclusion, the use of high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) applied over the ipsilesional hemisphere associated with local BoNT-A injection in the affected UL muscles could reduce spasticity and improve motor function in patients with post-stroke spastic UL muscles.

Sponsoring financially: Nil.
Competing interests: Nil.

REFERENCES

1. **Lundstrom E, Terent A, Borg J (2008):** Prevalence of disabling spasticity 1 year after first-ever stroke. Eur J Neurol., 15: 533-9.
2. **Welmer A, von Arbin M, Widen Holmqvist L *et al.* (2006):** Spasticity and its association with functioning and health related quality of life 18 months after stroke. Cerebrovasc Dis., 21: 247-53.

3. **Smania N, Picelli A, Munari D *et al.* (2010):** Rehabilitation procedures in the management of spasticity. Eur J Phys Rehabil Med., 46: 423-8.
4. **Barnes M (1998):** Management of spasticity. Age and Ageing, 27: 239–245.
5. **Petropoulou K, Panourias I, Rapidi C *et al.* (2007):** The importance of neurorehabilitation to the outcome of neuromodulation in spasticity. Acta Neurochirurgica, 97: 243–250.
6. **Simpson D, Alexander D, O'Brien C *et al.* (1996):** Botulinum toxin type A in the treatment of upper extremity spasticity: a randomized, double-blind, placebo-controlled trial. Neurology, 46: 1306-10.
7. **Richardson D, Sheean G, Werring D *et al.* (2000):** Evaluating the role of botulinum toxin in the management of focal hypertonia in adults. J Neurol Neuro- Surg Psychiatry, 69: 499-506.
8. **Brashear A, Gordon M, Elovic E *et al.* (2002):** Botox Post-Stroke Spasticity Study Group. Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after a stroke. N Engl J Med., 347: 395-400.
9. **Childers M, Brashear A, Jozefczyk P *et al.* (2004):** Dose-dependent response to intramuscular botulinum toxin type A for upper-limb spasticity in patients after a stroke. Arch Phys Med Rehabil., 85: 1063-9.
10. **Simon O, Yelnik A (2010):** Managing spasticity with drugs. Eur J Phys Rehabil Med., 46: 401-10**.**
11. **Mansur C, Fregni F, Boggio P *et al.* (2005):** A SHAM stimulation-controlled trial of rTMS of the unaffected hemisphere in stroke patients. Neurology, 64: 1802-4.
12. **Takeuchi N, Chuma T, Matsuo Y *et al.* (2005):** Repetitive transcranial magnetic stimulation of contralesional primary motor cortex improves hand function after stroke. Stroke, 36: 2681-6.
13. **Fregni F, Boggio P, Valle A *et al.* (2006):** A SHAM-controlled trial of a 5-day course of repetitive transcranial magnetic stimulation of the unaffected hemisphere in stroke patients. Stroke, 37: 2115-22.
14. **Wang X, Ge L, Hu H *et al.* (2022):** Effects of non-invasive brain stimulation on post-stroke spasticity: A systematic review and meta-analysis of randomized controlled trials. Brain Sci., 12: 836. doi: 10.3390/brainsci12070836.
15. **Yang W, Liu T, Song X (2015):** Comparison of different stimulation parameters of repetitive transcranial magnetic stimulation for unilateral spatial neglect in stroke patients. J Neurol Sci., 359: 219- 225.
16. **Cassidy J, Chu H, Anderson D (2015):** A comparison of primed low- frequency repetitive transcranial magnetic stimulation treatments in chronic stroke. Brain Stimulation, 8: 1074- 1084.
17. **Kaji R, Osako Y, Suyama K *et al.* (2010):** Botulinum toxin type A in post-stroke upper limb spasticity. Current Med Res Opin., 26: 1983-92.
18. **Hoyer E, Celnik P (2011):** Understanding and enhancing motor recovery after stroke using transcranial magnetic stimulation. Restor Neurol Neuroscience, 29: 395–409.
19. **Nowak D, Grefkes C, Ameli M (2009):** Interhemispheric competition after stroke: brain stimulation to enhance recovery of function of the affected hand. Neurorehabilitation Neural Repair., 23: 641–656. 100.
20. **Boddington L, Reynolds J (2017):** Targeting interhemispheric inhibition with neuromodulation to enhance stroke rehabilitation. Brain Stimulation, 10: 214–222.
21. **Lanza G, Cantone M, Aricò D (2018):** Clinical and electrophysiological impact of repetitive low-frequency transcranial magnetic stimulation on the sensory-motor network in patients with restless legs syndrome. Ther Adv Neurol Disorders, 11: 1756286418759973. doi: 10.1177/1756286418759973
22. **Hoogendam J, Ramakers G, Di Lazzaro V (2010):** Physiology of repetitive transcranial magnetic stimulation of the human brain. Brain Stimulation, 3: 95–118.
23. **Huerta P, Volpe B (2009):** Transcranial magnetic stimulation, synaptic plasticity and network oscillations. J Neuro Engineering Rehabilitation, 6: 7-12.
24. **Ben-Shachar D, Gazawi H, Riboyad-Levin J (1999):** Chronic repetitive transcranial magnetic stimulation alters beta-adrenergic and 5-HT2 receptor characteristics in rat brain. Brain Res., 816: 78–83.
25. **Zangen A, Hyodo K (2002):** Transcranial magnetic stimulation induces increases in extracellular levels of dopamine and glutamate in the nucleus accumbens. Neuroreport., 13: 2401–2405.
26. **Zhang X, Mei Y, Liu C (2007):** Effect of transcranial magnetic stimulation on the expression of c-Fos and brain-derived neurotrophic factor of the cerebral cortex in rats with cerebral infarct. J Huazhong Univ Sci Technol., 27: 415–418. 125.
27. **Brunoni A, Boggio P, Fregni F (2008):** Can the 'yin and yang' BDNF hypothesis be used to predict the effects of rTMS treatment in neuropsychiatry? Med Hypotheses, 71: 279–282.
28. **Chervyakov A, Chernyavsky A, Sinitsyn D (2015):** Possible mechanisms underlying the therapeutic effects of transcranial magnetic stimulation. Front Hum Neuroscience, 9: 303-6.
29. **Mally J, Dinya E (2008):** Recovery of motor disability and spasticity in post-stroke after repetitive transcranial magnetic stimulation (rTMS). Brain Research Bulletin, 76: 388–395.
30. **Centonze D, Koch G, Versace V *et al.* (2007):** Repetitive transcranial magnetic stimulation of the motor cortex ameliorates spasticity in multiple sclerosis. Neurology, 68: 1045–1050.
31. **Chen R, Classen J, Gerloff C *et al.* (1997):** Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology, 48: 1398–1403.
32. **Pascual-Leone A, Valls-Sole J, Wassermann E *et al.* (1994):** Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. Brain, 117: 847–858.
33. **Meunier S, Pierrot-Deseilligny E (1998):** Cortical control of presynaptic inhibition of 1a afferents in humans. Experimental Brain Research, 82: 750–755.
34. **Goldstein E (2001):** Spasticity management: An overview. Journal of Child Neurology, 16:16–23.
35. **Naro A, Leo A, Russo M *et al.* (2017):** Breakthroughs in the spasticity management: are non-pharmacological treatments the future? Journal of Clinical Neuroscience, 39: 16-27.