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ORIGINAL ARTICLE

Efficacy of Repetitive Transcranial Magnetic Stimulation on Spasticity in Egyptian Patients with Multiple Sclerosis

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Abstract

Background: **One of the most common neurologic disorders is multiple sclerosis. The aim was to improve quality of life, many tools have been employed. Repetitive transcranial magnetic stimulation (rTMS) is a new established technique to treat spasticity and improve the outcome of rehabilitation program in various neurologic conditions.**

Aim and objectives: **The aim was to assess the effect of high-frequency (HF) rTMS on improving spasticity in a sample of Egyptian patients with MS.**

Patients and methods: **: A total of 40 patients were recruited from the MS unit at Al-Azhar University hospitals with established diagnosis of MS and spasticity. Recruitment started from the beginning of January 2022 for 6 months. Patients were then randomly allocated into two groups.**

Study group: 20 patients received 12 sessions of HF rTMS over the period of 3 weeks, followed by physical therapy for 30 min.

rTMS protocol: contralateral primary motor cortex (M1) was the site of stimulation. A total of 1500 pulses (50 pulses per train with total 30 trains) per session with an intensity of 90% of the resting motor threshold at a frequency of 10 Hz were received. Each train had a duration of 30 s with intertrain delay of 25 s.

Control group: 20 patients received only physical therapy of 30 min over the period of 3 weeks.

Results: **Both groups received their medical treatment and physiotherapy. Compared with the control group, the study group had a statistically significant improvement.**

Conclusion: **HF rTMS could be beneficial in reducing spasticity and enhancing motor recovery in Egyptian patients with MS.**

Keywords: Expanded disability status scale (EDSS), Modified ashworth scale (MAS), Multiple sclerosis, Repetitive transcranial magnetic stimulation (rTMS), Spasticity

1. Introduction

As a noninvasive neurostimulation technology, repetitive transcranial magnetic stimulation (rTMS) sends magnetic pulses deep into the brain tissue using electromagnetic induction concept. Motor cortex stimulation results in corticospinal and intracortical modulation.[1]

rTMS was used to help in motor-related rehabilitation of neurological diseases such as stroke, Parkinson's disease, and multiple sclerosis.[2]

MS is a very common demyelinating disease. In MS, nerve cells insulated by myelin sheaths in the brain and spinal cord are destroyed. Physical, cognitive, and even psychiatric issues are among the signs and symptoms of this injury, which impairs the nervous system's ability to transmit signals.[3] Spasticity causes musculoskeletal issues such as contractures, pain, and subluxation. A trial to decrease spasticity may improve motor functions and quality of life.[4]

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Among various interventions used to manage spasticity, physical therapy (PT) is a major rehabilitation therapy that improves motor activity and decreases muscle stiffness.[5]

Additionally, noninvasive brain stimulations may also be one of the strategies for spasticity control.[6]

In this study, we aimed to assess the effect of high-frequency rTMS on spasticity in a sample of Egyptian patients with MS.

2. Patients and methods

An approval was obtained from the Ethics Committee in Faculty of Medicine, Al-Azhar University. Written informed consents were obtained from study participants before enrollment.

A total of 40 patients diagnosed as having MS with spasticity were selected from the MS unit of Al-Azhar University hospitals in the period from the beginning of January 2022 for 6 months.

2.1. Inclusion criteria

We included patients with established diagnosis of MS. They were diagnosed using clinical, laboratory, MRI, and matched the McDonald criteria 2017.

2.2. Exclusion criteria

The exclusion criteria followed were pregnant women or patients with history of seizures, pacemaker, or craniotomy.

The recruited patients were randomly assigned into the control group ($N = 20$) and the study group ($N = 20$). Both groups were matched for age and sex, with the same exclusion criteria, and undergoing the same PT and medical treatment.

Study group: 20 patients received 12 sessions of high-frequency rTMS (four sessions per week for 3 weeks), which was followed by 30 min of PT.

Control group: 20 patients received only PT of 40 min (four sessions per week for 3 weeks).

2.3. Stimulation device

With Magstim Rapid^2 having angulated figure-of-eight-shaped coil as well as two channels of Neuro-EMG–MS digital system, TMS device used in this study delivers repetitive trains of magnetic pulses.

2.4. rTMS procedure

All magnetically sensitive objects were left outside the TMS room. Patients were asked to sit comfortably on a chair to be relaxed as much as it is possible.

Before starting rTMS treatment, motor threshold (MT) of the study group participants was measured. Settings of the magnetic stimulator were adjusted to a single pulse working mode. Vertex was determined as a point of intersection of a line connecting the nasion and inion with another line connecting the right tragus to the left one. Motor cortex hot spot for the first dorsal interosseous muscle lies ~7 cm lateral to the vertex in a line perpendicular to parasagittal plan.

The center of the coil was placed on the scalp in a tangential line to the area of FDI and the handle is placed at 45° with the sagittal plane. Initial intensity was set and single pulse was started over the area and the muscle contraction was inspected. The intensity of stimulation was gradually decreased or increased until reaching the lowest intensity that produces muscle contraction in at least 5 of the 10 consecutive trials. This intensity is called MT. This was repeated before each TMS session in the study group. Stimulation intensity for the rTMS procedure was set at 90% of the MT.

The study group received 1500 pulses per session (50 pulses per train with total 30 trains) with an intensity of 90% of the MT at a frequency of 10 Hz. The coil was placed on the contralateral primary motor cortex (M1). Each train had duration of 30 s with intertrain delay of 25 s rTMS frequency of 10 Hz was kept constant based on previous studies using 5 and 10 Hz.[7]

2.5. Outcome measures

Before start of the study, scaling of spasticity using modified Ashworth scale (MAS) and expanded disability status scale (EDSS) were employed for all participants. After completion of 12 sessions, again postrecordings of both MAS and EDSS were performed. The PT sessions were delivered by trained experts who were kept blinded to the study's research protocol.

2.6. Statistical analysis

SPSS (Statistical Package for the Social Sciences) program version 25.0 (IBM Inc., Chicago, Illinois, USA) and Microsoft Corporation, Redmond, WA were used to calculate the statistical significance. Improvement was measured by mean change.

We used Kolmogorov–Smirnov test to validate normal distribution of data. Descriptive statistics were done for all studied parameters in the two studied groups. Percentages were used to represent qualitative data. Mean ± SD was used to represent quantitative parametric data. Difference between

qualitative variables in both groups was calculated using χ^2-test. Difference between parametric quantitative variables in both groups was calculated using independent *t*-test. Difference between two paired groups with qualitative variables was calculated using Wilcoxon signed-rank test. The obtained findings were evaluated at 5% significance level.

3. Results

The current study showed that there was no significant difference between the groups regarding age or sex (Table 1).

Before intervention, there was no significant difference between both groups regarding spasticity as assessed by EDSS and MAS. After intervention, there was a statistically significant difference between the two groups. In the control group, there was a statistically significant difference between preintervention and postintervention values regarding MAS and EDSS. In the study group, there was a statistically significant difference between pre-rTMS and post-rTMS recordings regarding MAS and EDSS (Tables 2 and 3).

There was no statistically significant difference ($P > 0.05$) between the control and the study groups regarding all lesion sites (Tables 4 and 5).

No adverse effects or seizures were recorded during the period of the study, so rTMS is considered a safe and effective treatment option (Figs. 1–5).

4. Discussion

MS is a neurodegenerative disease with manifestation and clinical evolution that can present themselves in many different ways.[8]

During this study, 40 patients were recruited. Patients were then randomly allocated into control group (20) and study group (20).

Regarding age and sex, no statistically significant differences were found between the control and study groups. Age and sex matching agreed with previous studies.[9,10,11,12,13]

In our study, mean ages were 39.15 ± 8.36 and 38.1 ± 12.3 years in control and study groups, respectively. Females represented 70 and 75% in control and study groups, respectively. MS affects women more frequently than men; the prevalence ratio is 3.2 : 1, respectively.[14] In a study on patients with MS in Egypt, the mean age was 32.2 ± 6.7 years in iTBS stimulated group and in sham was 31.1 ± 7.3 years, with female-to-male ratio of 18: 12.[12]

The epigenetic change of DNA, which may be brought on by environmental or hormonal factors that are different for men and women, may account for the higher prevalence of MS in females. Men and women may react differently to environmental influences like vitamin D supplementation and sun exposure, for instance Ref. [15].

Before stimulation, there was no significant difference between both groups regarding spasticity assessed by MAS, whereas after stimulation, there was a statistically significant difference between both groups. In addition, there was a statistically significant difference between pre-rTMS and post-rTMS regarding MAS in each group.

In response to rTMS, the current results of reduced spasticity are consistent with earlier findings.[9,10] These authors explained that spinal cord stimulation could cause a direct muscle response by direct stimulation of anterior horn cells or by triggering the descending pathways, and that this intensive and prolonged descending inhibition could account for the healing and depressive changes in the local reflexes responsible for voluntary working muscles. Another explanation is that repetitive TMS has antioxidant effect reducing oxidative stress in MS.[16]

Centonze et al.[17] and Abdel-Kader et al.[11] revealed a substantial decrease in lower limb spasticity when rTMS administrations were repeated over a 2-week period. This is consistent with our treatment protocol, which lasted 3 weeks for each of the two groups. The cumulative plastic changes produced by rTMS may help to explain this.

In the present study, the frequency was 10 Hz. Similarly, the effective dose reported by Korzhova et al.[18] was 10 Hz, whereas the effective dose reported by Centonze et al.[17] and Abdel-Kader et al.[11] was 5 Hz.

In our work, in the study group MS patients, prestimulation MAS was one in 50% of them, and poststimulation, MAS was 0 in 50% of them. In

Table 1. Participant characteristics in the control and study groups.

Variable	Control group ($N = 20$)	Study group ($N = 20$)	Tests	*P* value
Age (years)	39.15 ± 8.36	38.1 ± 12.3	Independent *t*-test = 0.03	0.767 (NS)
Minimum–maximum	20–52	18–59		
Sex [*n* (%)]				
Male	6 (30)	5 (25)	$\chi^2 = 0.125$	0.723 (NS)
Female	14 (70)	15 (75)		

Table 2. EDSS score of patients in both control group and study group with Multiple sclerosis (MS) before and after intervention.

Variable	Control group ($N = 20$)	Study group ($N = 20$)	Tests	P value
EDSS-pre score	3.92 ± 0.88	3.90 ± 1.12	Mann–Whitney test = 183.0	0.635 (NS)
Median (minimum–maximum)	3.75 (3–5.5)	3.5 (3–6)		
EDSS-post score	3.5 ± 1.01	2.85 ± 1.2	Mann–Whitney test = 495.5	0.021 (Significance*)
Median (minimum–maximum)	3, (2–5)	2.5 (1.5–5.5)		
Wilcoxon signed	P value	P value		
Rank test	0.009 (significance**)	<0.001 (significance***)		

EDSS, expanded disability status scale.

Table 3. MAS prescore and postscore of patients in both control group and study group with MS.

Variable	Control group ($N = 20$) [n (%)]	Study group ($N = 20$) [n (%)]	Tests	P value
MAS pre				
0	0	0	χ^2-test = 7.379	0.117 (NS)
1	3 (15)	10 (50)		
1+	8 (40)	4 (20)		
2	4 (20)	1 (5)		
3	4 (20)	3 (15)		
4	1 (5)	2 (10)		
MAS post				
0	1 (5)	10 (50)	χ^2-test = 13.03	**0.023 (Significance*)**
1	7 (35)	5 (25)		
1+	5 (25)	1 (5)		
2	4 (20)	2 (10)		
3	3 (15)	1 (5)		
4	0	1 (5)		
Wilcoxon signed-	P value	P value		
Rank test	0.009 (significance**)	<0.001 (significance***)		

MAS, modified Ashworth scale.

Table 4. Spinal lesion site in both control group and study groups with MS.

Spinal lesion site	Control group ($N = 20$) [n (%)]	Study group ($N = 20$) [n (%)]	Tests	P value
Cervical				
Yes	18 (90)	13 (65)	χ^2-test = 3.584	0.058 (NS)
No	2 (10)	7 (35)		
Dorsal				
Yes	13 (65)	14 (70)	χ^2-test = 0.114	0.736 (NS)
No	7(35)	6 (30)		

Table 5. Central lesion site in both control group and study groups with MS.

Central lesion site	Control group ($N = 20$) [n (%)]	Study group ($N = 20$) [n (%)]	Tests	P value
Brain stem				
Yes	4 (20)	7 (35)	$\chi^2 = 1.129$	0.288 (NS)
No	16 (80)	13 (65)		
Periventricular				
Yes	20 (100)	19 (95)	$\chi^2 = 1.026$	0.311 (NS)
No	0	1 (5)		
Cerebellar				
Yes	15 (75)	17 (85)	$\chi^2 = 0.625$	0.429 (NS)
No	5 (25)	3 (15)		
Cortical juxtacortical				
Yes	8 (40)	10 (50)	$\chi^2 = 0.404$	0.525 (NS)
No	12 (60)	10 (50)		
Basal ganglia (BG) and thalamus				
Yes	17 (85)	11 (55)	$\chi^2 = 4.286$	0.038 (Significance*)
No	3 (15)	9 (45)		

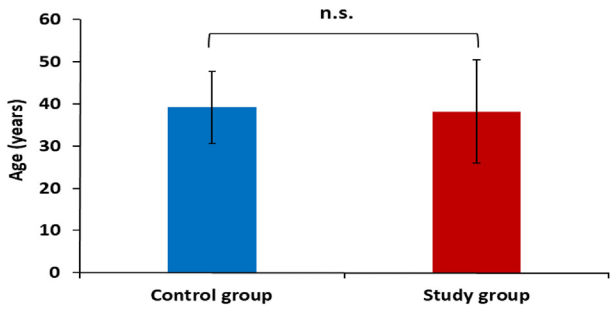

Fig. 1. Age distribution in the control and study group.

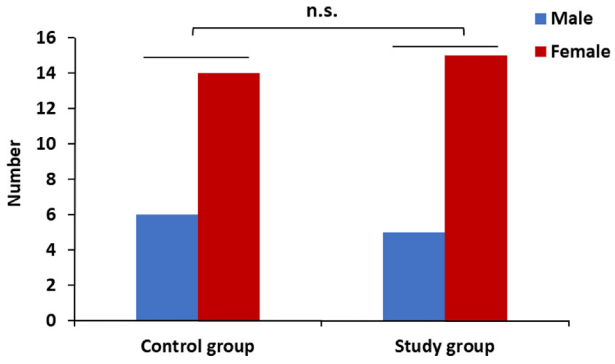

Fig. 2. Sex distribution in the control and study groups.

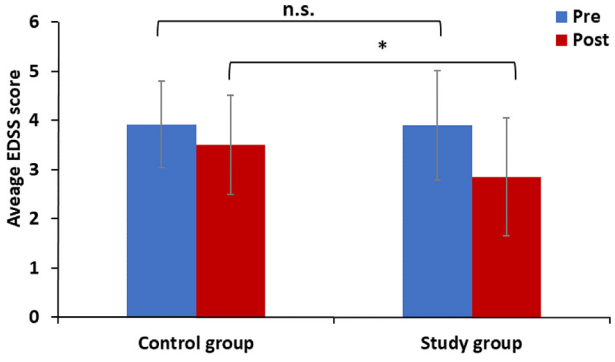

Fig. 3. Expanded disability status scale (EDSS) score of patients in both control group and study group with MS before and after intervention.

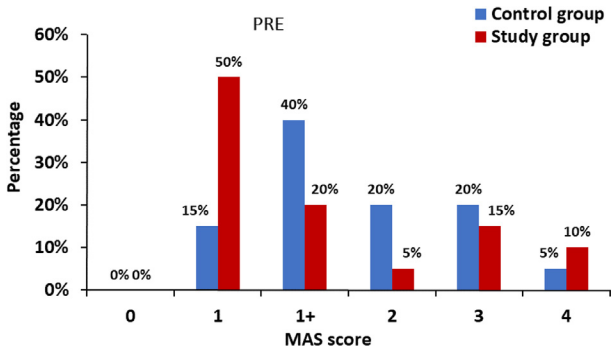

Fig. 4. Modified Ashworth scale (MAS) prescore of patients in both control and study group with MS.

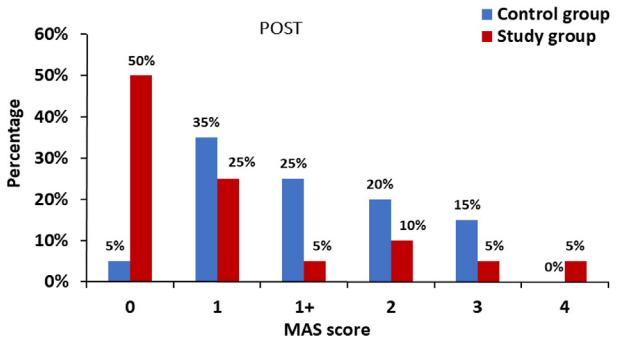

Fig. 5. Modified Ashworth scale (MAS) postscore of patients in both control and study group with MS.

control MS: prestimulation MAS was 1+ in 40%, and poststimulation MAS was one in 35%. Norbye et al.[19] found that the participants had spasticity scores of 0–3 points on the MAS with the median score for the ankles was 1+, and most of the participants had scores of 0 for the hip adductors and knee extensors in patients with MS.

In the present study, no statistically significant differences were found between both groups regarding MAS in right and left limb. However, Larson et al.[20] revealed that in eight ambulatory patients with mild MS with an EDSS score of 2.6 ± 1.6, there was bilateral differences regarding lower limb performance and metabolism during exercise. Evidence points to limitations in aerobic function as a possible explanation for the magnitude of these differences. Patients in the study by Abdel-Kader et al.[11] study were diagnosed as having relapsing remitting MS with spasticity that primarily affected one lower limb.

In terms of the EDSS score, which ranged from 3 to 5 in the control group and from 3 to 6 in the study group, there was no statistically significant difference between the control and study groups.

Similarly in the study by Tramontano et al.,[13] EDSS score was 5.8 ± 0.8 in iTBS and in sham was 5.7 ± 1.0. In the study by Darwish et al.,[12] EDSS score was 2 ± 1 in iTBS stimulated group and in sham was 3 ± 1. In the study by Boutière et al.,[21] EDSS score was 6–6.5 in both groups.

In the current work, no statistically significant differences were found ($P > 0.05$) between the control and the study groups regarding all lesion sites. The study of lesion localization has a successful history with several major quantitative results. In particular, it had been demonstrated that lesion burden and disability score EDSS are associated.[22] Such matching is necessary because the neuronal affection by rTMS is related to the site of lesion and its relation to the site of stimulation.

Overall, 90% of control group and 65% of study group patients had cervical spinal lesions. Similar to this, MS is known to frequently involve the cervical cord. In MS, cervical spinal cord pathology is thought to be a significant contributor to disability.[23] The most frequent site of involvement is the cervical cord, with peripheral white matter affection and often less than two segment involvement.[24]

In our study, intracranial lesions in PV were most common. They were found in 100% of the control group versus 95% in the study group, followed by BG and thalamus in 85% of the study group versus 55% in the control group. Then, cerebellar lesions were seen in 75% of the study group versus 85% in the control group. Cortical and juxtacortal were seen in 40% of the study group versus 50% of the control group. Least seen lesions were in brain stem in 20% of the study group versus 35% in the control group.

In line with our results, PV lesions were seen in all patients with MS followed by subcortical lesions.[25] Although less common, lesions in the midbrain and cerebellar peduncle, as well as those around the fourth ventricle and temporal horns, are more specific for MS. Along with the periventricular region, other frequently involved structures include the corpus callosum, subcortical region, brain stem subcortical U-fibers, optic nerves, and visual pathway.[24]

4.1. Conclusion

Our findings suggested that rTMS of 10 Hz applied for three weeks is effective in reduction of spasticity as detected by the MAS score in patients with MS.

A larger sample size could be used in further studies for confirmation of rTMS role in reduction of spasticity in patients with MS. Different protocols with different doses, frequencies, and durations could be used in further studies.

Conflict of interest

None declared.

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