OPEN AIMJ ORIGINAL ARTICLE

Neurology

The Role of Repetitive Transcranial Magnetic Stimulation in Spastic Hemiplegic Cerebral Palsy in a Sample of Egyptian Children

Ahmed Abdel Fattah Muhammad [1]*M.B.B.Ch; Hossam Mohamed Emam [1]MD and Abdel-Ghaffar Ismail Fayed [1]MD.

**Corresponding Author:*
Ahmed Abdel Fattah Muhammad
ahmadabdelfattah226@azhar.edu.eg

Received *for publication June 26, 2022;* ***Accepted*** *December 31, 2022;* ***Published online*** *December 31,2022.*

doi: *10.21608/aimj.2022.147297.2017*

Citation: *Ahmed A. , Hossam M. and Abdel-Ghaffar I.. The Role of Repetitive Transcranial Magnetic Stimulation in Spastic Hemiplegic Cerebral Palsy in a Sample of Egyptian Children. AIMJ. 2022; Vol.3-Issue 12 : 7-11.*

[1]Neurology Department, Faculty of Medicine, Al-Azhar University, Cairo , Egypt.

ABSTRACT

Background: One of the most common neurologic disorders is cerebral palsy. To improve quality of life, many tools have been employed. rTMS is a new established technique to treat spasticity and improve the outcome of rehabilitation program in various neurologic conditions.
Aim of The Work: To assess the effect of high frequency rTMS on improving spasticity and motor performance in spastic hemiplegic CP in a sample of Egyptian children.
Patients and Methods: 65 children aged between 4-18 years attending the Neuro-Pediatric Unit of Al-Azhar University hospitals were recruited in the period from beginning of Jan, 2022 to the end of June, 2022. They were randomly allocated into two groups :
Study Group: 40 patients received 8 sessions of high frequency rTMS (2 sessions per week for 4 weeks) followed by physical therapy (PT) of 30 minutes duration. 1500 pulses (50 pulses per train with total 30 trains) per session with an intensity of 90% of the motor threshold at a frequency of 10 Hz were received. Contralateral primary motor cortex (M1) was the site of stimulation. Each train had duration of 30 sec with inter- train delay of 25 seconds.
Control Group: 25 patients received only physical therapy (PT) of 30 minutes (2 sessions per week for 4 weeks).
Results: The study group has been improved statistically significantly as compared with the control group.
Conclusion: r-TMS essentially contributes to reducing spasticity and enhancing motor performance in hemiparetic CP children.

Keywords: *Cerebral palsy ; Spasticity ; Modified Ashworth Scale ; r-TMS ; Gross Motor Function Classification System.*

Disclosure: *The authors have no financial interest to declare in relation to the content of this article. The Article Processing Charge was paid for by the authors.*
Authorship: *All authors have a substantial contribution to the article.*

INTRODUCTION

As a noninvasive neurostimulation technology, repetitive TMS 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 treat motor-related neurological diseases such as stroke, and MS.[2] One such disease very common in infancy is cerebral palsy.[3]

CP is a collection of neurological disorders that begin in infancy or early childhood. It affects body mobility and muscle coordination permanently. Hemiplegia is a major form among spastic cerebral palsy accounting for 21 – 40% of CP cases.[4] Spasticity causes musculoskeletal issues such as contractures, pain, and subluxation. Removal of spasticity improves motor functions and life quality.[5]

Among various interventions used to manage spasticity in CP such as using antispastic drugs, botulinum injections and surgical procedures, physical therapy (PT) is a major rehabilitation therapy which improves motor activity and decreases muscle stiffness.[6]

Additionally, rTMS has a good effect in cerebral palsy[7] including improved motor activity [8] and reduced muscle tone.[6]

Following evidences from the reported literatures, we hypothesized that using rTMS combined with physical therapy in spastic hemiplegic CP children may improve motor functions and decrease muscle tightness. This will improve patients' quality of life.

We aim to assess the effect of high frequency rTMS on improving spasticity and motor performance in spastic hemiplegic CP in a sample of Egyptian children.

PATIENTS AND METHODS

The study was approved by the Ethics Committee of the Al-Azhar Faculty of Medicine and was registered in ClinicalTrials.gov (identifier: NCT05134259). We obtained written informed consent from parents/guardians before enrollment in this study.

Sixty-five children diagnosed with spastic hemiplegic CP by consultant pediatric neurologists and met our inclusion criteria were selected from the Neuro-Pediatric Unit of Al-Azhar University hospitals in the period from beginning of Jan, 2022 to the end of June, 2022.

Inclusion criteria:

In this study, we included patients aged 4 to 18 years, with mild to moderate muscle spasticity (Grade 1, 1+,2 on modified Ashworth scale), and ability to walk with limitation or holding on (level II, III, IV according to Gross Motor Function Classification System).

Exclusion criteria:

The exclusion criteria followed were: Any metallic implant, severe abnormalities (e.g. cognitive or sensory deficits), seizures, other central or peripheral nervous system dysfunction, botulinum toxin use in the previous 4 months, clinically suspected active inflammatory or pathologic changes in lower limb joints during the previous 6 months, fixed deformities in lower limbs, clinically suspected active medical problems (e.g. pneumonia, meningitis, or encephalitis, and finally, metabolic disorders, such as inborn error of metabolism, electrolyte, and endocrine disorders.

The recruited children were randomly assigned into control group (N: 25) and study group (N: 40). Both groups were matched in age, sex, degree of disability and cognitive functions, with the same exclusion criteria, undergoing the same physical therapy and medical treatment but with change of dose according to the body weight.

Study group; forty patients received 8 sessions of high frequency rTMS (2 sessions per week for 4 weeks) followed by 30 minutes of physical therapy (PT).

Control group; twenty-five patients received only physical therapy (PT) of 30 minutes (2 sessions per week for 4 weeks).

Stimulation device

With Magstim Rapid² 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.

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 study group participants was measured. Settings of the magnetic stimulator were adjusted to 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 approximately 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 degrees 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 produce muscle contraction in at least 5 of the 10 consecutive trials. This intensity is called motor threshold (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 (50 pulses per train with total 30 trains) per session 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 sec with inter- train delay of 25 seconds. rTMS frequency of 10 Hz was kept constant based on previous studies with 5 Hz and 10 Hz. [9&10]

Outcome measures

Prior to start of the study, scaling of spasticity and motor performance using Modified Ashworth Scale (MAS) and Gross Motor Function Classification System (GMFCS) were employed to all participants. After completion of 8 sessions, again post recording of both GMFCS and MAS were performed. The PT sessions were delivered by trained experts who were kept blinded to the study's research protocol.

STATISTICAL ANALYSIS

SPSS (Statistical Package for the Social Science) program version 25.0 (IBM Inc., Chicago, USA), Microsoft Office Excel 2016 software 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 represented qualitative data. Mean ± SD (Standard deviation) represented quantitative parametric data. Difference between qualitative variables in both groups was calculated using Chi square test ($\chi 2$). 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 ranks test. The obtained findings were evaluated at 5% significance level.

RESULTS

The current study showed that there was no significant difference between both groups regarding age, height, Weight, and gender. (table 1)

Pre intervention, there was no significant difference between both groups as regards spasticity assessed by MAS and gross motor activity assessed by GMFCS while post intervention, there was statistically significant difference between both groups. (Tables 2 & 3)

In control group, there was statistically significant difference between Pre and Post intervention as regards MAS and GMFCS. (Table 4)

In study group, there was statistically significant difference between Pre and Post rTMS regarding MAS and GMFCS. (Table 5)

The improvement in spasticity of participants in study group was 1.4% as compared to 0.68% in control group while the improvement in gross motor activity of participants in study group was 1.73% as compared to 0.76% in control group. (Table 6)

No adverse effects or seizures were recorded during the period of the study, so rTMS is considered safe and effective treatment option.

Variables		Control Group (N=25)	Study Group (N=40)	Test	P-value	Sig.
Age [year]	Mean ± SD	9.52 ± 3.9	8.47 ± 2.76	Independent t-test	0,21	**NS**
Height [cm]	Mean ± SD	140.9 ± 13.2	138.25 ± 15.01		0,46	**NS**
Weight [kg]	Mean ± SD	40.64 ± 4.75	42.23 ± 6.58		0,30	**NS**
Gender	Male	14 (56.0%)	22 (55.0%)	Chi-square test (χ^2)	0,93	**NS**
	Female	**11 (44.0%)**	**18 (45.0%)**			

NS: non significant

Table 1: Participant’s characteristics in the control and study group.

MAS		Control Group		Study Group		Test	P-value	Sig.
		NO.	%	NO.	%			
Pre-intervention	1	7	28%	11	27.5%	Chi-square test ($\chi 2$)	0.79	**NS**
	1+	8	32%	10	25%			
	2	10	40%	19	47.5%			
Post-intervention	0	4	16%	13	32.5%		0.017	**S**
	1	9	36%	21	52.5%			
	1+	9	36%	6	15%			
	2	**3**	**12%**	**0**	**0%**			

NS: non significant S: significant

Table 2: Modified Ashworth Scale (MAS) in Control group and Study group Pre and Post intervention.

GMFCS		Control Group		Study Group		Test	P-value	Sig.
		NO.	**%**	**NO.**	**%**			
Pre- intervention	II	10	40%	15	37.5%	Chi-square test (χ^2)	0.640	**NS**
	III	8	32%	17	42.5%			
	IV	7	28%	8	20%			
Post- intervention	0	0	0%	8	20%		0.001	**S**
	I	8	32%	21	52.5%			
	II	8	32%	10	25%			
	III	7	28%	1	2.5%			
	IV	**2**	**8%**	**0**	**0%**			

NS: non significant S: significant

Table 3: Gross Motor Function Classification System (GMFCS) in Control group and Study group Pre and Post intervention.

Control group		Pre	Post	Test	P-value	Sig.
		NO.=25	NO. =25			
MAS	0	0 (0%)	4 (16%)	Wilcoxon signed rank test	0.000	**HS**
	1	7 (28%)	9 (36%)			
	1+	8 (32%)	9 (36%)			
	2	10 (40%)	3 (23%)			
GFMCS	I	0 (0%)	8 (32%)		0.000	**HS**
	II	10 (40%)	8 (32%)			
	III	8 (32%)	7 (28%)			
	IV	**7 (28%)**	**2 (8%)**			

HS: highly significant

Table 4: Comparison between Pre and Post rTMS Regarding MAS, GMFCS, in the Control Group.

Study group		Pre	Post	Test	P-value	Sig.
		NO.=40	NO. =40			
MAS	0	0 (0%)	13 (32.5%)	Wilcoxon signed rank test	0.000	**HS**
	1	11 (27.5%)	21 (52.5%)			
	1+	10 (25%)	6 (15%)			
	2	19 (47.5%)	0 (0%)			
GFMCS	0	0 (0%)	8 (20%)		0.000	**HS**
	I	0 (0%)	21 (52.5%)			
	II	15 (37.5%)	10 (25%)			
	III	17 (42.5%)	1 (2.5%)			
	IV	**8 (20%)**	**0 (0%)**			

HS: highly significant

Table 5: Comparison between Pre and Post intervention regarding MAS, GMFCS, in the study Group.

	STUDY		CONTROL	
	MAS	GMFCS	MAS	GMFCS
PRE (Mean ± SD)	2,20 ± 0.85	2.83 ± 0.74	2.12 ± 0.83	2.88 ± 0.83
POST (Mean ± SD)	0.83 ± 0.67	1.1 ± 0.74	1.44 ± 0.91	2.12 ± 0.9
DIFFERENCE	1.4	1.73	0.68	0.76

Table 6: The improvement in spasticity and motor function of participants in study group VS control group.

DISCUSSION

More than 20% of the world's illness burden is caused by CP, with the majority of those affected are in Africa.[11]

During this study, 90 patients were assessed for eligibility and 65 patients were included in the study. Of all assessed patients, 25 patients were excluded from the study based on the inclusion criteria.

Choosing hemiplegic CP children as a study sample is a helpful presentation for a large sample of CP population. This comes in agreement with Odding et al. in 2006, who reports that, the spastic hemiplegic children constitutes a major form among spastic cerebral palsy accounting for 21 – 40% of CP cases.[4]

As regard description of demographic data, the mean age was 9.25 ± 3.9 years for control group, 8.47± 2.76 years for study group. Choosing the age of children in this study to be ranged from 4 to 18 years, to gain the child cooperation. This comes in agreement with the definition of child in UN Convention on the Rights of the Child (UNCRC) according to McMillan et al. in 2009.[12]

Choosing the muscle spasticity mild to moderate (Grade 1, 1+,2 on MAS), and the ability to walk with limitation or holding on (level II, III, IV according to GMFCS) comes in agreement with Suttipong Tipchatyotin in 2021, who showed no significant improvement in motor skills after including more than half of the subjects in his trial with GMFCS level 5.[13] Future research should be done with a sample of people who have less severe CP, according to him.

In this study, using rTMS frequency of 10 Hz comes in agreement with Korzhova et al. in 2019, who showed that the severity of spasticity as well as associated pain and fatigue were improved using high frequency rTMS (20 Hz).[14]

In our study, after eight sessions of high-frequency rTMS combined with physical therapy, there was highly significant improvement regarding spasticity (MAS) and mobility levels (GMFCS) compared to physical therapy only received by control group.

This comes in agreement with Gupta et al. in 2018, who stated that, children with brain injury can recover motor function and improve spasticity using different rTMS frequencies.[15] They also reported that, rTMS is more effective than standard therapy in treating spastic cerebral palsy children.

In contrary, Özkeskin et al. in 2017 found that, the MAS scores of both groups before and after the treatment remained the same. [16] In addition, Korzhova et al. in 2018 stated that rTMS had no significant effect in spasticity patients in his meta-analysis.[17]

The current study showed that spasticity and motor function of hemiplegic CP children was improved by rTMS. Spasticity was improved in study group by 1.4% as compared to 0.68% in control group. Motor function was improved in study group by 1.73% as compared to 0.76% in control group.

This reveals that rTMS modulate spasticity and motor function in children with spastic CP. Since physical therapy works only on the muscles and doesn't affect motor pathways, the change brought about by this therapy in control group was expected to be slow. Combined with PT, r-TMS revealed better results in improving spasticity of CP children observed in this study.

This comes in agreement with Uy et al. in 2003,[18] who stated that, in adults, TMS has modulatory effect on neuroplasticity which lasts form minutes to days to months. In children, this effect can be longer lasting as pediatric brain is more plastic than adult brain.

This comes in agreement with Heide et al. in 2006, who stated that, applying rTMS to contralateral hemisphere alter levels of excitability in both infarcted and non-infarcted hemispheres in hemiplegic CP children.[19]

Although our results show improved functional motor activity and reduced spasticity, yet we believe some limitations were present. First, assessment was done prior to and after completion of 8 session, no intermediate assessment was done. intermediate assessment may help to determine after how many sessions the r-TMS effect was evident. Second, there was no time interval between rTMS and physical therapy, both were delivered on the same day.

CONCLUSION

CP is a very common childhood disability and hemiplegia is a very common form of spastic CP. Medical treatment combined with physical therapy in combination with rTMS is effective in management of Spastic hemiplegic Cerebral Palsy. rTMS is an effective and safe approach to treat spasticity in CP children. It has a neuromodulatory effect leading to improvement of motor activity especially when added to Medical Treatment and Physical Therapy. As the number of literature and clinical trials about application of rTMS in CP is limited, further research is required to evaluate its efficacy and consistency.

Conflict of interest : none

REFERENCES

1. Valero-Cabré A, Pascual-Leone A. Impact of TMS on the primary motor cortex and associated spinal systems. *IEEE Eng Med Biol Mag.* 2005;24(1):29-35.
2. Kamble N, Netravathi M, Pal PK. Therapeutic applications of repetitive transcranial magnetic stimulation (rTMS) in movement disorders: a review. *Parkinsonism Relat Disord.* 2014;20(7):695-707.
3. Rajak BL, Gupta M, Bhatia D, Mukherjee A. Increasing Number of Therapy Sessions of Repetitive Transcranial Magnetic Stimulation Improves Motor Development by Reducing Muscle Spasticity in Cerebral Palsy Children. *Ann Indian Acad Neurol.* 2019;22(3):302-7.
4. Odding E, Roebroeck ME, Stam HJ. The epidemiology of cerebral palsy: incidence, impairments and risk factors. *Disabil Rehabil.* 2006;28(4):183-91.
5. Flett PJ. Rehabilitation of spasticity and related problems in childhood cerebral palsy. *J Paediatr Child Health.* 2003;39(1):6-14.
6. Gupta M, Rajak BL, Bhatia D, Mukherjee A. Effect of repetitive transcranial magnetic stimulation on motor function and spasticity in spastic cerebral palsy. *Int J Biomed Eng Techn*. 2019;31(4):365-74.
7. Ramezani S, Amini N, Sadeghi N, Safakheil H, Vousooghi N. Brain Stimulation Techniques in Cerebral Palsy. *J Ped Neurol & Med*. 2016;1.
8. Gupta M, Rajak B, Bhatia D, Mukhgerjee A. Transcranial Magnetic Stimulation Therapy in Spastic Cerebral Palsy Children Improves Motor Activity. *J Neuroinf Diseases*. 2016;7:1-4.
9. Anttila H, Autti-Rämö I, Suoranta J, Mäkelä M, Malmivaara A. Effectiveness of physical therapy interventions for children with cerebral palsy: a systematic review. *BMC Pediatr*. 2008;8:14.
10. Rossi S, Hallett M, Rossini PM, Pascual-Leone A; Safety of TMS Consensus Group. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol.* 2009;120(12):2008-39.
11. Frank-Briggs AI, D Alikor EA. Pattern of paediatric neurological disorders in port harcourt, Nigeria. *Int J Biomed Sci*. 2011;7(2):145-9.
12. McMillan AS, Simkiss D. The United Nations Convention on the Rights of the Child and HIV/AIDS. *J Trop Pediatr*. 2009;55(2):71-2.
13. Suttipong Tipchatyotin SP, and Atchara Boonmeeprakob. Long Term Effects of 5-Hz rTMS over M1 Cortex in Spastic Cerebral Palsy: A Pilot Randomized Controlled Trial. *J Thai Rehabil Med*. 2021.
14. Korzhova J, Bakulin I, Sinitsyn D, Poydasheva A, Suponeva N, et al. High-frequency repetitive transcranial magnetic stimulation and intermittent theta-burst stimulation for spasticity management in secondary progressive multiple sclerosis. *Eur J Neurol.* 2019;26(4):680-e44.
15. Gupta M, Rajak BL, Bhatia D, Mukherjee A. Neuromodulatory effect of repetitive transcranial magnetic stimulation pulses on functional motor performances of spastic cerebral palsy children. *J Med Eng Technol*. 2018 Jul;42(5):352-358.
16. Özkeskin M, Öztürk V, Cakmur R, Bilge K, Küçük F. The Effects of Navigated Repetitive Transcranial Magnetic Simulation and Brunnstrom Movement Therapy on Upper Extremity Proprioceptive Sense and Spasticity in Stroke Patients: A Double-Blind Randomized Trial. *J Basic Clin Health Sci*. 2017;1(2):29-35.
17. Korzhova J, Sinitsyn D, Chervyakov A, Poydasheva A, Zakharova M, et al. Transcranial and spinal cord magnetic stimulation in treatment of spasticity: a literature review and meta-analysis. *Eur J Phys Rehabil Med*. 2018;54(1):75-84.
18. Uy J, Ridding MC. Increased cortical excitability induced by transcranial DC and peripheral nerve stimulation. *J Neurosci Methods*. 2003;127(2):193-7.
19. Heide G, Witte OW, Ziemann U. Physiology of modulation of motor cortex excitability by low-frequency suprathreshold repetitive transcranial magnetic stimulation. *Exp Brain Res.* 2006;171(1):26-34.