

## Effect of Repetitive Transcranial Magnetic Stimulation Pulses on Muscle Spasticity of Cerebral Palsy Children

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### Abstract

**Background:** Spasticity is a common contributor to the quality of life of children with CP as it leads to musculoskeletal problems; however, it had been proved that removal of spasticity can improve motor functions in these children; thus, several invasive and non-invasive approaches are applied. Repetitive Transcranial magnetic stimulation (rTMS) is one such non-invasive brain stimulation approach that can induce motor functions in children with movement disorder depending on stimulation intensity and pulses.

**Objective:** This study was aimed to evaluate the effect of different rTMS pulses on muscle spasticity of spastic cerebral palsy (CP) children.

**Method:** Thirty spastic CP children participated in this study which was divided equally into three groups P15, P20 and P25 on the basis of stimulating pulses of 1500, 2000 and 2500 respectively. Modified Ashworth Scale (MAS) was employed for assessing the degree of muscle spasticity and prior to start of rTMS therapy, pre assessment of MAS was performed on selected muscles of both lower and upper limbs. rTMS therapy was administered at 10 Hz frequency to each of the participants for 15 min duration for 20 days followed by physical therapy (PT) of 30 min duration daily for 20 days. After completion of the therapy sessions, post-assessment of MAS on exactly the same muscles were recorded.

**Result:** Statistically significant result ( $p < 0.5$ ) was found on different muscles that responded to different rTMS pulses between groups along with reduction in muscle spasticity.

**Conclusion:** The result demonstrated that rTMS pulse of 1500 and 2000 was effective in both upper and lower limb muscles of spastic CP children but pulse of 2500 was effective in children with severe muscle tightness falling in higher age group range.

**Keywords:** Cerebral palsy; Brain stimulation; Repetitive transcranial magnetic stimulation; Spasticity

### Introduction

Spasticity is a common disability occurring in several neurological disorders such as multiple sclerosis [1], spinal cord injury [2], stroke [3] and cerebral palsy [4]. The pathophysiological cause of spasticity is attributed to motor cortex damage that leads to a decrease in the cortical input to the corticospinal tract, resulting in inhibition of spinal and segmental excitability thereby increasing the muscle tone [5]. The muscles appear stiff because the messages to the muscles are sent incorrectly through the damaged part of the motor cortex. The role of the motor cortex in the development of spasticity has been extensively demonstrated in primates [6] as well as in humans [7]. Spasticity is an important contributor to functional problems associated with activities of daily living (ADL) such as gait, feeding, washing, toileting and dressing. Over time, spasticity may also cause problems, such as muscle pain or spasms, trouble moving in bed, difficulty with transfers, poor seating position, impaired ability to stand and walk, contracture leading to joint deformity, bony deformation, joint subluxation or

dislocation and diminished functional independence [8]. Among various motor disorders that lead to spasticity, it is estimated that 70-80% of children suffering from Cerebral palsy (CP) are spastic [4].

Cerebral palsy (CP) is a common childhood clinical syndrome characterized by a persistent disorder of posture or movement due to an insult or injury caused to the developing brain. The prevalence of CP is 2 to 2.5 per 1,000 live births and its incidence is increasing secondary to improved care in neonatal intensive care units and improved survival of low birth-weight infants [9]. Management of spasticity in CP is a major challenge due to absence of standardized approach towards treatment of this disability. In general, treatment options for management of spasticity in children with CP include oral medications, physical and occupational therapy, splinting and casting, chemodenervation with botulinum toxin or phenol, selective dorsal rhizotomy, intrathecal baclofen, and orthopedic surgery [10-12]. All these interventions though do not cure but provide temporary muscle relaxation because it had been proved that reduction in spasticity can improve motor functions in these children [13]. However, physical management of spasticity which includes physiotherapy and

occupational therapy is still regarded as a key approach towards muscle strengthening and functioning [14].

Additionally, new non-invasive brain stimulation techniques such as deep brain stimulation and repetitive Transcranial magnetic stimulation (rTMS) is gaining importance due to its safety and neurological approach that can stimulate motor neurons [15]. rTMS is a neuromodulation technique based on the principle of electromagnetic induction of an electric field on selected brain areas [16]. rTMS induces changes in cortical excitability at the site of stimulation and trans-synaptically on the surrounding areas. However, the induced effects whether inhibition or excitation of the stimulated brain area directly depends on the frequency, intensity and the pulses of stimulation [15,17]. Our previous experience with rTMS frequency of 5 Hz and 10 Hz demonstrated that the latter was better in inducing functional gain in motor performances as compared to the former in spastic CP children [18,19]. Our findings were further validated by changes observed in the electrophysiological brain activity of the selected children before and after undergoing rTMS therapy [20]. In continuation to our previous line of research, first of a kind of this study was designed to evaluate the effect of different rTMS pulse train on motor functions of spastic CP children and their effect on muscle spasticity.

## Methods and Materials

### Participants

Thirty spastic CP children participated in this study after written consent from their parents or guardians. On the basis of age, sex and CP type the participants were divided into three groups namely, P15, P20 and P25. Each group consisted of 10 participants but one participant (in P20 group) did not complete the study due to personal reasons; his data was not considered for any analysis. Only participants that satisfied our inclusion criteria were selected in this study. The inclusion criteria followed was-willingness to participate; age group between 2 to 15 years; muscle tightness mild to moderate, cognitive deficiency nil to moderate, no metallic implants or muscle relaxant medication, no uncontrolled seizures or congenital diseases. The demographic characteristic of participants is given in Table 1.

Characteristics		P15	P20	P25
Age + (SD)		7.7 (4.4)	6.8 (5.3)	7.2 (5.1)
Sex	Male	8	7	8
	Female	2	2	2
CP Type	Diplegic	4	6	6
	Quadriplegic	6	3	4
Age Group	2-5 years	4	4	4
	6-9 years	4	2	3
	10-13 years	2	3	3

**Table 1:** Demographic distribution of participants in different groups.

### Brain stimulation device

The rTMS device used in this study was Neuro-MS/D Variant-2 therapeutic (Neurosoft, Russia) with angulated figure of eight shaped

coil (AFEC-02-100-C). The device had two channel Neuro-EMG-MS digital system for determining the motor threshold. The eight shaped coil generated magnetic field of up to 4 Tesla which when placed on the skull penetrates through the soft tissue of the brain and stimulates the motor neurons. In this study, the coil was placed on the primary motor cortex which is known to produce modulatory effect on muscle tightness of the limbs [21].

### Assessment tool

In this study, Modified Ashworth Scale (MAS) was used for measuring the changes in muscle tone, which is most frequently used clinical tool for assessing increase or decrease in muscle tone in spastic CP patient [14,15]. MAS is a score based scale that grades muscle spasticity between 0 to 4, where each grade signifying level of tightness (Table 2). Though MAS was used as assessment tool, but the grades were modified (mMAS) for the ease of data analysis and interpretation; and thus 1+ was converted to 2, 2 to 3, 3 to 4 and 4 to 5 whereas grades 0 and 1 were treated as per original convention.

MAS	mMAS	Description
0	0	No increase in muscle tone
1	1	Slight increase in muscle tone, manifested by a catch and release
1+	2	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance
2	3	More marked increase in muscle tone, but affected part(s) can easily be moved
3	4	Considerable increase in muscle tone, passive movement difficult
4	5	Affected part(s) rigid in flexion or extension

**Table 2:** Modified Ashworth Scale (MAS) and Modified-Modified Ashworth Scale (mMAS).

### Study design

The selection of participants and design of study protocol was performed only after approval from the institutional ethics committee for human samples or participants (IECHSP) of the host institution. Prior to start of rTMS therapy, MAS scoring was employed on the participants to access spasticity on selected muscles namely, hamstring, soleus, gastrocnemius and adductor of lower limb; and bicep, supinator and wrist extensor of upper limb. rTMS frequency of 10 Hz was delivered to each of the participants in the study for 15 min daily for 20 days (5 days a week for 4 weeks) followed by physical therapy (PT) of 30 min duration daily for 20 days. In this study, rTMS frequency of 10 Hz was kept constant based on our previous studies with 5 Hz and 10 Hz [14,15]; but number of pulses varied. Participants in group P15 was delivered 1500 pulses; groups P20 participants with 2000 pulses and those in P25 with 2500 pulses. After completion of 20 sessions of therapies, the participants were asked to undergo post-assessment of MAS on exactly the same muscles as recorded previously. Both PT and rTMS sessions were administered by trained professionals who was kept blinded to the research protocol used in the study.

### Statistical analysis

Paired sample t-test was performed on each of the selected muscles of both upper and lower limbs to determine statistical significance that demonstrated the effectiveness of different rTMS pulses administered to CP children. The mean and median scores of different muscles were used to evaluate reduction in muscle tightness among different groups. Moreover, the mean change in MAS score of each selected muscles were used to graphically evaluate decrease in muscle tightness based on spastic CP types and age groups. All statistical analysis was performed using SPSS 20.0 (Armonk, NY, IBM Corp., USA) and Microsoft Excel 2010. The p-value of less than 0.05 was considered statistically significant.

### Results

The results of both lower and upper limb muscles were found to respond to the stimulating effect of rTMS. The variation in the degree of muscle relaxation and tightness due to varying rTMS pulses are described below-

### Evaluating lower limb muscles

Statistically significant ( $p < 0.5$ ) results were observed in almost all the lower limb muscles of both left and right side (Table 3). Decrease in muscle tightness was observed in all the muscles especially hamstring, gastrocnemius and adductor which was evident from the change in mean and median values. From the mean change values it can be observed that rTMS pulse of 1500 and 2000 was effective in hamstring muscles of both left and right side as compared to 2500 pulses. Whereas in gastrocnemius and soleus muscles of either side, 2500 pulse was most effective; but the adductor muscles responded equally to all the stimulating pulses administered. The change in median values demonstrated that 1500 pulses lead to reduction of muscle tightness by an average 1 unit in all the four muscles of the left and right side. Additionally, the 2500 pulse stimulation leads to reduction of muscle tightness by 2 units (from 2 to 0) in gastrocnemius, soleus and adductor of either side indicating that slight catch in these muscles previously (before therapy) was converted to normal functional state due to combined effect of rTMS and PT.

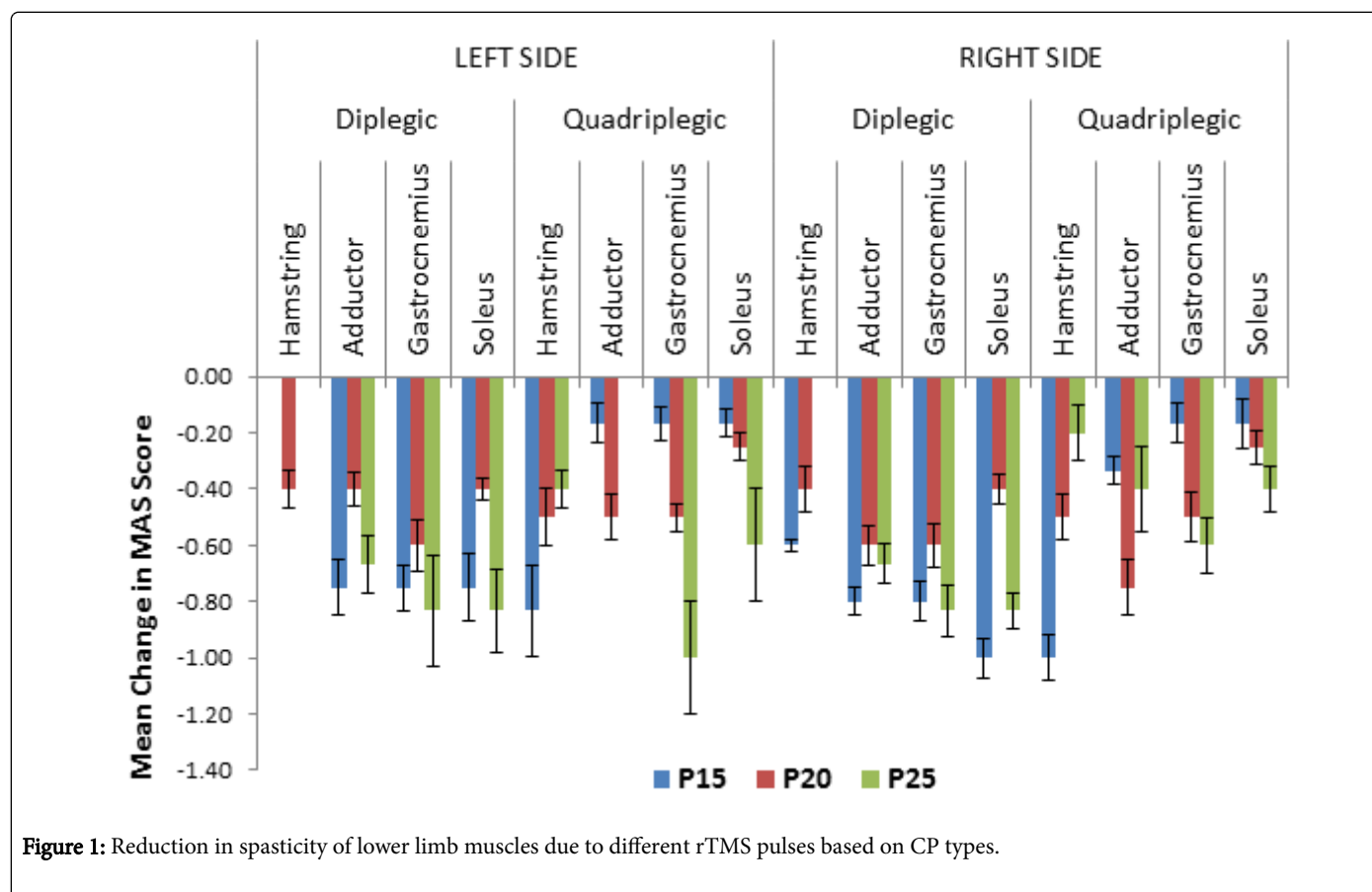
	Muscles	Groups		Median		Mean ± (SD)		Mean Change	p-value	Confidence Interval (95%)	
		Pre	Post	Pre	Post	Lower	Upper				
Left Side	Hamstring	P15	2.5	1.5	2.30 (2.0)	1.80 (1.8)	-0.50	0.05	-0.006	1.006	
		P20	0	0	1.11 (1.7)	0.67 (1.3)	-0.44	0.03	0.039	0.859	
		P25	0	0	1.18 (1.7)	1.00 (1.5)	-0.18	0.16	-0.089	0.453	
Gastrocnemius		P15	2.5	1.5	2.10 (1.6)	1.70 (1.6)	-0.40	0.10	-0.100	0.900	
		P20	0	0	1.33 (1.8)	0.78 (1.4)	-0.56	0.05	-0.002	1.113	
		P25	2	0	1.73 (1.5)	0.82 (1.5)	-0.91	0.01	0.350	1.467	
Soleus		P15	2.5	1.5	2.20 (1.7)	1.80 (1.7)	-0.40	0.10	-0.100	0.900	
		P20	0	0	1.33 (1.8)	1.00 (1.8)	-0.33	0.19	-0.210	0.876	
		P25	2	0	1.73 (1.5)	1.00 (1.5)	-0.73	0.01	0.199	1.255	
Adductor		P15	1.5	1	1.90 (1.5)	1.50 (1.4)	-0.40	0.04	0.031	0.769	
		P20	1	1	1.67 (1.4)	1.22 (1.5)	-0.44	0.04	0.039	0.849	
		P25	2	1	1.82 (1.5)	1.46 (1.6)	-0.36	0.04	0.024	0.702	
Right Side	Hamstring	P15	2	0	2.36 (2.0)	1.55 (2.0)	-0.82	0.01	0.231	1.405	
		P20	0	0	1.11 (1.6)	0.67 (1.3)	-0.44	0.03	0.039	0.849	
		P25	0	0	1.27 (1.7)	1.18 (1.7)	-0.09	0.34	-0.111	0.293	
Gastrocnemius		P15	2	1	1.91 (1.4)	1.46 (1.6)	-0.45	0.05	-0.007	0.916	
		P20	1	0	1.44 (1.7)	0.89 (1.5)	-0.56	0.05	-0.002	1.113	
		P25	2	0	1.73 (1.5)	1.00 (1.5)	-0.73	0.01	0.199	1.255	
Soleus		P15	2	1	2.10 (1.6)	1.55 (1.7)	-0.55	0.05	-0.005	1.096	
		P20	0	0	1.33 (1.8)	1.00 (1.8)	-0.33	0.19	-0.210	0.876	
		P25	2	0	1.64 (1.4)	1.00 (1.5)	-0.64	0.03	0.092	1.179	
Adductor		P15	2	0	1.91 (1.6)	1.44 (1.1)	-0.55	0.03	0.835	1.007	

	P20	2	1	1.78 (1.4)	1.10 (1.1)	-0.67	0.01	0.282	1.051
	P25	2	1	1.82 (1.5)	1.27 (1.5)	-0.55	0.01	0.194	0.896

**Table 3:** Effect of different rTMS pulses on muscles of lower limb.

When MAS mean change scores of each muscles was graphically interpreted based on CP types, interesting observation were recorded (Figure 1). rTMS pulse of 2000 showed average response in all the selected muscles of right and left side both in diplegic and quadriplegic children. On the contrary, 1500 and 2500 pulses showed appreciable

response in adductor, gastrocnemius and soleus muscles of either side. From these findings, it can be concluded that average pulse of 2000 is good enough to reduce muscle tightness in both diplegic and quadriplegic children when frequency (10 Hz) and therapy duration (20 sessions) were kept constant.



**Figure 1:** Reduction in spasticity of lower limb muscles due to different rTMS pulses based on CP types.

Additionally, in order to evaluate the responses of different muscles to varying rTMS pulses, the mean change of MAS scores were further analyzed based on the age groups of the selected children (Figure 2). Three age groups were studied namely, 2-5 years, 6-9 years and 10-13 years. In younger children of 2 to 5 years, 1500 pulses were good

enough to reduce muscle tightness in all the selected muscles as compared to 2000 and 2500 pulses. In children of higher age group (age>6 years) higher pulse rate (2000 and 2500) were found to be most effective in all the selected muscles to relieve tightness as compared to pulse of 1500.

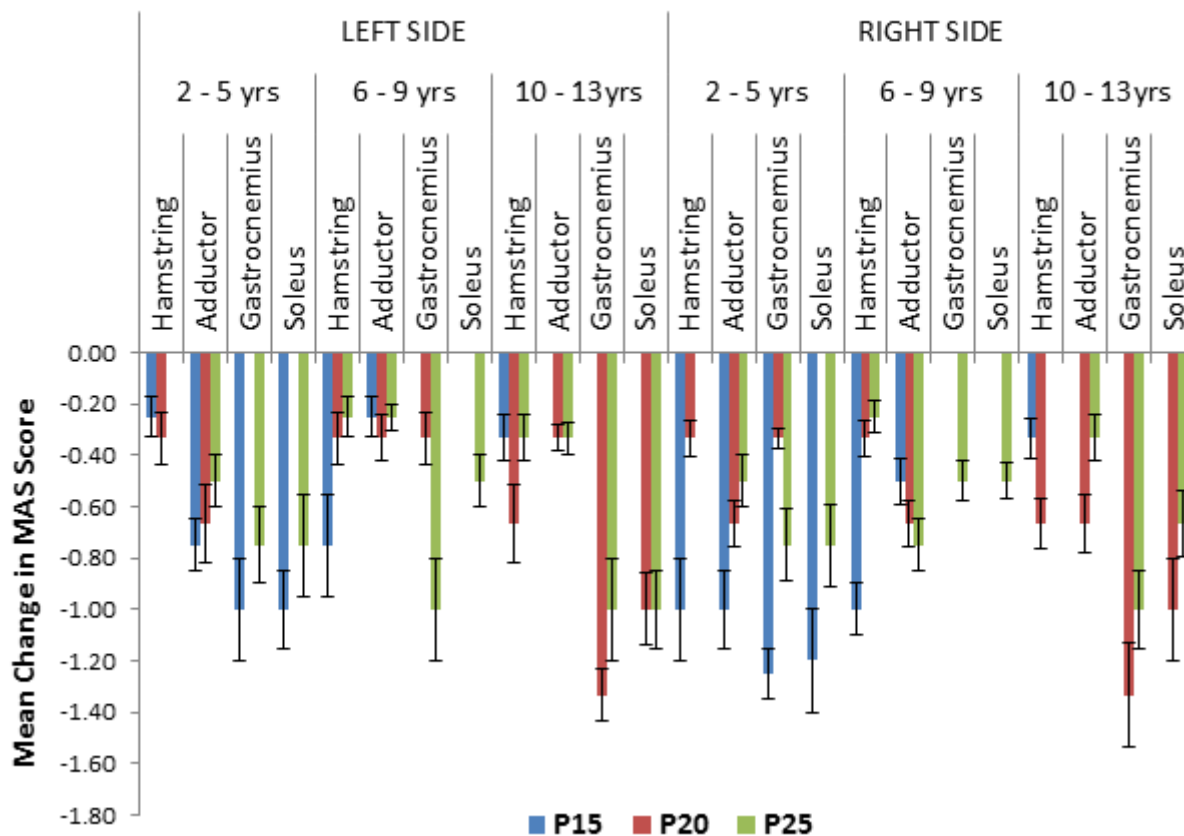


Figure 2: Reduction in spasticity of lower limb muscles due to different rTMS pulses based on age group.

### Evaluating upper limb muscles

The selected upper limb muscles were bicep, supinator and wrist extensor. Statistical analysis was performed on these three selected muscles of all the children in different groups. The results were found to be statistically significant ( $p < 0.5$ ) in almost all the muscles of both left and right side (Table 4). On an average -0.5 unit reduction in

muscle tightness was observed in all the muscles on either side as evident from the change in mean and median values. From the mean change values it can be observed that all the rTMS pulses employed were able to drive an average muscle response which may be due to the stimulation site being the Cz or central position of the brain which corresponds to the lower limb movement.

	Muscles	Group	Median		Mean $\pm$ (SD)		Mean Change	p-value	Confidence Interval (95%)	
			Pre	Post	Pre	Post			Lower	Upper
Left Side	Bicep	P15	1.5	0	1.70 (1.5)	1.00 (1.3)	-0.7	0.04	0.0213	1.378
		P20	0	0	0.78 (1.3)	0.33 (1.0)	-0.44	0.04	0.039	0.849
		P25	1	0	0.91 (1.2)	0.45 (1.2)	-0.45	0.05	-0.007	0.916
	Supinator	P15	2	0.5	1.90 (1.5)	1.30 (1.6)	-0.6	0.05	-0.003	1.203
		P20	0	0	0.89 (1.4)	0.67 (1.3)	-0.22	0.34	-0.29	0.734
		P25	1	0	1.36 (1.5)	0.82 (1.4)	-0.55	0.09	-0.096	1.005
Wrist Extensor	P15	0.5	0	0.70 (0.8)	0.30 (0.6)	-0.4	0.04	0.031	0.769	

		P20	0	0	0.67 (1.7)	0.44 (1.00)	-0.22	0.16	-0.116	0.561
		P25	0	0	0.73 (1.6)	0.27 (0.91)	-0.45	0.01	0.194	0.896
Right Side	Bicep	P15	0	0	1.00 (1.2)	0.82 (1.1)	-0.18	0.16	-0.089	0.453
		P20	0	0	0.78 (1.1)	0.56(0.7)	-0.22	0.16	-0.116	0.561
		P25	1	0	0.91 (1.1)	0.46 (0.8)	-0.45	0.01	0.103	0.805
	Supinator	P15	2	1	1.73 (1.5)	1.18 (1.3)	-0.55	0.19	-0.161	0.707
		P20	0	0	0.78 (1.1)	0.44 (0.5)	-0.33	0.34	-0.145	0.367
		P25	0	0	1.18 (1.5)	0.64 (1.0)	-0.55	0.03	0.024	0.702
	Wrist Extensor	P15	0	0	0.48 (0.8)	0.18 (0.6)	-0.27	0.05	-0.005	1.096
		P20	0	0	0.33 (1.0)	0.22 (0.7)	-0.11	0.19	-0.21	0.876
		P25	0	0	0.55 (0.7)	0.18 (0.6)	-0.36	0.02	0.083	1.007

**Table 4:** Effect of different rTMS pulses on muscles of upper limb.

In upper limb muscles, it was observed that rTMS pulse of 1500 was most effective in diplegic children whereas 2500 pulse demonstrated better muscle response in quadriplegic children (Figure 3). Pulse rate of 2000 were found to be not much effective in upper limb muscles. From these findings, it can be concluded that when frequency (10 Hz) and therapy duration (20 sessions) were kept constant, diplegic children need to be treated with lower number of pulses as compared to the quadriplegics where higher pulse rate were required. The reason of lower number of pulses being required in diplegic children may be due to lesser number of muscles being spastic whereas in case of quadriplegics most of the muscles were rigid and thus needed higher pulse rate to evoke the response.

Similar to the above response were observed when mean change data were analyzed based on the different age groups (Figure 4). The muscles of children in lower age group (2-5 years) responded well to 1500 pulse as compared to 2000 and 2500 pulses; but those in higher age group (above 7 years) their muscles responded better to 2500 pulse rate. These finding demonstrated that 1500 pulse rate can be used for children below 6 years of age and higher number of pulses to children above 7 years when the therapy is administered targeting upper limb muscles.

## Discussion

The treatment approach in order to reduce muscle spasticity and improve quality of life of children suffering from spastic CP, multiple sclerosis, stroke, etc., are diverse and emerging. Most treatment procedures are invasive with some adverse effects whereas non-invasive interventional tool such as rTMS are becoming therapeutically acceptable in the treatment of several neurological disorders associated with motor cortex [22]. Motor cortex stimulation in spastic CP children employing rTMS were initially provided by Valle et al. which showed that high frequency (5 Hz) was safe and helped in reducing spasticity [23]. TMS stimulation of prefrontal and motor cortical areas gave rise to trans-synaptic activation of subcortical circuits which is responsible for motor activity and in the management of spasticity [24,25]. Several studies have shown positive effects of rTMS for treating spasticity. For example, Abdelkader et al. showed that rTMS increased H/M amplitude ratio with significant improvement of the

lower limb spasticity that contributed to the improvement of multiple sclerosis induced spasticity in 21 patients [26]. In stroke, the facilitation and modulation of neural plasticity was induced employing rTMS that helped to improve gait ability of the patient as well as their fast frequency band of the electroencephalogram [27,28].

In spinal cord injured patients, Kumru et al. demonstrated that high-frequency rTMS over the leg motor area can improve affected muscles by reducing spasticity [29] and in CP, rTMS combined with rehabilitation therapy was most effective in reducing muscle spasticity [30]. However, report on improvement of motor score and gait pattern with high-frequency rTMS combined with rehabilitation therapy demonstrated its effectiveness in the management of motor impairment and spasticity than rehabilitation therapy alone [29]. Studies to understand the pathophysiology of spasticity revealed that injury to cortical motor neurons decreases the inhibitory input to the reticulospinal and corticospinal tract, decreasing the level of  $\gamma$ -aminobutyric acid neurotransmitter which is the primary cause of muscle spasticity in CP patients. Recently, Feng et al. demonstrated that GABA in spastic cerebral palsy was lower as compared to healthy controls; which was stabilized after rTMS treatment for 3 months [31].

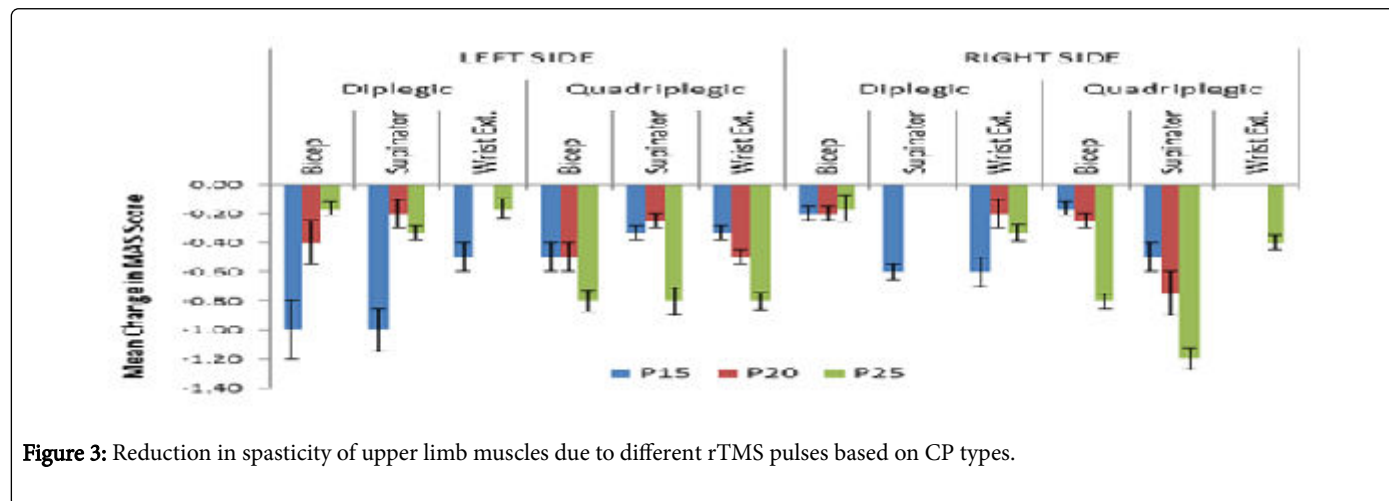
Based on these evidences and our previous experience with rTMS frequencies, this study was designed to evaluate the effect of number of rTMS pulses administered to CP patient and their subsequent effect on muscle tightness. The results demonstrate that pulse train of 2500 was able to reduce muscle tightness of both upper and lower limb muscles of elder spastic CP patients that were quadriplegic as compared to pulse train of 1500 and 2000 that was most effective in patients of lower age group. The benefit of different rTMS pulses demonstrated in this study, provide encouraging results for those who believe in non-invasive brain stimulation technique. However, we do not consider that the results of this study should be interpreted as the final answer to the above important question, since there are no reported literatures on number of rTMS pulses; neither can we claim that increasing numbers of pulses would lead to faster muscle relief. In this study, we observed that the spastic CP children did not complain of any adverse effect of higher pulses nor any seizures were witnesses. In order to evaluate the effectiveness of rTMS using different parameters (intensity, number of



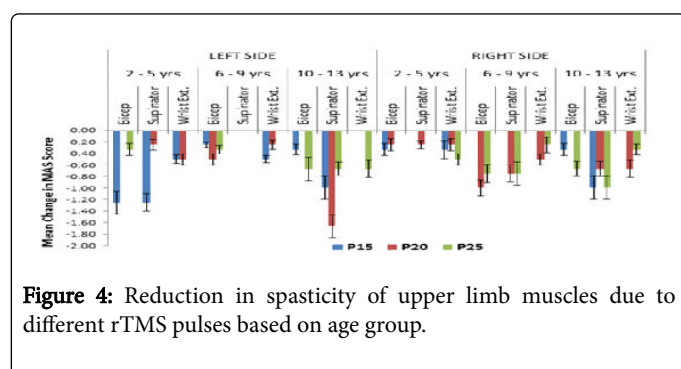
trains, etc.) in spastic CP children, additional research are planned that will enable to establish its consistency and safety over a period of time.

The study had some limitations. First, the study had a small sample size which might have underpowered some analysis and corresponding statistical significances. Second, we did not perform m-MAS scoring midway during the therapy which might have shown after how many

sessions r-TMS effect was evident, instead we recorded only pre (before start of therapy) and post (after completion of therapy) assessment. Third, the outcome measure was only limited to m-MAS. However, more parameters with regard to stimulation effect of r-TMS on motor area of the brain need to be studied and its effect in treating spasticity need to be established.



**Figure 3:** Reduction in spasticity of upper limb muscles due to different rTMS pulses based on CP types.



**Figure 4:** Reduction in spasticity of upper limb muscles due to different rTMS pulses based on age group.

responses were observed in upper limb muscles. From this study, it can be concluded that rTMS pulse of 2000 was effective in both upper and lower limb muscles of spastic CP children but higher number of pulses of 2500 was effective in children with severe muscle tightness falling in higher age groups range.

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### Conclusion

Since the inhibition or excitation of the stimulated brain area directly depends on the frequency, and the pulses of stimulation, as demonstrated in our previous studies [18,19]. Several reports have demonstrated that different rTMS frequency facilitates the recovery of motor function and spasticity in children with brain injury, suggesting that rTMS is a useful modality to improve the motor function in disabled patients due to cerebral impairment [32,33]. However, no paper on the effect of number of rTMS pulses has been reported till date to our knowledge. In this study, it was found that the mean change values of P15 and P20 groups was effective in hamstring muscles of both left and right side of lower limbs as compared to P25 group, whereas in gastrocnemius and soleus muscles of either side, 2500 pulses was most effective; but the adductor muscles responded equally to all the stimulating pulses. However, rTMS pulse of 2000 showed average response in all the selected lower limb muscles of right and left side both in diplegic and quadriplegic children but adductor, gastrocnemius and soleus muscles responded better to 1500 and 2500 pulses stimulation. Additionally, 1500 pulse stimulation was effective in children of lower age group (below 5 years) and higher age group children responded well to higher pulses. Similar kind of muscle

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