Original Article

Increasing Number of Therapy Sessions of Repetitive Transcranial Magnetic Stimulation Improves Motor Development by Reducing Muscle Spasticity in Cerebral Palsy Children

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Abstract

Background: Repetitive TMS (rTMS), a non-invasive neuro-stimulation tool based on the principle of electromagnetic induction is recently being employed both for investigational and interventional purposes. The stimulating effect of rTMS on motor cortex areas of the brain leads to increased motor activity and decreased muscle tone in spastic cerebral palsy (CP) patients. **Objective:** This modulatory effect of rTMS is used in this study to evaluate its effect on motor function and spasticity by increasing the number of therapy session and keeping frequency of 10Hz and pulse train of 2500 constant. **Methods:** Total thirty spastic CP patients participated in this study after written informed consent from their parents/guardians. The participants were equally divided into three groups, namely, S-20, S-30 and S-40 depending on the number of therapy sessions. The mean age±SD of participants in different groups were 8.9±3.6, 9.5±2.9 and 8.4±3.5 in S-20, S-30 and S-40 respectively. Participants in S-20, S-30 and S-40 were provided 20, 30 and 40 sessions of rTMS therapy respectively followed by physical therapy of 30 minutes daily. Each rTMS session was of 25 minutes duration and was administered once daily for 5 days a week. Prior to start and after completion of the therapy, pre and post assessment of gross motor function measure (GMFM) for motor function and modified Ashworth scale (MAS) for muscle spasticity was performed on all the participants. **Outcomes:** The result of pre-versus-post GMFM score showed that 4.27%, 3.12% and 2.36% motor gain was obtained after 40, 30 and 20 sessions of therapy respectively. In addition, significant reduction in spasticity in both upper and limb muscles was also observed in all the three groups.

Keywords: Cerebral palsy, gross motor function measure, Modified Ashworth Scale, spasticity, transcranial magnetic stimulation

Introduction

Transcranial magnetic stimulation (TMS) is a well-known brain stimulation tool used both for investigational purpose to study various neural processes and interventional purpose to treat a variety of neurological illnesses. Repetitive TMS (rTMS) is a modern noninvasive neurostimulation technique based on the principle of electromagnetic induction where a focused magnetic pulse is delivered by a coil deep into the brain tissue. The stimulating effect of magnetic pulses penetrating the brain leads to corticospinal and intracortical modulation of the motor cortex.[1] The motor cortex is the center for controlling and modulating motor action which relies on a sensitive balance between cortical excitatory and inhibitory mechanisms. It is reported that rTMS stimulation of prefrontal and motor cortical areas gave rise to transsynaptic activation of subcortical circuits which is responsible for motor activity[2] and reduction of muscle spasticity.[3,4] Several other studies have demonstrated that rTMS can stimulate motor neurons both in animals[5,6] and humans.[7] The therapeutic application of rTMS toward treatment of motor-related neurological disorders such as Parkinson's, Alzheimer's diseases, multiple sclerosis, and stroke is due to the paradigm change of the clinicians that is shifting from the drug-related medication to modulation of the neural circuitry of the brain for better efficacy and rehabilitation.[8,9] Most of the neurological disorders are rehabilitation dependent and one such disorder common in children is cerebral palsy (CP). CP refers to a group of neurological disorders that appear in infancy or early childhood and permanently affect body movement and muscle coordination of the affected individual. CP is a result of damage or abnormalities caused inside the developing brain that disrupts its ability to control movement and maintain posture and balance.[10] In CP, the input from the corticospinal tracts is inhibited due to an increased activity of gamma and alpha neurons which lead to rigid muscle tone or commonly known as spasticity. Spasticity is an important

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contributor to the quality of life (QOL) of CP patients, as it leads to musculoskeletal problems such as contractures, pain, and subluxation, but it has been proved that removal of spasticity can improve motor functions and QOL.[11] To improve motor function and remove spasticity in CP, several interventional treatment approaches such as oral medication using antispastic drugs, botulinum injections and surgical procedures are followed, which provide limited relief but cause adverse side effects in patients.[12] Among various interventions employed for management of CP, physical therapy (PT) which includes muscle stretching, weight-bearing exercises, antigravity positioning, and handling and grasping techniques is still regarded as a key approach toward muscle strengthening and functioning that helps in improving motor skills.[13] In view of the requirement of alternative treatment approach for spastic CP, rTMS combined with PT has been reported to provide safe therapeutic effects. The safe use of rTMS on CP children and its positive effect on motor function has already been confirmed by Kirton and Gillick *et al.*[14,15] In addition, our previous experience on treating spastic CP children with rTMS combined with PT has demonstrated that higher frequency of 10 Hz was more effective than 5 Hz both in improving motor activity and reducing muscle spasticity by keeping patient safety in mind.[16-18] Moreover, when variation in pulse train was studied, keeping rTMS frequency of 10 Hz constant, it was found that pulse of 2500 leads to decrease in muscle spasticity as compared to 1500 and 2000 pulses again not compromising on patient safety due to high dosages involved.[19] Now, in the current study, for the first time, we report the effect of rTMS on motor functions and muscle spasticity of spastic CP children by varying the number of therapy sessions to be administered. We found that by increasing the number of rTMS therapy sessions, there was remarkable improvement in functional gain of the motor abilities in CP children which might be due to the increase neural processing that enhanced cortical excitability.

Materials and Methods

Participants

Thirty children participated in this study with an established diagnosis of spastic CP confirmed by their consultant physician and neurologists. Participants that met our inclusion criteria were recruited from the Outpatient Department of UDAAN-for the Differently Abled, Delhi, after informed consent from their parents or guardians. The inclusion criteria followed were: (i) willingness to participate, (ii) age group between 2 and 15 years, (iii) absence of severe abnormalities such as cognitive or sensory deficits and seizures, (v) absence of any remedial surgery or medication nor any metallic implants, and (vi) any comorbidity making them unfit for the study. The selected participants were divided randomly into three groups, namely, S-20, S-30, and S-40. The mean age ± SD of participants in different groups were 8.9 ± 3.6, 9.5 ± 2.9, and 8.4 ± 3.5 in S-20, S-30, and S-40, respectively.

Instrumentation

In this study, Neuro-MS/D Variant-2 therapeutic (Neurosoft, Russia) with angulated figure of eight-shaped coil (AFEC-02-100-C) was used. The device comprised two-channel Neuro-EMG-MS digital system for determining the motor threshold of the patients that was used for establishing the threshold intensity for stimulation. The figure of eight-shaped coil generated a magnetic field of up to 4 Tesla that penetrates the cranium, enters into the soft tissue of the brain and henceforth stimulates the motor neuron.

Measurement

Gross motor function measure (GMFM) and Modified Ashworth Scale (MAS) were used as an assessment tool in this study. GMFM is used to measure the child's capacity to perform in a standardized environment to reflect developmental milestone of a growing child such as rolling, crawling, sitting, standing, and walking/running.[20] GMFM has been widely used to measure changes in gross motor function over time and evaluate the effectiveness of different interventions.[21,22] Items on the GMFM – 88 are grouped into five dimensions: A: lying and rolling (17 items); B: sitting (20 items); C: crawling and kneeling (14 items); D: standing (13 items); and E: walking, running, and jumping (24 items). In addition, MAS was used for measuring changes in muscle tone and spasticity. MAS are most frequently used clinical tool for measuring increase or decrease in muscle tone in spastic CP patient.[23,24] MAS is a score-based scale that grades muscle spasticity between 0 and 4, where each grade signifying level of tightness. Although MAS was used as assessment tool, the grades were modified (mMAS) for the ease of data analysis and interpretation and thus 1 + was converted to 2, 2–3, 3–4, and 4-5 whereas grades 0 and 1 were treated as per original convention [Table 1].

Study design

This study was designed to evaluate the effect of rTMS on motor development of spastic CP children by varying number of therapy sessions. The rTMS frequency of 10 Hz and pulse train of 2500 was kept constant after establishing their stimulating effect published in our previous communicated studies.[16,19] Participants in S-20, S-30, and S-40 were provided 20, 30, and 40 sessions of rTMS therapy, respectively. Each rTMS session was of 25-min duration and was administered once daily for 5 days a week for 4 weeks to S-20 group, for 6 weeks to S-30 group, and for 8 weeks to S-40 group. Each rTMS session was then followed by PT of 30 min once daily for as long as rTMS therapy was continued. Although each group initially comprised 10 patients, but one patient each from S-20 and S-40 and two from S-30 discontinued the study due to personal reasons. Hence, their GMFM and mMAS data were not used for any data analysis. GMFM and mMAS assessment on all the participants was performed before and after the therapy sessions to determine the modulatory effect of rTMS on motor activity and spasticity. These assessments were performed by trained physiotherapists who were kept blinded to the study groups. In addition, the selection of participants and design of study protocol was performed only after approval from the institutional ethics committee for human samples or participants of the host institution.

Before starting of the rTMS therapy, motor threshold (MT) of each of the participants was determined. MT is defined as the minimum intensity of single pulse of TMS required to produce a predefined motor-evoked potential in abductor pollicis brevis (ABP) muscle in at least 50% of the trials.[25] In short, it can be said that MT is the intensity to evoke a peripheral motor response in an individual. Determination of MT is of great importance in TMS studies because it is a way to calibrate the coil's output magnetic energy both for dose and safety.[26] For determining the MT, the child was made to sit in a comfortable position on the chair and the ABP muscle was cleaned with alcohol swab. Electrodes were placed on the ABP muscle and connected to the Neuro EMG-MS system. The angulated eight-shaped magnetic coil was placed on the M1 area of the primary motor cortex and single-pulse magnetic stimulation was delivered. This single-pulse stimulation is responsible for producing a twitching effect on the ABP muscle at particular output intensity. Varying the stimulation intensity using the TMS unit, some 10 to 12 trials were performed till an end-to-end peak of MT was captured by the Neuro EMG-MS system. An average MT of 70% was observed in each of the groups, which suggest that participants of different groups received more or less same intensity of rTMS stimulation. This MT was fixed for each of the patients and repetitive biphasic stimulation was delivered by positioning the coil on the motor cortex area of the brain.

Statistical analysis

The scores of both the assessment scales were used for statistical analysis and for determining gain in functional motor activity of CP participants. Mean change in GMFM scores of different groups were analyzed to evaluate improvement in motor performances and the changes in mMAS scores were used to reflect reduction in muscle spasticity. A paired-sample *t*-test on pre- versus post-mean GMFM scores of different groups was performed to determine statistical significance. An alpha value of 0.01 was considered significant. All statistical analysis was performed using SPSS 20.0 (Armonk, N.Y, IBM Corp., USA).

Results

The GMFM scores of different groups used for the statistical analysis are given in Table 2. The paired sample *t*-test between the pre- and post-mean GMFM scores in S-20 group revealed significant differences with $t = -6.05$, df = 8, $P = 0.0005$, confidence interval (CI): −3.276 to − 1.435 and that of S-30 revealed $P = 0.0001$ with $t = -7.27$, df = 7, and CI: –2.022 to –7.279. In addition, *t*-test of group S-40 demonstrated $P = 0.00001$ with $t = -9.44$, df = 8, and CI: −5.309 to − 3.225. The analysis showed that rTMS combined with PT was statistically significant ($P < 0.01$) in each of the three groups. This analysis revealed that the employed therapy regime is responsible for inducing functional gain in all the participants of each group. The improvement in motor activity of CP patients can also be seen from the change in the median values [Figure 1]. The median change in GMFM scores was 2.70%, 3.13%, and 5.33% in S-20, S-30, and S-40 groups, respectively.

In addition, the percentage gain in motor function observed were 2.36%, 3.12%, and 4.27% in S-20, S-30, and S-40 groups, respectively [Figure 2]. After analyzing the mean change in the GMFM scores of all the three groups, it can be noticed that as the number of rTMS session increased, the improvement in gross motor function simultaneously increased with no perceived side effects [Figure 3].

The improvement observed in motor function of spastic CP patients must be due to reduction in muscle spasticity after rTMS therapy. This can be seen from the change in mMAS score of both upper and lower limb muscles of different groups in this study. The negative change in mMAS score of selected muscles of both the limbs indicates reduction in spasticity. Figure 4 shows change in muscle tightness of lower limb muscles due to different treatment regime. Here, it can be observed that all the selected muscles of lower limbs of either side showed significant change in mMAS score. Except for gastrocnemius, all other lower limb muscles, namely, hamstring, adductor, and soleus responded well against 40 sessions of the therapy as compared to the other two sessions. Similar changes were observed in the upper limb muscles of both left and right side [Figure 5].

Although rTMS therapy was effective in all the CP patients under treatment as evident from the GMFM and mMAS scores,

Table 1: Modified Ashworth Scale and Modified-Modified Ashworth Scale

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

MAS=Modified Ashworth Scale, mMAS=Modified-Modified Ashworth Scale

Table 2: Descriptive statistics of gross motor function measure scores of different groups

Groups	Minimum		Maximum		Median		Mean	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
S-20	13.73	15.66	61.54	63.08	21.26	24.39	31.90	34.26
S-30	12.91	17.01	96.42	98.82	24.50	27.20	36.77	39.88
S-40	20.19	23.88	59.78	63.98	36.76	42.09	39.59	43.86

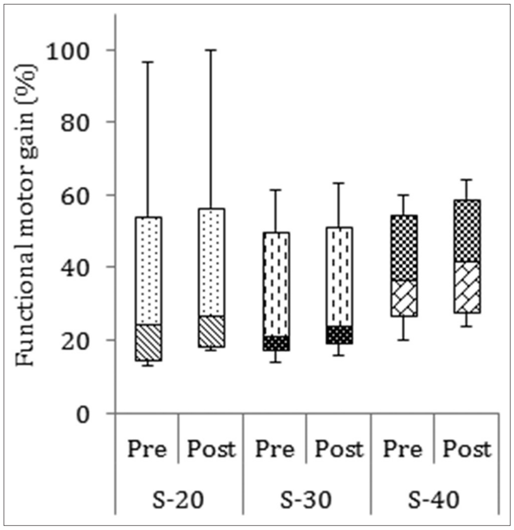

Figure 1: Box-plot showing change in median values of gross motor function measure scores of different groups obtained from a range of functional values

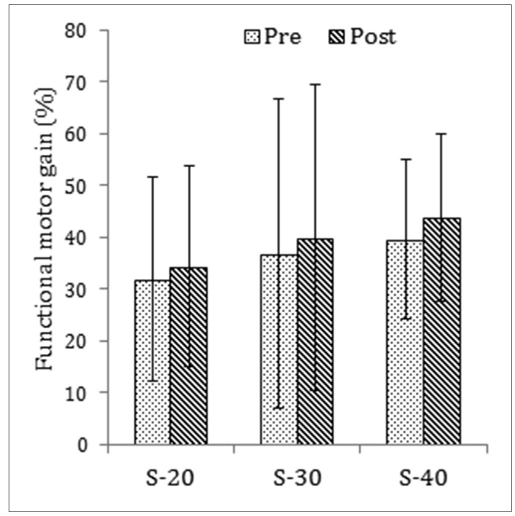

Figure 2: Gross motor function measure scores of different groups obtained from a range of functional values

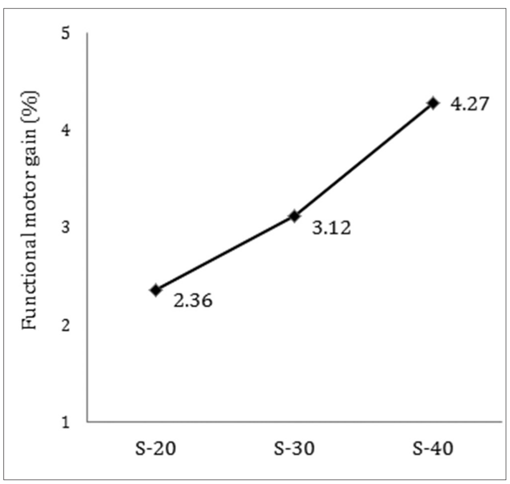

Figure 3: Increased motor gain due to increased repetitive TMS sessions

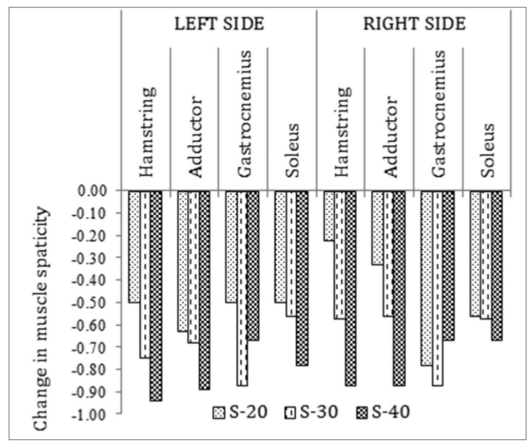

Figure 4: Reduction in spasticity of lower limb muscles observed in different groups

but patients in group S-40 that were delivered 40 sessions of therapy showed much better functional performance in motor activity as compared to S-20 and S-30 groups. This indicates that when rTMS and PT are combined, faster milestone can be achieved by spastic CP children in lesser time. As PT is well known and mostly employed by several such centers for disabled patients, if it could be combined with rTMS, it would result in better performance of activities of daily living and improve the QoL of these individuals benefitting the society in the long run.

Discussion and Conclusion

Our study showed an improvement of 4.27% in motor function when spastic CP patients were provided 40 sessions of rTMS with PT as compared to 3.12% and 2.36% motor gain with 30 and 20 sessions. The gain in the motor function can be directly attributed to reduction in muscle spasticity of both lower and upper limbs as evident from the change in mMAS scores of different groups. As previously mentioned, in the present study, we focused on evaluating the influence of number of therapy sessions keeping frequency and pulse train constant; because the inhibition or excitation of the stimulated brain area directly depends on the frequency and the pulses of stimulation which was determined from our previously published studies. Our earlier rTMS studies on both the parameters (frequency and pulse train) had reported increased motor performances both with higher frequency and pulse train. It has been previously stated and determined in our studies that rTMS was more effective than PT or standard therapy alone in control group.[16-19] These interesting results can lead to better acceptability of a new treatment regime for CP that is required for inducing faster gain in motor activity and in achieving developmental milestone since these children show delayed motor and cognitive growth patterns.

The findings of the current study clearly demonstrate that increasing rTMS therapy sessions leads to functional gain in motor abilities which may be due to increase in the ongoing

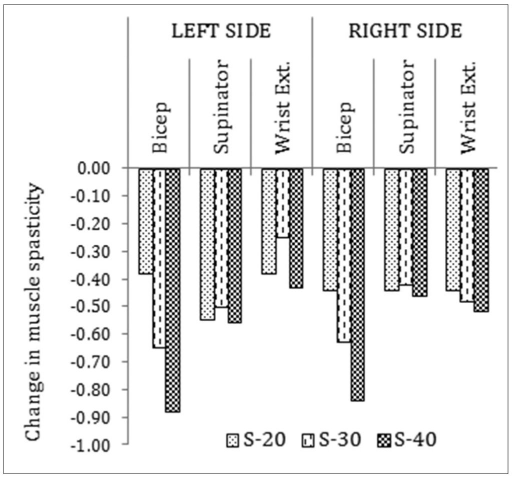

Figure 5: Reduction in spasticity of upper limb muscles observed in different groups

neural processing that enhances cortical excitability[27] and it is known that rTMS at higher frequencies (>5 Hz) promotes neuronal excitation.[28] The stimulation of the motor cortex of patients with CP leads to increase in the inhibitory input of the corticospinal tract and reduces the hyperactivity of the gamma and alpha neurons responsible for spasticity thereby reducing muscle tightness.[29] This is further supported by a report on improvement of motor score and gait pattern with high-frequency rTMS combined with rehabilitation therapy in the management of motor impairment and spasticity.[30] In another study, that employed 10 Hz rTMS treatment with 2000 pulses of 20 sessions over bilateral leg motor areas significantly increased walking velocity in stroke patients.[31] These reports provide good evidence that rTMS through cortical modulation leads to increase in the neuronal activities of motor cortex that descends down the motor pathway and improves muscle function. Furthermore, there are reports that rTMS regulates the γ-aminobutyric acid (GABA) neurotransmitter which is lower and the glutamate neurotransmitter which is higher in spastic CP patients as compared to healthy individuals. Increasing the level of GABA and lowering the level of glutamate help improve motor function in these patients.[32] In addition, rTMS treatment of CP patients demonstrated improvement both in the motor and cognitive functions due to increased functional connectivity and network of the neurons.[33] Moreover, a good number of evidence have accumulated showing that rTMS can modulate neuronal networks to improve motor functions in patients suffering from stroke, multiple sclerosis, and CP.[9,34,35]

Although the results of this study are encouraging that reflects improvement in functional motor activity and reduction in spasticity, yet we believe that there were some limitations. First, the sample size was small as there were only ten patients in each group and equal distribution of hemiplegic, diplegic, and quadriplegic was not possible based on the availability of children at the center. Second, the outcome measures employed was GMFM and mMAS; and assessment was performed before and after the therapy sessions, no intermediate assessment was performed. Third, though rTMS and PT was provided on the same day, no time interval was maintained between them. In spite of the limitations, there was no emergence of any adverse effects or seizures during the study period as they are considered relatively safer and effective treatment options.

To conclude, it can be stated that rTMS combined with PT can provide a new treatment approach for the management of spastic CP. This study clearly demonstrated that increasing the number of therapy sessions significantly increased motor function and reduced muscle spasticity in CP children. Although significant improvement in spastic CP children was observed in this study, yet we do not consider that these results be interpreted as the final answer to the management of CP; instead, it may be treated as a new achievement that shows an alternative approach for treating this neurological disorder at any early stage. The reason being limited number of literature and clinical trials are available on the application of rTMS in CP. Thus, to completely evaluate the effectiveness of rTMS in spastic CP patients further research with larger population of participants is required to establish its efficacy and consistency.

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Conflicts of interest

There are no conflicts of interest.

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