**Original Article**

# Long Term Effects of 5-Hz rTMS over M1 Cortex in Spastic Cerebral Palsy: A Pilot Randomized Controlled Trial

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## ABSTRACT

*Objectives:* To determine long term effect of repetitive transcranial magnetic stimulation (rTMS) on muscle tone reduction and mobility in children with spastic cerebral palsy (CP).

*Study design:* A pilot randomized controlled trial.

*Setting:* Southern Rehabilitation Center, Songklanagarind Hospital.

*Subjects:* Spastic CP aged 5-18 years old with modified Ashworth Scale (MAS) of extremities graded 1 to 3.

*Methods:* Participants were randomized into 2 groups, rTMS and sham groups. The rTMS group received 1500 stimuli of 5-Hz stimulation, 90% resting motor threshold stimulation over the primary motor cortex for 10 consecutive working days. The sham group received 10% resting motor threshold intensity over the same area and duration of stimulation. Both groups received a standard rehabilitation program during experimental periods. Outcome measurements included MAS of extremity muscles and joint range of motion (ROM) at angle of catch (Tardieu's R1) for muscle tone and the Gross Motor Function Classification System - expanded and revised (GMFCS-ER) Thai version for mobility, were assessed before intervention, immediately after intervention, and follow up at 1, 2, 4 and 8 weeks after the last treatment session.

*Results:* Eighteen children were recruited, mean age (SD) was 95.9 (31.7) months in the rTMS group and 93.8 (20.4) months in the sham group. Their GMFCS-ER was classified as level 3 to 5. After completion of 10 sessions, there were no significant changes in MAS. ROMs at angle of catch tended to increase post intervention and during follow up period in the rTMS group. Mobility levels according to GMFCS-ER were constant within group and no difference between groups. No serious adverse event was reported entire this study.

*Conclusion:* 5-Hz rTMS over the primary motor cortex for 10 days had no additive effects of spasticity or muscle tone reduction or functional improvement in children with spastic cerebral palsy.

*Keywords:* cerebral palsy, spasticity, repetitive transcranial magnetic stimulation

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## Introduction

Cerebral palsy (CP) is a static brain lesion, which occurs in a child's developing brain and results in delayed development,[1] especially as it regards gross and fine motor functions, muscle tone, and primitive and postural reflexes. One common positive symptom of motor function is spasticity; it can be found in 60-80 percent of all cerebral palsy children.[2,3] Spasticity is defined as a velocity-dependent increase in tonic stretch reflex with exaggerated tendon jerk resulting from the hyperexcitability of the stretch reflex.[4] On the positive side of things, spasticity helps children maintain muscle mass, improve standing balance, etc; on the other hand, it could disturb hand functions or ambulation as well as cause pain or joint contracture.[5] In cases when it is disadvantageous, patients need some treatment to reduce spasticity. There are many options to reduce spasticity including pharmacological therapy, physical therapy, chemical neurolysis, selective dorsal rhizotomy, etc.[6] Treatment selection depends on multiple factors such as regional or total body involvement and severity of symptoms. However, these therapies are associated with side effects like drowsiness from medication or pain on passive stretching, which can be a limitation to treatment continuation. New interventions have been tried to alleviate these problems, one of them is transcranial magnetic stimulation (TMS).

TMS is a procedure which utilizes a non-invasive machine to stimulate the brain and expecting brain plasticity; it is typically combined with standard therapy in a rehabilitation program. TMS has been used to study children suffering from multiple neurological disorders, e.g., stroke, CP, and neuropsychiatric disorders.[7] In comparison to other forms of treatment, the advantages of TMS consist in the fact that it is less invasive, less pain and less complicated procedure for clinical applications. So, its most important advantages are safety and well-tolerable in children.[8] TMS has been studied in children for many years; only a few benign complications have been reported. A systematic review of TMS studies involving more than 1,000 children reported adverse events

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at a rate of around 3-6 percent, and such incidences were mainly minor and resolved spontaneously.[9]

Applications of TMS in treatment of spasticity in patients with stroke and spinal cord injury have been studied.[10] The effectiveness of TMS in the treatment of spasticity in CP was reviewed in 2014; they reported that 5 sessions of high-frequency repetitive transcranial magnetic stimulation (rTMS) over the primary motor cortex was effective in reduction of spasticity in upper extremities.[11] Another study in 2016, researchers found a similar outcome concerning spastic reduction after 20 sessions of 5-Hz frequency rTMS, and also demonstrated effective outcomes in motor function improvement.[12] However, both studies evaluated only the post-interventions effects of rTMS.

Although many researches have reported positive effects of rTMS on spasticity, most of them have shown only immediate effects. Our study was conducted to investigate any additional and long-term effects of high-frequency rTMS over the M1 cortex on reduction of spasticity in cerebral palsy children. We also assessed the benefit of rTMS combined with a standard rehabilitation program on functional ambulation level.

## Methods

*Study design*

This randomized controlled trial (RCT) was approved by the Ethical Committee of Faculty of Medicine, Prince of Songkla University (EC No: 55-195-11-1-2).

*Participants*

Spastic CP children between 5 and 18 years old with modified Ashworth Scale (MAS) of extremity muscles graded 1 to 3 were invited to enter the study. The recruitment process was conducted between early 2013 and the end of 2016 at Songklanagarind Hospital, Faculty of Medicine, Prince of Songkla University, Thailand. The parents of eligible participants were informed about the study details and then asked to sign the informed consent. All participants had to be able to participate in the treatment program for 2 consecutive weeks. We excluded other types of CP, e.g., athetoid and hemiballismus types, and those who had received botulinum toxin injections or chemical neurolysis within 6 months prior to the study. Patients with contraindications for rTMS therapy, uncontrolled seizures, metallic implants in the head and neck areas, implanted pacemaker or programmable VP shunt, and medication to reduce seizure threshold (bupropion, clomipramine, maprotiline, chlorpromazine, clozapine, methylphenidate), were also excluded due to safety reasons.[13]

*Randomization*

Eligible participants were randomized into either the intervention (rTMS) or sham group using the block-of-4 method. Regarding sample size calculation for RCT based on the study of Valle, et al.,[14] each group should have 37 subjects recruited.

*Intervention*

All participants were requested to stop all antispastic drugs at least 2 weeks prior to the commencement of the intervention. Thereafter, muscle tone of extremity muscles and mobility level were assessed by the investigator (ST) throughout the study period. Both the assessor and all participants were blinded as what group they belonged.

A Magstim®, model rapid,[2] magnetic stimulation machine was employed in this study. An air-cooled coil consisting of two 92-mm diameter coils was used in the entire study. This type of coil has a peak magnetic field of 0.93 Tesla. During intervention, a registered nurse who was trained for TMS application, performed the brain stimulation for all participants. The primary motor (M1) cortex was stimulated to identify hotspot and the resting motor threshold (RMT) of the lesioned side of the brain or the more severe cortex; the motor evoked potential (MEP) of abductor pollicis brevis muscle was also recorded. If we could not detect the MEP of the lesioned side, we used the RMT of the contralateral cortex instead.

In the intervention group, the M1 cortex was stimulated with 90.0% RMT, at a 5-Hz frequency, 300 stimuli per train, an intertrain interval of 2 minutes, for 5 trains, and a total of 1500 stimuli per session. The sham group received 10.0% resting motor threshold intensity over the M1 cortex area with the same duration of stimulation. Following each rTMS therapy, all participants received the same rehabilitation program which consisted of physical therapy and occupational therapy twice a week for 2 weeks then they received home program during follow up period. All had rTMS therapy for 10 consecutive working days. Following the risk mitigation guide, all participants were provided earplugs for hearing protection at every rTMS session.[15] During the study period, all parents were informed not to give any antispastic and sedative medication, receive other rehabilitation program at other medical facilities, or apply a new orthosis, to their children.

*Outcome measurements*

The outcome measurements were recorded immediately post-intervention and at 1 week, 2 weeks, 4 weeks, and 8 weeks after the last day of the intervention. The primary outcome measure was the MAS grade. The secondary outcomes were range of motions (ROMs) at the first catch of sensation, Tardieu's R1, which is a joint angle where examiner can feel a "catch" as an increase in muscle tone reflex is elicited during fast stretch of tested joint.16 The following muscles: elbow flexors, elbow extensors, wrist flexors, finger flexors (flexor digitorum superficialis, FDS of middle finger), hip adductors, knee extensors, and ankle plantar flexors, were assessed for MAS. Joint ROMs at the first catch of sensation were measured using a manual goniometer. Another secondary outcome was mobility level according to the Gross Motor Function Classification System - Extended and Revised, Thai version (Thai GMFCS-ER).[17]

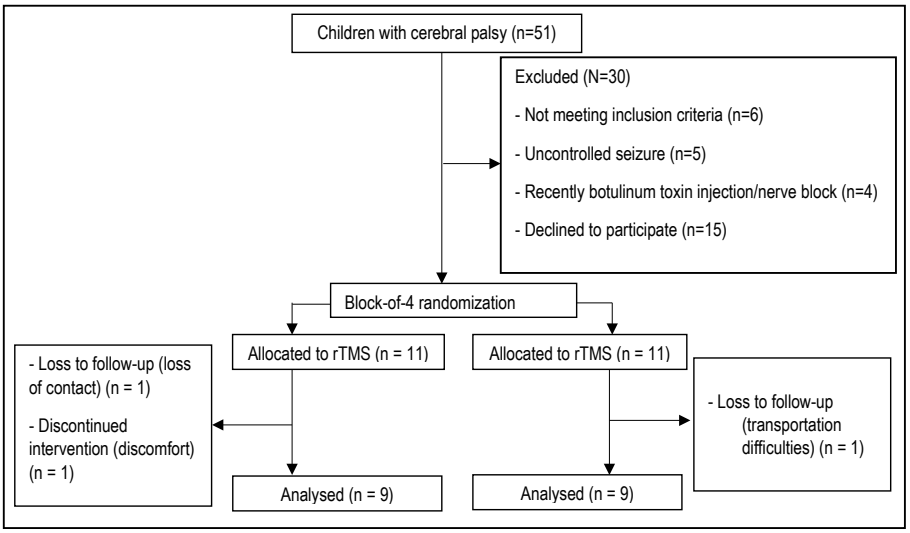


**Figure 1.** CONSORT flow diagram of the study
rTMS = intervention group, received repetitive transcranial magnetic stimulation
Sham = sham group, received sham magnetic stimulation

**Table 1.** Baseline characteristics

| | rTMS (N = 9) | Sham (N = 9) | *p*-value |
|---|---|---|---|
| Age (months) | | | 0.869 |
| Mean (SD) | 95.9 (31.7) | 93.8 (20.4) | |
| Median [Min, Max] | 84.0 [64.0, 168] | 96.0 [72.0, 124] | |
| Sex | | | 1 |
| Male | 5 (55.6) | 6 (66.7) | |
| Female | 4 (44.4) | 3 (33.3) | |
| Causes | | | 0.801 |
| Perinatal | 3 (33.3) | 3 (33.3) | |
| Postnatal | 1 (11.1) | 2 (22.2) | |
| Prenatal | 5 (55.6) | 4 (44.4) | |
| Types | | | 0.856 |
| Diplegia | 2 (22.2) | 3 (33.3) | |
| Hemiplegia | 2 (22.2) | 2 (22.2) | |
| Tetraplegia | 5 (55.6) | 4 (44.4) | |
| GMFCS-ER | | | 1 |
| Level 1, n (%) | 0 | 0 | |
| Level 2, n (%) | 0 | 0 | |
| Level 3, n (%) | 1 (11.1) | 2 (22.2) | |
| Level 4, n (%) | 2 (22.2) | 1 (11.1) | |
| Level 5, n (%) | 6 (66.7) | 6 (66.7) | |

rTMS, repetitive transcranial magnetic stimulation; SD, standard deviation; GMFCS-ER, Gross Motor Function Classification System - Extended and Revised, Thai version;

*Statistical methods*

The statistical data was analyzed via R program version 3.2.2. The baseline characteristics data are reported as mean and percentage. T-test and Chi-square test were used to compare the baseline data. A comparison between the MAS scores and the ROMs pre- and post-intervention was carried out, and the level of statistical significance was set at a *p*-value less than 0.05. For the in-between group data analysis, the MAS grades were classified into two groups; non-spastic (MAS gr 0 to 1+) and spastic (MAS gr 2 to 4). The Generalized Linear Mixed Effects Model (GLMM) was selected to analyze the repeated measures of MAS and ROMs between the groups (rTMS and sham) over time. The pre- and the post-intervention Thai GMFCS-ER grades were compared betwen groups using Fisher's exact test.

## Results

Fifty-one children with CP were recruited into the screening process (Figure 1). Six did not meet the inclusion criteria, five had uncontrolled seizures, and four had recently received chemical neurolysis/botulinum toxin injections. Thirty-six eligible subjects were informed in details about the study's aims and protocol. Eleven were allocated to the rTMS group; one of them requested to withdraw from the study after 2 sessions of rTMS due to inconvenience to continue

**Table 2.** Comparison of pre- and post- intervention modified Ashworth Scale (MAS) outcomes between the rTMS and the sham groups

| | rTMS (N = 9) | | | | | | Sham (N = 9) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | T0 | T1 | T2 | T3 | T4 | T5 | T0 | T1 | T2 | T3 | T4 | T5 |
| Elbow flexors | | | | | | | | | | | | |
| Non-spastic | 8 (88.9) | 6 (66.7) | 9 (100) | 8 (88.9) | 9 (100) | 9 (100) | 9 (100) | 8 (88.9) | 9 (100) | 6 (66.7) | 9 (100) | 9 (100) |
| Spastic | 1 (11.1) | 3 (33.3) | 0 (0) | 1 (11.1) | 0 (0) | 0 (0) | 0 (0) | 1 (11.1) | 0 (0) | 3 (33.3) | 0 (0) | 0 (0) |
| Elbow extensors | | | | | | | | | | | | |
| Non-spastic | 9 (100) | 9 (100) | 9 (100) | 9 (100) | 9 (100) | 9 (100) | 9 (100) | 9 (100) | 9 (100) | 9 (100) | 9 (100) | 9 (100) |
| Spastic | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Wrist flexors | | | | | | | | | | | | |
| Non-spastic | 7 (77.8) | 8 (88.9) | 9 (100) | 8 (88.9) | 9 (100) | 9 (100) | 6 (66.7) | 6 (66.7) | 9 (100) | 6 (66.7) | 9 (100) | 9 (100) |
| Spastic | 2 (22.2) | 1 (11.1) | 0 (0) | 1 (11.1) | 0 (0) | 0 (0) | 3 (33.3) | 3 (33.3) | 0 (0) | 3 (33.3) | 0 (0) | 0 (0) |
| Finger flexors | | | | | | | | | | | | |
| Non-spastic | 8 (88.9) | 8 (88.9) | 8 (88.9) | 8 (88.9) | 6 (66.7) | 8 (88.9) | 6 (66.7) | 6 (66.7) | 6 (66.7) | 6 (66.7) | 6 (66.7) | 6 (66.7) |
| Spastic | 1 (11.1) | 1 (11.1) | 1 (11.1) | 1 (11.1) | 3 (33.3) | 1 (11.1) | 3 (33.3) | 3 (33.3) | 3 (33.3) | 3 (33.3) | 3 (33.3) | 3 (33.3) |
| Hip adductors | | | | | | | | | | | | |
| Non-spastic | 1 (11.1) | 8 (88.9) | 5 (55.6) | 8 (88.9) | 8 (88.9) | 5 (55.6) | 6 (66.7) | 7 (77.8) | 7 (77.8) | 7 (77.8) | 8 (88.9) | 7 (77.8) |
| Spastic | 8 (88.9) | 1 (11.1) | 4 (44.4) | 1 (11.1) | 1 (11.1) | 4 (44.4) | 3 (33.3) | 2 (22.2) | 2 (22.2) | 2 (22.2) | 1 (11.1) | 2 (22.2) |
| Knee extensors | | | | | | | | | | | | |
| Non-spastic | 8 (88.9) | 8 (88.9) | 8 (88.9) | 8 (88.9) | 8 (88.9) | 8 (88.9) | 6 (66.7) | 6 (66.7) | 6 (66.7) | 6 (66.7) | 6 (66.7) | 6 (66.7) |
| Spastic | 1 (11.1) | 1 (11.1) | 1 (11.1) | 1 (11.1) | 1 (11.1) | 1 (11.1) | 3 (33.3) | 3 (33.3) | 3 (33.3) | 3 (33.3) | 3 (33.3) | 3 (33.3) |
| Ankle plantar flexors | | | | | | | | | | | | |
| Non-spastic | 1 (11.1) | 3 (33.3) | 1 (11.1) | 0 (0) | 2 (22.2) | 2 (22.2) | 3 (33.3) | 3 (33.3) | 3 (33.3) | 3 (33.3) | 3 (33.3) | 3 (33.3) |
| Spastic | 8 (88.9) | 6 (66.7) | 8 (88.9) | 9 (100) | 7 (77.8) | 7 (77.8) | 6 (66.7) | 6 (66.7) | 6 (66.7) | 6 (66.7) | 6 (66.7) | 6 (66.7) |

Non-spastic, MAS gr 0 to 1+; spastic, MAS gr 2 to 4; rTMS, repetitive transcranial magnetic stimulation;
T0, pre-intervention; T1, immediate post-intervention; T2, 1-week post-intervention; T3, 2-week post-intervention, T4, 4-week post-intervention; T5, 8-week post-intervention

**Table 3.** Generalized linear mixed effects models (GLMM) for modified Ashworth Scale (MAS) and angle of catch

| Muscles | MAS | *p*-value | Angle of catch | *p*-value |
|---|---|---|---|---|
| Elbow flexors | 0.248 (-1.142, 1.639) | 0.73 | -24.3 (-53.4, 6.0) | 0.14 |
| Elbow extensors | 0.725 (-1.905, 1.346) | 0.25 | -18.0 (-35.5, -0.3) | 0.06 |
| Wrist flexors | -1.866 (-6.012, -1.866) | 0.38 | -14.2 (-31.1, 1.8) | 0.11 |
| Finger flexors | -0.545 (-4.303, 3.213) | 0.78 | 7.2 (-17.5, 31.9) | 0.58 |
| Hip adductors | 2.047 (-0.413, 4.506) | 0.10 | 1.9 (-6.1, 9.4) | 0.65 |
| Knee extensors | -3.262 (-15.542, 9.017) | 0.60 | -22.3 (-42.2, -0.7) | 0.05 |
| Ankle plantarflexors | 1.088 (-6.889, 9.064) | 0.79 | 2.6 (-7.1, 11.8) | 0.58 |

the program. Another two, one in each study group, were lost to follow-up after the last rTMS session. Nine from the rTMS and nine from the sham group, completed the study, and their data underwent statistical analysis. The participants' baseline characteristics are shown in Table 1; there was no statistical different in terms of age, gender, cause and type of CP, and mobility between the groups.

The primary outcome, MAS, was assessed and graded immediately post-intervention and followed over an 8-week period. The participants were divided into the spastic and the non-spastic groups for statistical analysis as shown in Table 2. The GLMM of MAS scores for each muscle over time are shown in Table 3. Some reduction of MAS in rTMS group by time with GLMM of the wrist flexors, hip adductors and knee extensors was observed, but was not statistically significant.

Figure 2 shows the first catch ROM values between the pre- and post-intervention (8 weeks) period. No tendency for an increased ROM post-intervention and its maintenance until the last visit of the study was observed. Meanwhile, the differences in the GLMM of the first catch ROM for each muscle did not reach statistical significance as shown in Table 3. The GMFCS-ER scores were constant immediately post-intervention and during the follow-up period.

There were only minor complications related to the intervention employed in this study. Only two participants in the rTMS group reported mild headache and dizziness after rTMS (22.2%); none of the participants in the sham group experienced these side effects. In both cases, the symptoms resolved spontaneously within a day without any medication or treatment. No other adverse events or serious complications like seizure or loss of conscious were reported.

## Discussion

After ten sessions of high-frequency rTMS over the M1 cortex in combination with the standard rehabilitation program, no statistically significant differences in muscle tone or

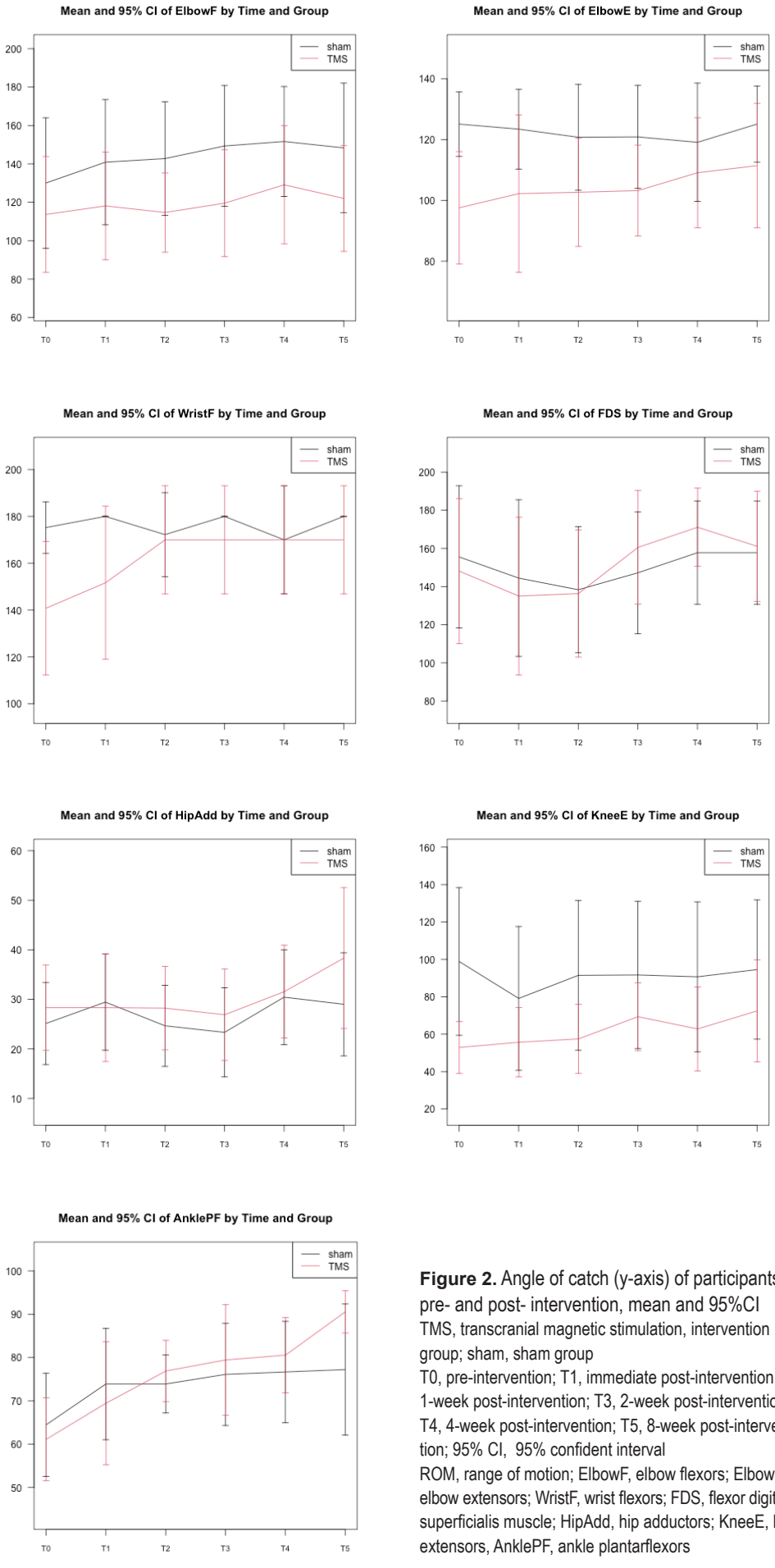


**Figure 2.** Angle of catch (y-axis) of participants pre- and post- intervention, mean and 95%CI
TMS, transcranial magnetic stimulation, intervention group; sham, sham group
T0, pre-intervention; T1, immediate post-intervention; T2, 1-week post-intervention; T3, 2-week post-intervention, T4, 4-week post-intervention; T5, 8-week post-intervention; 95% CI, 95% confident interval
ROM, range of motion; ElbowF, elbow flexors; ElbowE, elbow extensors; WristF, wrist flexors; FDS, flexor digitorum superficialis muscle; HipAdd, hip adductors; KneeE, knee extensors, AnklePF, ankle plantarflexors

spasticity (MAS grade and first catch ROM) of the tested muscles or the mobility levels (GMFCS-ER) were detected. However, we found a tendency of an increase in the first catch ROM in the intervention group during the 8-week follow-up period as it regards the wrist flexor, hip adductor, and ankle plantar flexor muscles.

Our results were different from those of the 2007 study by Valle, et al.[14] They found an immediate reduction of spasticity in upper extremity muscles after a single session following the 5-Hz rTMS protocol. They did not compare the treatment outcomes with those obtained from standard physical and occupational therapy.[14] Our study, which simulated the routine clinical practice by combining brain stimulation and physiotherapy program, showed similar outcomes for both the standard rehabilitation program and the rTMS therapy in spastic reduction. In another study by Gupta,[18] an experimental study in children with spastic CP, the subjects received rTMS over the motor cortex followed by standard therapy for 20 consecutive days; after that, they compared MAS and functional outcomes. They found a significant change in both parameters, but the magnitude of change was small; the MAS scores reduced by 0.13-0.63, and the GMFM scores leveled up to 0.6%-2.6%. Meanwhile, a minimal detectable change (MDC) in the MAS score, defined as a change of one point,[19] reflects a real change, not only a statistically significant change. Moreover, similar to our results, positive outcomes could have been a result of standard therapy (20 to 40 sessions along with rTMS).

During statistical analysis, we divided the MAS grades into two categories based on clinical application. An MAS grade between 0 and 1+ impacts minimal disadvantage; this severity does not disturb most functional activities. According to the results of this study, the combined rTMS protocol could not add on any positive effect in spastic reduction. More than 10 treatment sessions may be required in order to obtain any benefit because the proposed mechanism of rTMS in spastic CP has been described in light of the cortical plasticity and central motor reorganization theory,[20] which takes time to initiate. In addition, high-rate rTMS could enhance the descending control pathway via the cortico-spinal and the cortico-reticulo-spinal tracts,[21] which results in spasticity reduction and voluntary motor improvement.

Another reason for the negative outcomes of this protocol could be the site of brain stimulation due to differences in pathology in spastic CP brains. For example, hemiplegic CP mostly involves one side of the brain, but diplegic and tetraplegic CP may have bilateral cortical lesions.[22,23] Hence, single ipsilesional brain stimulation may not be enough when bilateral cortical lesions are at play, especially in tetraplegic or diplegic CP. Even in hemiplegic CP, there is evidence that contralesional brain stimulation with rTMS can improve hand function.[24] Thus, the rTMS protocol should be adjusted according to the specific type of patient.

Severity of brain lesion and neural system in our participants might be affect outcomes of the study. More than half of participants had GMFCS-ER level 5, this finding reflected more severe neural damage and poor integrity of corticospinal tract. Our TMS protocol aim to enhance neural plasticity through corticospinal tract via M1 cortex and surrounding connected areas. This reason could explain an insignificance improvement of motor functions. Future study should be conducted with subgroup study of less severity of CP or alternative TMS protocol.

Major limitation of this study was its small numbers of population, only one-fourth of the calculated sample size were recruited into an experiment. As our pilot study results indicated non-superior effects of rTMS over standard rehabilitation program, we decided to discontinue our study. In addition, other factors supported premature termination including many eligible participants refused to stop antispastic drugs, uncontrolled seizure subjects, too long recruitment period. Other limitations were varying types of spastic cerebral palsy and the non-specific functional assessment employed. Further research might focus on specific stimulation protocols for each type of CP, especially as it regards both site and side of stimulation. Multiple-site brain stimulation, such that of a neural network, has been proposed by a recent study in order to achieve better brain plasticity.[25] Finally, the assessment tools, e.g., “box and blocks test” for hand muscles, “reaching time” for the elbow flexors, etc., should be specific to the targeted muscle involvement.

## Conclusion

The combination of high frequency repetitive transcranial magnetic stimulation (rTMS) on the primary motor cortex and rehabilitation therapy over 10 sessions had no additive effects on spasticity reduction or functional improvement over rehabilitation program only in children with spastic cerebral palsy.

## Disclosure

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