The Impact of Repetitive Transcranial Magnetic Stimulation on Affected and Unaffected Sides of a Child with Hemiplegic Cerebral Palsy*

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*Abstract***— The purpose of this study was to investigate the therapeutic effects of neuro-navigated repetitive transcranial magnetic stimulation (rTMS) combined with occupational therapy (OT) on gait impairment of a child (male, age: 13.2) with spastic hemiplegic cerebral palsy (CP). The treatment included 4 days a week of rTMS sessions for 3 weeks and 4 days of rTMS and OT sessions per week for 3 weeks. Transcranial magnetic stimulation (TMS) was used to evaluate corticospinal tract (CST) activities and H-reflex test was used to assess reflex hyper-excitability. Common clinical tests demonstrate the clinical status of the patient. Evaluations were performed in 4 time steps: baseline, 3 weeks after the beginning of the treatment, at the end of the treatment, and 1 month after the end of the treatment. The patient did not receive any specific treatment after the end of the treatment up to the follow up evaluations. The tests' results were compared between the affected and unaffected legs of the patient. Four parameters of the TMS test were calculated (motor evoked potential (MEP) latency, MEP peak-to-peak amplitude, cortical silent period (cSP), and stimulation intensity). These parameters were all improved for the affected side and cSP improved for the unaffected side, but MEP p-p amplitude and intensity got worse slightly for the unaffected side. Recruitment curves of H response and M-wave of the H-reflex test for both sides were obtained. Improvements could be seen after the treatment for both sides. Max H response on max M-wave (H/M) and H response latency got better after the treatment for both sides. Walking speed for self and fast velocity, timed up and go, and walking endurance improved during and after the treatment. All the improvements persisted after one month of the end of the treatment in the follow up evaluations. These findings indicate that rTMS combined with OT can have effective and long-lasting impact on neuromuscular impairments in spastic CP children.**

Keyword – spasticity, gait, impairment, TMS, navigation, reflex, neurorehabilitation, rehabilitation

I. Introduction

Spasticity is a common disorder among children with cerebral palsy (CP). It can affect the ability of the patient to move properly. This neurological disorder is caused by brain lesion when the brain is under development. This can affect the controlling role of the brain and the descending pathways. Since this disease affects the quality of life of the patients, proper treatments should be taken into consideration since the childhood [1]. Spasticity can have different origins and the exact contribution of each of these causes are not known to date. Single pulse transcranial magnetic stimulation (TMS) can be used to investigate the corticospinal tract (CST) activities and its integrity, but we cannot determine the contribution of cortical and spinal mechanisms separately. Therefore, Hoffman reflex (H-reflex) can be used to examine spinal pathways functionality. In H-reflex test, a muscle twitch occurs following the electrical stimulation of the corresponding muscle's nerve [2] and different features of this response help quantify reflex and study the hyper-excitability of the patient. Different treatments are being performed to help the patients live more easily, but none of them is approved as the best treatment or has long lasting effects. New systematic therapies should be studied to help the patients advance their quality of life. Repetitive transcranial magnetic stimulation (rTMS) is a modern noninvasive neurorehabilitation technique that is shown to have long lasting positive effects in treatment of different diseases. A systematic protocol of rTMS treatment and a proper number of sessions can lead to enhanced lasting of the impacts [3]. In this study, we used inhibitory rTMS (frequency=1Hz) to avoid seizure and force the affected side to function better.

We evaluated the CST activity and integrity via single pulse TMS, reflex hyper-excitability via H-reflex test, and general clinical status of the patient via common clinical tests. Assessments were performed in 4 time steps, the last assessment being the follow up. Hence, we studied the effects of rTMS treatment and rTMS treatment combined with OT and the durability of the treatment's impacts.

II. Experimental Protocol

A child (male, age: 13.2) with spastic hemiplegic cerebral palsy and GMFCS level II participated in this research. The right side of the patient was affected. the TMS, H-reflex, and clinical tests were performed for both sides in 4 time steps: the baseline before the treatment, after 3 weeks of rTMS treatment, after 3 weeks of rTMS combined with occupational therapy (OT), 1 month after the treatment.

The subject's parent provided written informed consent. The study has ethical approval from the Tehran University of Medical Sciences Institutional Review Board.

A. The treatment

Resting motor threshold (rMT) is the intensity of stimulation in which the peak-to-peak amplitude of the resulting motor evoked potential (MEP) in the target muscle is above 50μV in at least 5 out of 10 pulses [4]. The

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treatment lasted for 6 weeks. The patient received 1200 pulses of 1Hz rTMS (20 minutes) with the intensity of 100% of his rMT in each rTMS session on the healthy side of the brain (on leg area of primary motor cortex), 4 days per week for 3 weeks. Then the treatment continued for another 4 days per week for 3 weeks and this time, each rTMS session was followed by an OT session that lasted for 45 minutes.

Figure-of-8 coil was used for the treatment. We used Magstim Rapid^2 device for performing rTMS and Brainsight system (which is compatible with Magstim device) for neuro-navigation; thus, we minimized any possible changes that might occur during the treatment (Fig. 1). This protocol is inhibitory, which means that the function of the healthy hemisphere will be inhibited, so that the other side is forced to function better.

Figure 1. The patient during an rTMS session

B. Single pulse TMS

Single pulses of TMS were applied to both sides of the patient's brain. We started with low intensity and increased it in 5% steps to find the rMT. The MEP of the tibialis anterior muscle was recorded using Ag-AgCl surface electrodes and Keypoint Dantec system with sampling frequency of 48kHz in four evaluations. The same figure-of-8 coil as the treatment was used for the evaluations.

C. H-reflex test

By using H-reflex, we aimed to study the spinal mechanisms for both affected and unaffected sides of the patient's lower limbs. This test was done by electrical stimulation of the tibial nerve in the popliteal fossa. The resulting electromyography (EMG) was recorded from the soleus muscle using Ag-AgCl surface electrodes and Keypoint Dantec system with sampling frequency of 48kHz. The stimulation duration was 1ms. First we applied low intensities (starting from 1 mA), then increased the intensity little by little to get the H response. By increasing the intensity, the H response increased in amplitude until it reached a maximum amplitude and then started to decrease and M-wave appeared. Finally, when we got to a point where the peak-to-peak amplitude of the M-wave did not increase anymore and the H response disappeared, we stopped the test [5].

D. Clinical Evaluations

There are some common clinical tests that are used to assess the clinical status of CP patients. Walking speed of the patient is evaluated using 10 meter walk test (10MWT) in which the patient has to walk a path of 10 meters, the time is recorded for 6 meters of the path in the middle of it, then the 6 meter is divided by the time in seconds. Therefore, we get the walking speed of the patient. We assessed 10MWT for self and fast velocity of the patient in three trials for each evaluation and averaged the trials. Walking endurance of the patient is assessed using 6 minute walk test (6MWT) in which the patient walks for 6 minutes and the path that he has passed is recorded in meters. Timed up and go (TUG) is another clinical test in which the patient stands up from a seat, walks a 6 meter path and returns to the seat. The time is recorded during this movement. The 6MWT and TUG tests were performed in 3 trials and averaged as well in all four evaluations. Time measurements were done using a chronometer.

III. Data Analysis

A. Single pulse TMS

An IIR notch filter was applied to remove powerline interference. Four parameters of the MEP signal at rMT intensity, which were calculated using custom MATLAB written program, are: MEP latency (the latency from the stimulation pulse to the onset of the MEP in milliseconds), MEP p-p amplitude in microVolts, cortical silent period (cSP) (the silent period of the muscle voluntary contraction after applying a TMS pulse, which starts from the beginning of the MEP to the beginning of the EMG background), and the stimulation intensity to get the rMT [6].

B. H-reflex test

An IIR notch filter helped remove the powerline interference from the signals. Also, a wavelet based principal component analysis was performed to get the principal signal. Twenty stimulations were applied and recorded for each leg and in each of the evaluations. The resulting recruitment curves were obtained. Recruitment curve of H-reflex test is the intensity versus the p-p amplitude of H response and M-wave normalized to maximum M-wave. Moreover, the max H response on max M-wave and the H response latency (the time from the stimulation to the onset of max H response) were computed using custom written MATLAB code [7].

IV. Results

A. Single pulse TMS

The baseline evaluation versus other 3 evaluations for 4 parameters of the TMS test are shown in Fig. 2. The green markers represent the affected side (right side) and the red markers show the unaffected side. The triangle markers show the evaluation after 3 weeks of rTMS, the square markers represent the evaluation after 3 weeks of rTMS+OT, and the circle markers are the follow up evaluations after 1 month of the end of the treatment. The changes during the treatment express improvement in these features.

B. H-reflex test

Recruitment curves for H response and M-wave were drawn for both sides for 4 assessments (Fig. 3). The p-p amplitude of responses were normalized to the max M-wave. Furthermore, the results for H/M ratio and H response latency for both sides are given in Fig. 4. The results express improvement of these feature for the affected side.

C. Clinical evaluations

Results for clinical tests are demonstrated in Fig. 5. The averaged values among trials for each evaluation and for 4 evaluations can be seen. The clinical status of the patient has improved during and after the course of the treatment.

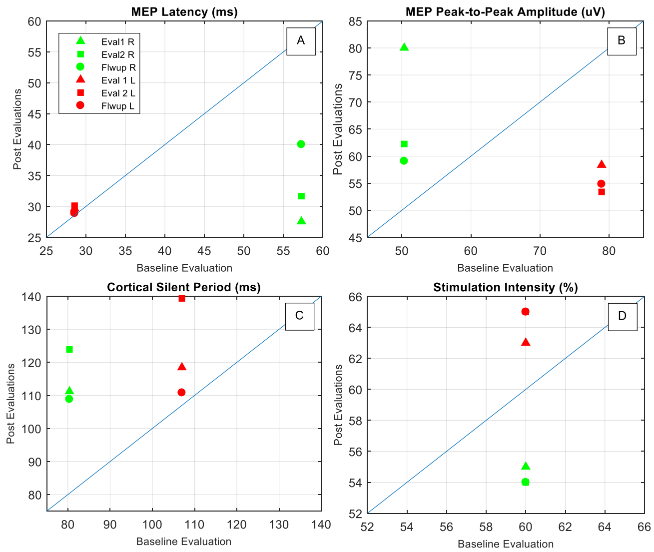

Figure 2. Baseline versus other evaluations for TMS parameters; (A) MEP latency, (B) MEP p-p amplitude, (C) cSP, (D) Stimulation intensity. Triangle: the evaluation after week 3, Square: the evaluation after week 6, Circle: the follow up evaluation. Green: affected, Red: unaffected.

V. Discussion and Conclusion

The MEP latency represents the propagation time of the pulse in the CST. This feature is higher in CP patients compared to normal people [8]. According to Fig. 2(A), MEP latency decreased after the treatment and even in the follow up evaluation for the affected side, but slightly increased for the unaffected side. This was expected since we inhibited the unaffected side with 1Hz rTMS. Although, the MEP latency did not change significantly on the unaffected side.

The MEP p-p amplitude demonstrates the integrity of the CST and peripheral tracts to muscles. In CP patients, this feature is lower than normal people [9]. As shown in Fig. 2(B), this feature improved for the affected side as a result of the treatment. It decreased for the unaffected side, but the final value for both sides were almost similar.

Cortical silent period (cSP) is a combination of inhibition in spinal and cortical tracts. First 50ms of it is because of spinal inhibitory mechanisms and the rest of it is because of the cortical inhibitory mechanisms. The cSP is lower in CP patients compared to normal people due to the impaired cortical inhibition [10]. As you can see in Fig. 2(C), the treatment improved this feature for both sides of the patient, although the final changes were higher for the affected side compared to the unaffected side. It seems that the cortical inhibition has improved in both hemispheres. Further investigations on the cortical inhibition mechanism of hemiplegic spastic CP patients should be done to further explain this result.

Finally, the stimulation intensity was decreased on the affected side and increased on the unaffected side. Both of the follow up evaluations stayed the same as the post evaluations. This illustrates that this protocol of treatment has a significant durability (at least for 1 month) [11].

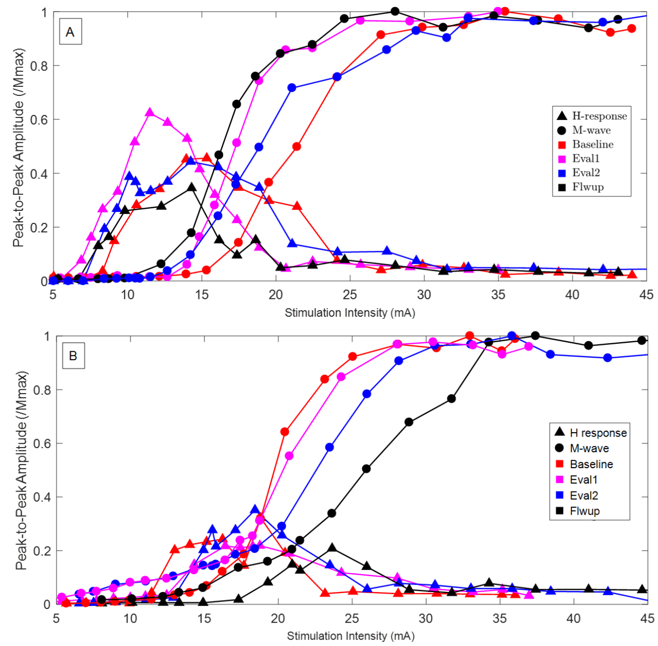

Figure 3. Recruitment Curves for H response and M-wave; (A) affected side, (B) unaffected side. Colors represent evaluations. Triangles are H response and circles are M potentials.

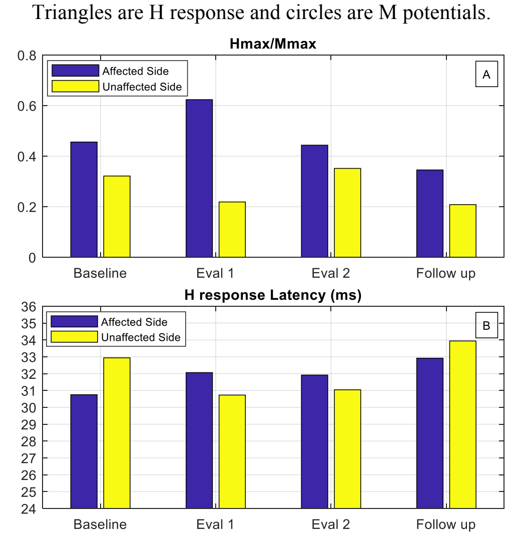

Figure 4. H-reflex results; (A) Hmax/Mmax, (B) H response latency.

The recruitment curves of the H-reflex test for both sides were obtained and normalized to max M-wave. As demonstrated in Fig. 3, the M-wave did not change significantly after the treatment. The H response of the affected side got worse on first evaluation and then improved on the second and follow up evaluations. The H response of the unaffected side improved for the first evaluation and then got worse slightly on the second evaluation after the treatment. The results of the follow up evaluation for H response recruitment curve of the unaffected side showed some improvements compared to the baseline evaluation. One-Hz rTMS on the motor cortex depresses MEP amplitude and enhances effects on the H-reflex. It also does not change the M-wave, which is generated by peripheral nerve stimulation [8-9]. As we can see, this mechanism is true when we just had rTMS treatment. So improvement of the H-reflex for the unaffected side and deterioration of the affected side on the first evaluation can be explained.

Since the H response is higher in spastic CP patients and the M-wave is similar to normal people, CP patients have higher H/M ratio [14]. As illustrated in Fig. 4(A), the H/M ratio followed the mechanism that we just mentioned. Thus, H/M amplitude ratio was increased due to 1Hz rTMS in first evaluation for the affected side and decreased for the unaffected side. Inhibitory rTMS treatment might facilitate monosynaptic spinal cord reflexes by inhibiting the corticospinal projections that modulate spinal excitability. When the rTMS treatment is combined with OT, we observe improvement for the affected side and a slight deterioration on the unaffected side. We should note that the follow up evaluations for both sides were improved compared to the baseline evaluations, which means that the facilitation of the descending pathways by rTMS treatment is observable in long term.

The H response latency is lower in CP patients due to the impaired inhibition of the spinal reflexes [15]. As demonstrated in Fig. 4 (B), this feature improved gradually for the affected side and got worse slightly for the unaffected side. But in the follow up evaluations, it has improved for both sides compared to the baseline evaluations.

According to Fig. 5, clinical status of the patient was improved during the treatment in terms of the clinical tests. Walking speed for self and fast velocity, timed up and go, and walking endurance of the patient were developed during the treatment. The follow up evaluations show that this improvement had lasting results and the general clinical status of the patient was enhanced even 1 month after the treatment without receiving any kind of treatment.

These promising results indicate that the rTMS treatment combined with OT can have therapeutic effects that are long lasting. Further studies with a larger sample sizes are required to verify and generalize these outcomes and approve this intervention as an effective therapy for spastic CP children.

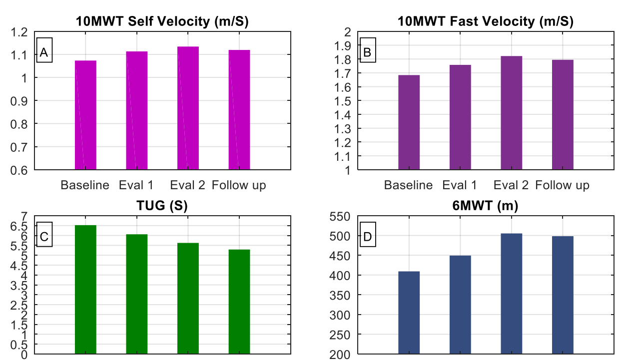

Figure 5. Clinical evaluations; (A) 10MWT self-velocity, (B) 10MWT fast-velocity, (C) TUG, (D) 6MWT.

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