Reduction of Spasticity in Cerebral Palsy by Anodal Transcranial Direct Current Stimulation

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Objective: *To evaluate the anti-spasticity effects of anodal transcranial direct current stimulation (tDCS) in individuals with spastic cerebral palsy (CP).*
Material and Method: *Forty-six children and adolescents with cerebral palsy were randomly assigned to either active (1 mA anodal) or sham (placebo) tDCS over the left primary motor cortex (M1) on five consecutive days. Both group also received routine physical therapy. Measures of spasticity and passive range of motion (PROM) were administered before treatment, immediately after treatment, and at 24- and 48-hours follow-up.*
Results: *Participants assigned to active tDCS treatment evidenced significantly more pre- to immediately post-treatment reductions in spasticity than participants assigned to the sham ($p = 0.004$, $p<0.001$, and $p = 0.004$ for shoulder, wrist, and fingers respectively) and these improvement in spasticity maintained for at least 48 hours for wrist joints ($p = 0.023$). There was only one participant in the active tDCS condition developed erythematous rash. However, all participants tolerated the tDCS well without any serious adverse events.*
Conclusion: *Anodal tDCS appeared to reduce CP-related spasticity (but not PROM) in the short term. Researches examine the long term benefits of this intervention on spasticity are warranted.*

Keywords: *Cerebral palsy, Spasticity, Transcranial direct current stimulation, Noninvasive brain stimulation, Children*

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Cerebral palsy (CP) is the most common motor disorder in children[1], with an incidence of more than 2.0 per 1000 live births[2] or about 10,000 infants per year in the United States[3]. Although the incidence of CP in Thailand is less, about 0.61 per 1,000 live births[4], but there are still a significant numbers of CP in Thailand.

The two most common types of cerebral palsy are spastic diplegia and hemiplegia[5]. Spasticity is an upper motor neuron syndrome characterized by a velocity-dependent increase in the tonic stretch reflexes with exaggerated tendon jerks resulting from hyperexcitability of this reflex[6]. One cause of spasticity in this population is motor cortex damage, which leads to a decrease in the cortical input to the corticospinal tract, resulting in a disinhibition of spinal segmental excitability and an increase in the muscle tone[1]. Standard treatment for spastic CP usually includes muscle stretching[1]. However, no treatment has yet been successfully eliminates spasticity in all individuals with CP[1]. There is continuing need to develop and evaluate the efficacy of additional treatments for CP-related spasticity.

Although the precise mechanisms that underlie tDCS are not yet completely understood, the effects of tDCS on cortical activity are consistent and reliable; specifically, anodal tDCS facilitates cortical activity and cathodal tDCS depresses cortical activity[7]. Given that, a possible cause of spasticity in individuals with CP is a decrease in cortical input into the corticospinal tract, and the effects of anodal tDCS on increasing cortical activity, it is reasonable to examine the potential beneficial

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effects of anodal tDCS stimulation on individuals with spastic CP.

Further support for this possibility came from a clinical study showing that 5 Hz of repetitive transcranial magnetic stimulation (rTMS) applied on the left primary motor cortex (M1) for five consecutive days (10 minutes of stimulation per day) improved upper limb range of motion in patients with spastic CP for at least two hours following treatment[8]. However, the rTMS is more costly than other noninvasive brain stimulation methods, such as transcranial direct current stimulation (tDCS).

The authors hypothesized that 20 minutes of tDCS stimulation for five consecutive days would result in significantly more pre- to post-treatment decreased in muscle spasticity than five days of sham (placebo) tDCS stimulation, and that the improvements in spasticity in the treatment group would maintain for at least 48 hours post-treatment. In addition to testing the primary hypothesis, and consistent with the call to assess the effects of treatments on more than just spasticity[8], we also explored the effects of tDCS, relative to a sham condition, on measuring of both passive range of motion on the affected side.

Material and Method

Participant recruitment and informed consent

Patients with CP and spasticity of the right upper limb were recruited via poster and brochure advertisements placed in our pediatric outpatient neurology clinic, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University and Srisangwal School, a special school for handicapped children in Khon Kaen, Thailand.

Study inclusion criteria were (1) diagnosis of spastic CP based on standard diagnostic criteria[9], (2) CP with gross motor function classification system (GMFCS) levels II-IV[10], (3) age between 8 and 18 years, and (4) upper limb spasticity grade 1 to 3, based on the modified Ashworth Scale[11]. Study exclusion criteria were (1) severe spasticity and contractures, (2) autism, mental retardation, psychosis, drug addiction, pregnancy, skull defect, epilepsy, (3) receiving concomitant alternative therapies such as herbs or massage, (4) orthopedic surgery on the upper limb, (5) initiation or change in dosage of oral antispastic drug within five days, and (6) botulinum toxin (type A or B) injections less than 90 days prior to start this study. All of the participants were provided verbal informed assent for participation, and all of the participants' guardians were provided written informed consent. The study conformed to the Declaration of Helsinki and was approved by the Ethics Committee of Khon Kaen University (identifier number HE 531161).

Sample size calculation

The number of subjects needed in each study group to have adequate power to test the primary study hypothesis was determined based on previous clinical trials assessing elbow passive range of motion. A prior study testing the effects of rTMS on elbow ROM found that a sample size of 17 individuals divided into three groups (1 Hz rTMS [n = 6], 5 Hz rTMS [n = 5], sham rTMS [n = 6]) had an effect associated with a power of 0.90 with an alpha level of 0.05[8]. If tDCS had a similar effect on our primary outcome measure, the authors determined that 46 participants (23 per condition) would provide a power of 0.90 to detect significant effects with an alpha of 0.05 (0.90).

Experimental design

The present study was organized into the following three phases. (1) A 1-day baseline evaluation which included an evaluation of (a) the degree of spasticity (primary outcome) and (b) passive range of motion (PROM; secondary outcome) of the right upper limb. (2) Five consecutive daily treatments with 1 mA anodal tDCS over the left M1 for 20 minutes each day. (3) Another evaluation of (a) the degree of spasticity and (b) PROM assessment immediately post-treatment, as well as at 24 and 48 hours after treatment. Finally, adverse events were recorded by the participant's guardians. At the time of enrollment, the patients were informed about possible adverse events.

Randomization and blinding

Just before the treatment phase, study participants were randomized in a 1:1 ratio in blocks of four randomizations (by AA) to receive either (1) routine physical therapy plus active tDCS stimulation or (2) routine physical therapy plus sham tDCS stimulation. Participants were asked to continue their routine medication regimen throughout the trial.

The staff who generated the random allocation sequence, enrolled participants, and assigned participants to interventions were not involve in any assessments. After assignment to the intervention groups, the physiotherapist who carried out the spasticity and PROM assessments (TJ) was also blinded to treatment condition.

Active and sham transcranial direct current stimulation

The tDCS was applied via 0.9% NaCl-soaked pair of surface sponge electrodes (35 cm^2) and delivered through battery-driven power supply. The constant current stimulator had a maximum output of 10 mA (Soterixmedical, Model 1224-B, New York, USA). The stimulation site over the left M1 or the C3 locus according to the international electroencephalography (EEG) 10/20 electrode placement system, per protocol published by Valle et al, 2007[8], the cathode (reference) electrode was placed on the right shoulder.

The tDCS device was designed to mask sham or active stimulation. The control switch was in front of the instrument, which was covered by an opaque adhesive during stimulation. The power indicator was on the front of the machine, which lit up during the time of stimulation both in active and sham stimulations. However, in sham stimulation, the current was discontinued after 30 seconds while the power indicator remained on. The staff who examined the outcomes was unaware of the device setting (active or sham mode) and thus were blind to the treatment condition.

Routine physical therapy

All study participants were provided with routine physical therapy treatment program at their school setting. Passive stretching exercise was provided by a physical therapist once a week[12]. The intensity of passive stretching exercise was based on each subject's tolerance on that day. Patients were also asked to perform stretching movements three times in all directions and then maintain the stretch in each direction for 40 to 60 seconds. In addition, participants were also asked to perform active stretching exercise, therapeutic positioning, and exercise on treadmill or endurance training using cycling for at least 30 minutes each day.

Clinical motor assessment

The clinical assessment included a physical examination, gross motor function assessment, spasticity assessment, and PROM. The spasticity and PROM assessments were performed at the same time every day (about 9:00 am) by the same experienced physical therapist (TJ).

Degree of spasticity

Degree of spasticity, the primary study outcome, was measured by using the modified Ashworth Scale (MAS) for the following right upper limb joints, shoulder, elbow, wrist, and fingers. With the MAS, severity of spasticity is scored on a 0 to 4 scale with 0 = normal with no increase in tone, 1 = slight increased in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part is moved in flexion or extension, 1+ = slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the reminder (less than half) of the ROM, 2 = more marked increase in tone through most of the ROM, but the affected part easily moved, 3 = considerable increase in tone, passive movement difficult, and 4 = maximum spasticity, with passive movement extremely difficult. Participants were seated comfortably upright during the MAS examination. The severity of spasticity for each participant was rated by an experienced physical therapist (TJ), who was blind to treatment condition.

Passive range of motion

Passive range of joint motion (PROM) refers to the number of degrees of motion that are present in a joint. PROM was measured in the right upper limb using a goniometer and documented as the full range of motion by an experienced physical therapist (TJ) at each assessment point. In order to minimize measurement error, PROM was measured once in each direction for each joint assessed[13]. PROM testing was performed on shoulder flexion, shoulder extension, shoulder abduction, shoulder adduction, elbow flexion, wrist flexion, and thumb (carpometacarpal) abduction using the procedures described by Norkin and White[14].

Adverse events

Patients' guardians were asked to report adverse events as well as any signs and symptoms every day after treatment. The self-recording terminated at one week after the end of stimulation. Patients were also observed closely by physicians during the stimulation.

Statistical analyses

The authors first computed means and standard deviations of the demographic and outcome variables for descriptive purposes. Next, we compared the two treatment conditions (active tDCS versus sham tDCS) on all baseline outcome measures to ensure baseline equivalence using a series of paired t-tests. Because dropouts could indicate either treatment

failure or lack of improvement leading subjects to discontinue participation, we used intent-to-treat analyses, using last observation carried forward for imputing the endpoint scores for tests of the primary and exploratory hypotheses. Results are presented as means and SD. Both the primary (spasticity) and exploratory (PROM) variables were tested using repeated measures analysis of variance (ANOVA). The authors conducted a group analysis by performing a series of repeated measures analyses of variance with time, treatment condition (tDCS vs sham tDCS), and the interaction between time and treatment condition as the independent variables. If a significant Time X Treatment Condition interaction emerged, we planned to perform LSD's for post-hoc multiple comparisons to identify differences between groups at each time point. Satisfaction with daily activity was examined as the proportions of participant responses to the different satisfaction response options. Finally, we planned to report any adverse events that occurred with either treatment condition. The *p*-value of <0.05 was considered statistically significant. Analyses were using Stata software, version 10.0 (StataCorp, College Station, TX).

Results

Baseline demographic data

Forty-eight children with spastic CP were enrolled between September 2011 and January 2013, and 46 of these met the study inclusion criteria. The participants were randomized to receive sham (n = 23) and active (n = 23) tDCS. Forty-five participants completed the entire protocol; one participant in the sham group dropped out at the 48-hour follow-up. Both groups were equivalent respected to age and sex, baseline GMFCS was not different between the groups (sham: 3.0±0.52 vs active: 3.1±0.55). The diagnosis, etiologies, baseline gross motor function, medication used, modified Ashworth scale, and PROM of included patients are presented in Table 1.

Degree of spasticity

Shoulder

Repeated-measures ANOVA with group as a between-subjects factor and time as a within-subjects factor revealed a significant main effect for treatment condition ($F(1, 44) = 4.85$; $p = 0.033$), time ($F(3, 44) = 10.27$; $p<0.001$) and for the Time X Treatment Condition interaction ($F(3, 44) = 4.79$; $p = 0.003$) for shoulder spasticity. Post-hoc analyses showed no difference in MAS between the treatment condition groups at the baseline. However, there were significant differences in MAS for shoulder spasticity at post-treatment ($p = 0.004$), and at 24 hours post-treatment ($p = 0.016$). There was also a statistical trend for

Table 1. Baseline demographic information, abilities/limitations of GMFCS, modified Ashworth scale and passive range of motion, for active tDCS and sham groups (n = 46)

Items	Active tDCS	Sham tDCS
Number of subject	23	23
Age: mean ± SD (years)	13.00±3.16	14.00±3.02
Sex: male	56.52%	47.83%
Type of cerebral palsy		
Spastic diplegia	14	15
Spastic hemiplegia	5	6
Spastic quadriplegia	4	2
Etiologies of cerebral palsy		
Hypoxia-ischemia	12	10
Intraventricular hemorrhage	3	2
Kernicterus	5	7
Traumatic brain injury	1	2
CNS infection	1	2
Idiopathic	1	0
Gross motor function		
Level II	2	3
Level III	16	17
Level IV	5	3
Medications used		
Diazepam	3	3
Oral baclofen	2	3
None	18	17
Baseline modified Ashworth scale (mean ± SD)		
Shoulder joint	1.30±0.70	1.35±0.65
Elbow joint	2.17±0.83	1.83±0.83
Wrist joint	1.87±0.76	1.87±0.69
Fingers joint	1.65±0.71	1.43±0.66
Baseline passive range of motion (mean ± SD)		
Shoulder flexion	169.78±9.35	172.39±7.52
Shoulder extension	60.83±8.15	60.61±6.60
Shoulder abduction	174.69±9.08	176.74±4.52
Shoulder adduction	79.13±11.14	81.52±10.71
Elbow flexion	125.43±24.81	134.35±14.95
Wrist flexion	93.04±22.60	98.70±23.94
Thumb abduction	74.73±11.27	76.09±14.06

GMFCS = gross motor function classification system; tDCS = transcranial direct current stimulation, SD = standard deviation; CNS = central nervous system

between-group difference in MAS at 48 hours (p = 0.052) after treatment (Fig. 1A).

Elbow

Repeated-measures ANOVA of elbow MAS revealed a significant main effect for treatment condition (F (1, 44) = 228.80; p<0.001), time (F (3, 44) = 10.85; p<0.001) and the Time X Treatment Condition interaction (F (3, 44) = 3.32; p = 0.022) for elbow spasticity. Post-hoc analyses showed no difference in the MAS scores for elbow spasticity between the treatment condition groups at any time point. However, within group analysis revealed significant decreased in the elbow MAS score from pre-treatment to immediately post-treatment (p<0.001), 24 hours post-treatment (p<0.001), and 48 hours post-treatment (p<0.001) for the active tDCS group. No statistically significant decreased in the elbow MAS score in the sham group was observed at any time point after treatment (Fig. 1B).

Wrist

Repeated-measures ANOVA of the wrist joint MAS score showed a significant main effect for treatment condition (F (1, 44) = 6.03; p = 0.018), time (F (3, 44) = 10.79; p<0.001) and the Time X Treatment Condition interaction (F (3, 44) = 6.76; p<0.001). Post-hoc analyses revealed no significant differences in the wrist MAS score between the treatment condition groups at the baseline. However, the results showed significant differences in the wrist MAS score at post-treatment (p<0.001), 24 hours post-treatment (p = 0.022), and 48 hours post-treatment (p = 0.023) (Fig. 1C).

Fingers

Repeated-measures ANOVA with group as a between-subjects factor and time as a within-subjects factor revealed no significant main effect for treatment condition (F (1, 44) = 0.72; p = 0.399) for the finger MAS score. However, a significant effect for time (F (3, 44) = 22.10; p<0.001) and a significant Time X Treatment Condition interaction (F (3, 44) = 9.22; p<0.001) emerged. Post-hoc analysis revealed no difference in MAS between the treatment condition groups at baseline, a short-lived improvement that could be detected immediately after treatment (p = 0.004), followed by a MAS score that returned to baseline by 24 hours and that then maintained at the 48 hour assessment point (Fig. 1D).

Passive range of motion

Repeated-measures ANOVA, using shoulder abduction PROM as a dependent variable, revealed a significant main effect for treatment condition (F (1, 44) = 4.85; p = 0.033), a significant time effect (F (3, 44) = 7.09; p<0.001) and a significant Time X Treatment Condition interaction (F (3, 44) = 5.01; p = 0.003). Post-hoc analysis showed no significant differences in the shoulder abduction PROM score

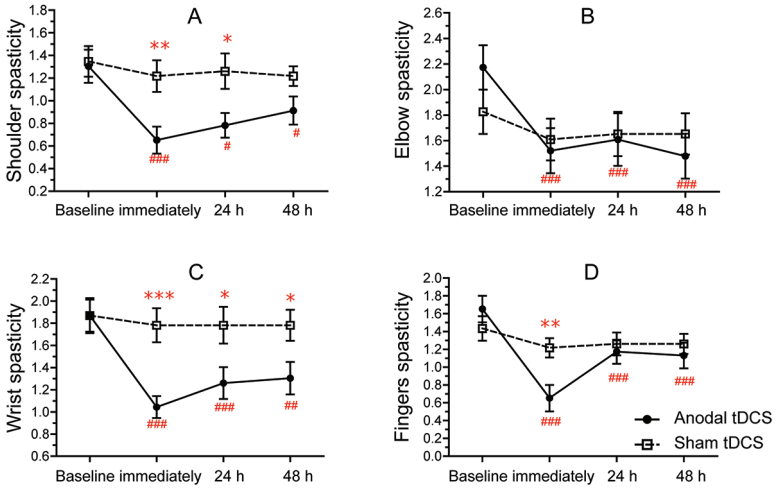

Fig. 1 Effect of tDCS on degree of spasticity by modified Ashworth scale (MAS): A = shoulder; B = elbow; C = wrist; D = fingers. Data are presented as mean of MAS at baseline and various time points after treatment: immediately, 24-, and 48-hour. Vertical line represent SEM, *** p<0.001, ** p<0.01, * p<0.05 between group difference, ### p<0.001, ## p<0.01, # p<0.05 difference from baseline in tDCS group.

between the treatment condition groups at the baseline, but significant increases in shoulder abduction PROM for the active tDCS group at post-treatment ($p = 0.046$). However, this change did not maintain at the 24 hour assessment point ($p = 0.382$), and there continued to be no significant group differences at the 48 hour assessment point ($p = 0.683$). None of the other PROM scores (for shoulder flexion, shoulder extension, shoulder adduction, elbow flexion, wrist flexion, and thumb abduction) yielded significant effects (Table 2).

Adverse events

One participant in the active tDCS condition developed a 2 mm diameter erythematous rash, 0.5 mm deep, and mild skin burn at the center under the reference electrode on the third day of stimulation and mild pruritus; however, there was no pain, peeling, or infection. On the fourth and fifth day of stimulation, the electrode was moved to other site on the same shoulder, and operators took good care to saturate the stimulating electrode pads more thoroughly with 0.9% NaCl. No other skin lesion appeared from then on. The rash spontaneously resolved in two hours, and skin burn completely resolved within three days with no scarring. No other adverse event was noted in any active or sham tDCS participants.

Discussion

To the best of our knowledge, this was the first randomized controlled trial (RCT) to examine the efficacy of anodal tDCS when combined with standard care in the treatment of children with spastic CP. The primary outcome revealed a significant greater pre- to post-treatment decreased in the degree of spasticity across different joints and maintained for 48 hours among participants of active tDCS compared to those who received sham tDCS. We also found statistically significant between-group differences in shoulder abduction from pre- to post-treatment, although this improvement did not maintain more than 24 hours. However, statistically significant increased ROM of shoulder flexion, shoulder abduction, shoulder adduction, elbow flexion, wrist flexion and thumb abduction were found at immediately post treatment in active group and then slightly declined. ROM of shoulder flexion and adduction were last for 48 hours after treatment of active tDCS. Encouragingly, most participants expressed satisfaction with their activity following tDCS treatment, and tolerated the procedure well. There was only one case of mild first degree burn with active tDCS, which resolved within two days.

Table 2. Passive range of motion of the active tDCS (n = 23) and the sham (n = 23) group at baseline, immediately post-treatment, 24- and 48-hour after treatment (mean values and standard error)

Passive range of motion (PROM)	Baseline				Immediately after treatment				24 hours after treatment				48 hours after treatment			
	tDCS		Sham		tDCS		Sham		tDCS		Sham		tDCS		Sham	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Shoulder flexion	169.8	9.4	172.4	7.5	173.5$^{\#\#}$	6.6	172.4	6.9	173.7$^{\#\#}$	6.4	171.3	8.0	172.6$^{\#}$	9.1	172.2	7.4
Shoulder extension	60.8	8.2	60.6	6.6	59.6	8.4	62.0	7.9	60.4	8.4	59.3	6.9	62.4	7.9	60.0	5.8
Shoulder abduction	174.7	9.1	176.7	4.5	179.1*$^{\#}$	2.9	177.0	3.9	178.5$^{\#}$	4.6	177.4	3.6	176.5	7.7	177.3	3.8
Shoulder adduction	79.1	11.1	81.5	10.7	86.3$^{\#\#\#}$	9.8	84.6	7.5	83.6$^{\#}$	9.6	82.4	6.9	83.5$^{\#}$	8.8	81.5	8.3
Elbow flexion	125.4	24.9	134.3	14.9	137.7$^{\#}$	17.3	134.4	13.3	133.9	16.6	134.1	14.8	131.9	16.2	134.1	14.7
Wrist flexion	93.0	22.6	98.7	23.9	98.9$^{\#}$	21.8	95.2	28.4	97.2	25.3	99.3	24.3	97.2	24.5	98.3	23.2
Thumb abduction	74.7	11.3	76.1	14.1	81.3$^{\#}$	9.2	76.7	14.0	79.1	10.9	77.0	13.8	78.3	11.3	77.6	13.7

tDCS = transcranial direct current stimulation, SD = standard deviation
Mean value was significantly different between groups * $p<0.05$, ** $p<0.01$, *** $p<0.001$ (factorial ANOVA)
Mean value was significantly different to that at baseline $^{\#}$ $p<0.05$, $^{\#\#}$ $p<0.01$, $^{\#\#\#}$ $p<0.001$ (repeated measure ANOVA)

Because this was the first study to evaluate anodal tDCS in patients with spastic CP, comparison of our findings with previous results is not possible. One study that examined the effects of 5 Hz rTMS in spastic CP showed similar improvement as ours[8]. Although the mechanism of action of tDCS and rTMS are not fully understood, both techniques appear to produce similar changes in the activity of pyramidal neurons, and thus may lead to similar clinical outcomes. However, the effect of anodal tDCS in our trial was evident over the entire upper limb, whereas the rTMS procedure reported in the single study cited above, resulted tentative in improvements at the elbow joint spasticity. One possible reason for the discrepancy in findings was the broader area of stimulation of tDCS as compared to rTMS[8].

The most severe adverse event in the present study was a skin burn, which is similar to the rate of skin irritation in ours and other groups' studies[15,16]. Palm and colleagues found that five out of 15 patients (33%) had skin burn under the cathodal electrode at the right supraorbital region of daily repeated 2 mA tDCS[15]. Frank and colleagues reported that three out of 15 cases (20%) of the similar skin lesions under the electrode 1.5 mA repeated anodal stimulation[16]. Our study resulted in only one out of 46 (2%) incidence of skin burn under the cathodal electrode in 1 mA repeated tDCS in active group. Thus, the occurrence of such skin lesions appeared to be more common with higher intensity of direct current stimulation. The transient erythema surrounding the area of skin burn could have been vasodilation resulting from skin conductance of the electrical current[17], and was similar to that found in our previous study, despite some differences in the session number and patient populations[18].

A primary limitation of the present study was using the MAS to assessed spasticity. Unlike other measures, such as the Tardieu scale, the MAS cannot assess the presence and severity of contracture. The MAS detects the resistance at the period of passive movement, so it cannot distinguish between the peripheral contribution to spasticity due to muscle adaptations versus the neural contribution associated with the increasing of stretch reflexes. However, the MAS is a relatively comprehensive measure that is less time-consuming and burdensome than other measures. Moreover, we excluded subjects with severe spasticity and contractures from the study, so measures that monitor contracture would not produce findings that differed from those reported here[19,20]. A second limitation was that we did not confirm that the electrode was directly over the motor cortex, for example by using transcranial magnetic stimulation to locate motor responses[21,22]. Instead, we depended on the standard procedure of using the international 10 to 20 system for the tDCS electrode placement. In addition, the tDCS electrodes are large (35 cm^2) and therefore tDCS procedures may result in more generalized (hemicortical) stimulation than very specific stimulation. As a result, it was not possible to confirm that the M1 cortex (and only the M1 cortex) was stimulated in the present study. Therefore, we do not know with certainty that as only M1 stimulation (vs. other areas) explained or underlined the benefits found. Another limitation was that we did not seek to treat or assess lower limb spasticity or ROM, because motor homunculus of leg area is located deeply in the inter-hemispheric fissure, which may be too deep for tDCS electrode located at scalp to be influenced. Finally, we only assessed outcome to 48 hours after stimulation treatment. We cannot therefore draw any conclusions regarding the long-term effects of this intervention.

Despite the study's limitations, it was the first that we are aware of to evaluate the potential beneficial effects of anodal tDCS over the motor cortex on CP-related spasticity. The findings were very encouraging, and indicated that active tDCS may reduce, at least in the short term, spasticity and might have meaningful effects on increasing PROM. Further research is needed to determine whether the benefits observed here maintain for longer than 48 hours.

What is already known on this topic?

Cerebral palsy (CP) is the most common motor disability of childhood. Spastic CP is the most common form of CP. One cause of spasticity is motor cortex damage, which leads to a decrease in the cortical input to the corticospinal tract, resulting in a disinhibition of spinal segmental excitability and an increase in the muscle tone.

Standard treatment for spastic CP usually includes physical therapy such as muscle stretching. However, no treatment has yet been found for successfully eliminates spasticity in all individuals with CP. Therefore, there is a pressing need to develop and evaluate the efficacy of additional treatments for spastic CP. Right now, there is a non-invasive technique of cortical stimulation, such as transcranial magnetic stimulation (TMS), and transcranial direct current stimulation (tDCS). When stimulation is low frequency

TMS or cathodal tDCS, they will suppress in cortical excitability. In contrast, when stimulated by high frequency TMS or Anodal tDCS, they will increase in cortical excitability. However, the real mechanism of action is still unclearly known.

In previous study, Valle and co-workers performed in spastic CP patients by applied high frequency TMS (5Hz) on the primary motor cortex for five consecutive days. The study showing that 5 Hz rTMS improved upper limb range of motion in patients with spastic CP for at least two hours following treatment.

What this study adds?

This is the first RCT to examine the efficacy of anodal tDCS when combined with standard care in the treatment of children with spastic CP. The study showed that anodal motor cortex tDCS could exert a beneficial role in spastic cerebral palsy for decreasing degree of spasticity and increase ROM. In addition, anodal motor cortex tDCS was safe in individuals with CP. Further studies should evaluate the long-term effects of tDCS treatment.

Our findings suggest that deep brain stimulation at primary motor cortex in spastic CP patients may have a potential role in reducing muscle spasticity and decreasing joint contracture.

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Potential conflicts of interest

None.

References

1. Swaiman KF. Cerebral palsy. In: Swaiman KF, Ashwal S, Ferriero DM, Schor NF, editors. Swaiman's pediatric neurology: principles and practice. 5th ed. St. Louis: Elsevier; 2012: 999-1008.
2. Panteliadis CP, Pavlidou EL, Bibi C. Clinical characteristics. In: Panteliadis CP, Strassburg HM, editors. Cerebral palsy: principles and management. New York: Thieme; 2004: 60-79.
3. Hurley DS, Sukal-Moulton T, Msall ME, Gaebler-Spira D, Krosschell KJ, Dewald JP. The cerebral palsy research registry: development and progress toward national collaboration in the United States. J Child Neurol 2011; 26: 1534-41.
4. Lang TC, Fuentes-Afflick E, Gilbert WM, Newman TB, Xing G, Wu YW. Cerebral palsy among Asian ethnic subgroups. Pediatrics 2012; 129: e992-8.
5. Bax M, Tydeman C, Flodmark O. Clinical and MRI correlates of cerebral palsy: the European Cerebral Palsy Study. JAMA 2006; 296: 1602-8.
6. Lance JW. Pathophysiology of spasticity and clinical experience with baclofen. In: Feldman RG, Young RR, Koella WP, editors. Spasticity, disordered motor control. Miami, FL: Symposia Specialists; 1980: 185-203.
7. Nitsche MA, Cohen LG, Wassermann EM, Priori A, Lang N, Antal A, et al. Transcranial direct current stimulation: State of the art 2008. Brain Stimul 2008; 1: 206-23.
8. Valle AC, Dionisio K, Pitskel NB, Pascual-Leone A, Orsati F, Ferreira MJ, et al. Low and high frequency repetitive transcranial magnetic stimulation for the treatment of spasticity. Dev Med Child Neurol 2007; 49: 534-8.
9. Levine MS. Cerebral palsy diagnosis in children over age 1 year: standard criteria. Arch Phys Med Rehabil 1980; 61: 385-9.
10. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol 1997; 39: 214-23.
11. Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. Phys Ther 1987; 67: 206-7.
12. Fragala MA, Goodgold S, Dumas HM. Effects of lower extremity passive stretching: pilot study of children and youth with severe limitations in self-mobility. Pediatr Phys Ther 2003; 15: 167-75.
13. Cheng HY, Ju YY, Chen CL, Chang YJ, Wong AM. Managing lower extremity muscle tone and function in children with cerebral palsy via eight-week repetitive passive knee movement intervention. Res Dev Disabil 2013; 34: 554-61.

14. Norkin CC, White DJ. Measurement of joint motion: A guide to Goniometry. 4th ed. Philadelphia: F.A. Davis; 2009.
15. Palm U, Keeser D, Schiller C, Fintescu Z, Nitsche M, Reisinger E, et al. Skin lesions after treatment with transcranial direct current stimulation (tDCS). Brain Stimul 2008; 1: 386-7.
16. Frank E, Wilfurth S, Landgrebe M, Eichhammer P, Hajak G, Langguth B. Anodal skin lesions after treatment with transcranial direct current stimulation. Brain Stimul 2010; 3: 58-9.
17. Durand S, Fromy B, Bouye P, Saumet JL, Abraham P. Vasodilatation in response to repeated anodal current application in the human skin relies on aspirin-sensitive mechanisms. J Physiol 2002; 540: 261-9.
18. Auvichayapat N, Rotenberg A, Gersner R, Ngodklang S, Tiamkao S, Tassaneeyakul W, et al. Transcranial direct current stimulation for treatment of refractory childhood focal epilepsy. Brain Stimul 2013; 6: 696-700.
19. Scholtes VA, Becher JG, Beelen A, Lankhorst GJ. Clinical assessment of spasticity in children with cerebral palsy: a critical review of available instruments. Dev Med Child Neurol 2006; 48: 64-73.
20. Alhusaini AA, Dean CM, Crosbie J, Shepherd RB, Lewis J. Evaluation of spasticity in children with cerebral palsy using Ashworth and Tardieu Scales compared with laboratory measures. J Child Neurol 2010; 25: 1242-7.
21. Sparing R, Buelte D, Meister IG, Paus T, Fink GR. Transcranial magnetic stimulation and the challenge of coil placement: a comparison of conventional and stereotaxic neuronavigational strategies. Hum Brain Mapp 2008; 29: 82-96.
22. Herwig U, Satrapi P, Schonfeldt-Lecuona C. Using the international 10-20 EEG system for positioning of transcranial magnetic stimulation. Brain Topogr 2003; 16: 95-9.

การลดเกร็งในผู้ป่วยโรคสมองพิการโดยการกระตุ้นด้วยไฟฟ้ากระแสตรงผ่านกะโหลก

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วัตถุประสงค์: *เพื่อประเมินประสิทธิภาพการลดเกร็งของการกระตุ้นด้วยไฟฟ้ากระแสตรงผ่านกะโหลกในผู้ป่วยสมองพิการชนิดเกร็ง*
วัสดุและวิธีการ: *อาสาสมัครทั้งหมด 46 ราย เป็นผู้ป่วยเด็กโรคสมองพิการชนิดเกร็ง ซึ่งผู้ป่วยถูกสุ่มออกเป็น 2 กลุ่ม คือ กลุ่มกระตุ้นจริงหรือกลุ่มกระตุ้นหลอก กลุ่มกระตุ้นจริงถูกกระตุ้นด้วย tDCS ขั้วบวก 1 mA เป็นเวลา 20 นาที วันละ 1 ครั้ง เป็นเวลา 5 วันต่อเนื่อง โดยทั้งสองกลุ่มได้รับการรักษาทางกายภาพบำบัด การประเมินผลการทดลองโดยวัดการเกร็งของกล้ามเนื้อและองศาการเคลื่อนไหว ซึ่งถูกประเมินก่อนการรักษาและหลังการรักษาทันที และ 24 และ 48 ชั่วโมง หลังการรักษา*
ผลการศึกษา: *อาสาสมัครในกลุ่มกระตุ้นจริงการเกร็งของกล้ามเนื้อลดลงหลังการรักษาอย่างมีนัยสำคัญทางสถิติเมื่อเปรียบเทียบกับกลุ่มกระตุ้นหลอก ($p = 0.004$, $p<0.001$, และ $p = 0.004$ สำหรับข้อไหล่ ข้อมือ และนิ้วมือ ตามลำดับ) และผลของการลดเกร็งนี้คงค้างได้นานถึง 24 ชั่วโมง ในข้อมือ ($p = 0.023$) นอกจากนี้พบว่ามีเพียงอาสาสมัคร 1 รายเท่านั้นที่เกิดผื่นแดงใต้ขั้วกระตุ้น อย่างไรก็ตามผู้ป่วยทุกรายยอมรับการกระตุ้น tDCS ได้เป็นอย่างดีและไม่พบผลข้างเคียงที่รุนแรง*
สรุป: *tDCS ขั้วบวกให้ผลดีในการลดเกร็งในเด็กสมองพิการชนิดเกร็ง (ไม่มีผลต่อองศาการเคลื่อนไหว) ในระยะสั้น อย่างไรก็ตามการประเมินผลระยะยาวยังคงต้องมีการศึกษาต่อไป*
