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Safety and tolerability of anodic transcranial direct current stimulation in children and adolescents with cerebral palsy tDCS safety in children with cerebral palsy

Segurança e tolerabilidade da estimulação transcraniana por corrente contínua anódica em crianças e adolescentes com paralisia cerebral

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ABSTRACT
The focus of this study is to investigate the safety and tolerability of anodic tDCS in children and adolescents with cerebral palsy (CP). Ten children and adolescents with hemiplegic and diplegic PCs, aged eight to 17 years (mean = 11.40, dp = 2.83) participated in this study. The subjects participated in five sessions of anodic tDCS in the right posterior parietal córtex (PPC), with the cathode positioned in the left deltoid muscle. After each stimulation session, a standardized questionnaire was used to assess adverse effects. The results showed the following adverse effects: pruritus rates (62%), burning sensation (16%) and tingling (23%). Most of the effects were classified as mild intensity by the participants, thus demonstrating the high tolerability and safety of tDCS in children and adolescents with CP.
Keywords: Cerebral Palsy. Children. Transcranial direct current stimulation. Tolerability.

RESUMO
O foco deste estudo é investigar a segurança e tolerabilidade da ETCC anódica em crianças e adolescentes com paralisia cerebral (PC). Participaram desse estudo dez crianças e adolescentes com PC do tipo hemiplégica e diplégica, com idade entre oito e 17 anos (média = 11,40, dp = 2,83). Os sujeitos participaram de cinco sessões de ETCC anódica no córtex parietal posterior (CPP) direito, com o cátodo posicionado no músculo deltoide esquerdo. Após cada sessão de estimulação foi aplicado um questionário padronizado para avaliação de efeitos adversos. Os resultados revelaram os seguintes efeitos adversos: as taxas de prurido (62%), sensação de queimação (16%) e formigamento (23%). A maior parte dos efeitos foi classificada como de intensidade leve pelos participantes, demonstrando a alta tolerabilidade e segurança da ETCC em crianças e adolescentes com PC.
Palavras-chave: Crianças. Estimulação transcraniana por corrente contínua. Paralisia cerebral. Tolerabilidade.

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INTRODUCTION

Cerebral palsy (CP) is a non-progressive, but generally changeable, disorder of motor changes secondary to injury or anomalies of the developing brain, which occur before the age of three.[1] The prevalence of CP varies between 1,5 and 2,5 per 1000 live births, with little or no difference between Western nations.[2] In Brazil, there are almost no epidemiological data on CP.[3] The set of neurophysiological changes present in CP not only affect the motor domain, but also cognitive development, emotional and social status of these children. Clinically, the most frequent cognitive changes are disorders of language, praxis and social behavior[4].

Transcranial direct-current stimulation - tDCS is a non-invasive and painless cortical modulation technique, which through the application of low intensity direct current over the skull, can modulate cortical excitability and thus interfere with the performance of different functions, including motor and cognitive functions[5]. Current transmission starts from the anode that is excitatory to the cathode that is inhibitory. This way tDCS is polarity dependent, and the anodic stimulation generally increases cortical excitability and cathodic stimulation results in opposite effects.

In studies with children, the current intensity varies from 0.5 to 1 mA, being distributed in short sessions of approximately 20 minutes, and due to its portability and operational simplicity, it has advantages in clinical application that guarantees the flexibility of application in ecological environment (for example at home or at school) and it can even be paired with cognitive training[6].

Transcranial direct-current stimulation has been used in research in a pediatric population with localized brain injuries, neurological and neurodevelopmental disorders such as autism spectrum disorder, dyslexia, attention deficit hyperactivity disorder or even to increase linguistic and mathematical skills, attention, executive performance related to problem solving, memory, and coordination in individuals with typical performance[7].

Although CP is one of the most prevalent clinical neurological syndrome in the pediatric population, there are a limited number of studies that have analyzed the effects of transcranial stimulation in children with CP. [8-15] These studies are limited to investigating the effects of tDCS on motor or phonological gain in these children, and demonstrate that tDCS is a safe and easy to apply technique, with adequate tolerance by this audience and with minimal side effects described (sensation of tingling and local redness) .[8-9] As it is an innovative and relatively new technique, published clinical trials exclusively show the combined use of tDCS with treadmill gait training, in static swing training, virtual reality or the isolated use for the treatment of spasticity. [8-15] So far none of these surveys have recorded data on side effects produced by tDCS in children and adolescents with cerebral palsy, other than mild itching or tingling.

The safety and tolerability of neuromodulation techniques are decisive for its choice as viable forms of treatment in childhood.[5] Tolerability refers to the presence of undesirable effects that bring discomfort to the patient, in the case of tDCS an example would be itching. Safety refers to the assessment of more persistent harmful effects, which can result in functional or structural damage.

There is a growing need for safe and tolerable protocols for the association of tDCS with other cognitive intervention strategies in CP. It is known that exposure to enriched sensory environments and insertion into early cognitive development programs improve cognitive functions in children with CP.[4] Novak et al.[16] carried out a systematic review of effective therapies for CP, however, cognitive intervention was not on the list of treatments, only physical rehabilitation. Thus, the aim of the present study was to investigate the safety and tolerability of anodic tDCS for stimulation of brain areas associated with cognition, such as the right posterior parietal cortex (PPC), in children and adolescents with CP.

METHODOLOGY

This study complies with the Regulatory Guidelines and Norms for research involving human beings, formulated by the National Health Council,

Ministry of Health, established in October, 1996 and updated in resolution 466, in 2012. The study was approved by the Research Ethics Committee with human beings from the Federal University of São Paulo, São Paulo, Brazil, CEP 777.179 of 09/03/2014. The clinical trial was registered on the Brazilian Registry of Clinical Trials platform (ReBEC) under identification RBR-3H95H7. Those responsible for the participants agreed to participate in the study, by signing a Free and Informed Consent Form, and the participants agreed by signing the Term of Assent.

This is a single-blind, open-label, non-randomized clinical trial with a case series design.

The participants were recruited based on the indication of professionals from private neurology clinics and assistance services for children and adolescents with brain injury, constituting a convenience sample initially of 29 participants. The final sample consisted of ten participants who met the eligibility criteria, namely: (a) age between 8 and 17 years, (b) diagnosis of hemiplegic or diplomatic cerebral palsy, (c) enrolled in regular schools of education and not having a school delay of more than two years. Participants were excluded if they: (a) used medication with action on the central nervous system, (b) had diagnosed psychiatric, genetic, metabolic or degenerative disease, (c) epilepsy, (d) sleep disorders, (e) congenital malformations, and (f) had an intelligence quotient (IQ) of less than 75.

Parents who showed interest and completed the informed consent form were invited to an anamnesis interview, in which they provided data on their children's medical history, development and current health condition. Participants who met the eligibility criteria underwent a neuropsychological assessment session and then participated in the intervention protocol that consisted of five sessions of anodic tDCS as described in the design of the experiment.

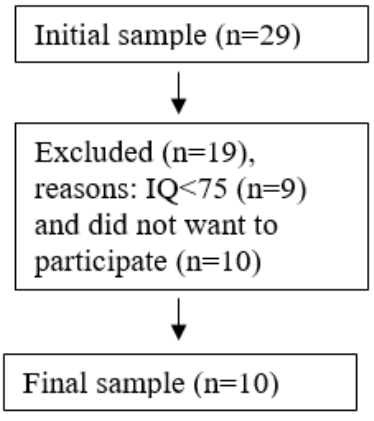

Figure 1. Flowchart of sample screening

EXPERIMENT DESIGN

Participants performed the following intervention procedures: right anodic tDCS (+) with an electrode applied to the region of the right posterior parietal cortex and the reference electrode to the contralateral extracephalic region (left deltoid muscle). Participants and researchers (except researchers who applied tDCS) were blind to the treatment condition (single-blind). The sessions were applied for 5 consecutive days (from Monday to Friday) in the same period of the day (morning or afternoon), totaling 5 sessions of 20 min.

In active stimulation (tDCS), a direct current (intensity of 1 mA) was applied through a pair of electrodes, anode and cathode, surrounded by sponges moistened with saline solution, saline, with dimensions of 5 x 7 cm (35 cm^2). The electrode (anode) was positioned under the P4 references of the international 10-20 EEG system, which correspond to the region of the right posterior parietal cortex. The reference electrode (cathode) was positioned over the extracephalic region, the left deltoid muscle, contralateral.

The device used was a TCT Research Model 101 1CH stimulator. It has a digital display that monitors the current intensity, the stimulation time, the current acceleration and deceleration and the type of stimulation (whether direct or pulsed current). The device also automatically controls the resistance level of the skin (bioimpedance), and can interrupt the stimulation if the resistance is excessive. The maximum

allowed duration of stimulation by the device is 30 min, and the possible current settings are 0.5 to 2 mA, with increases of 0.1 mA. The device worked by using a disposable 9v battery. After each stimulation session, lasting 20 min, the battery was discarded and replaced with a new one.

During the application of anodic tDCS, participants performed cognitive training on the computer. The cognitive activity training lasted 20 minutes, starting with the application of active stimulation (anodic tDCS), totaling five cognitive training sessions (one per day). The cognitive activity proposed in this study was the Number Race software. The software provides intensive cognitive training, through a running game on a numerical line, enabling numerical comparisons and connections between numbers and space.[17]

INSTRUMENTS FOR CHARACTERIZING THE SAMPLE AND TECHNICAL SAFETY ASSESSMENT

Wechsler Intelligence Scale for Children (WISC- IV) [18] is a clinical instrument of individual application that aims to assess children's intellectual capacity and the problem-solving process. Age range: 6 years and 0 months to 16 years and 11 months. It consists of 15 subtests, ten of which are main and five supplementary, and it has four indices, namely: Verbal Understanding Index, Perceptual Organization Index, Operational Memory Index and Processing Speed Index, in addition to the Total IQ.

Gross Motor Function Classification System (GMFCS).[3] Children and adolescents with CP are classified according to their functional independence in gross motor functions with an emphasis on "sitting" and "walking" movements. This system is divided into ages (0-2, 2-4, 4-6, and 6-12 years) and five functional levels. Children who have motor problems similar to those classified at level I can generally walk without restrictions, but tend to be limited in some of the more advanced motor skills. Children classified as level V are generally very limited in their ability to move even with the use of assistive technology.[3]

Adverse Effects Questionnaire - standardized questionnaire proposed by Brunoni et. al.[19] The questionnaire lists most of the adverse effects reported in studies with tDCS, and also assesses its intensity (referred by the parents as mild, moderate or severe, according to their perception of importance) and the child's parents' perception about the association between adverse effect and tDCS. These data were always collected at the end of each stimulation session through questions addressed to the participants and their parents or guardians, who were present during the tDCS.

DATA ANALYSIS

The data were analyzed through frequencies, percentages, means and standard deviation analysis, using the statistical software SPSS 21.0. This way, only descriptive statistical methods were employed.

RESULTS

The characteristics of the participants are shown in table 1. The average age was 11.40 years (dp = 2.83). Seven of the participants were male (70%) and three female (30%), both hemiplegic and diplegic CP were equally distributed (50%). Seven of the participants attended private schools (70%) and three attended public schools (30%).

Table 1. Clinical and demographic characteristics of the participants, expressed as mean, ± standard deviation or percentage (%)

Variable	Intervention (N=10)
Male (%)	7 (70%)
Age	11,40 ± 2,83
WISC-IV (Iq)	89,50 ± 7,93
Type of CP	
Hemiplegic (%)	5 (50%)
Diplegic (%)	5 (50%)
Scores ABEP(*)	
A2	3 (30%)
B1	4 (40%)
B2	1 (10%)
C1	1 (10%)
C2	1 (10%)
School	
Public	3 (30%)
Private	7 (70%)

(*) ABEP = Brazilian Criteria of Economic Classification.

Regarding the classification of gross motor function, it was observed that three of the participants walked without limitations (GMFCS level I) and five of the participants had some limitation, either for walking, running, jumping, or when going up and down stairs (level II of the GMFCS). One participant needed external support to sit (GMFCS level III) and one participant had limited self-mobility, requiring the use of a wheelchair (GMFCS level IV).

The percentage of adverse effects of tDCS reported by the participants can be seen in table 2. Based on the subjective report of the participants, in none of the sessions did headache occur, in 2% of the sessions cervical pain was reported, being classified as mild. In 2% of the sessions, mild scalp pain was reported. Tingling was reported in 23% of the sessions, and the intensity was considered mild in 18% of the sessions, and in 5% it was considered moderate. The presence of pruritus occurred in 62% of the sessions, being classified as mild (30%), moderate (18%) or severe (14%). The burning sensation was reported in 16% of the sessions, being classified as mild (10%) or moderate (6%). In 44% of the sessions, mild flushing was reported. In 8% of the sessions, mild drowsiness occurred. The presence of concentration difficulties occurred in 12% of the sessions, being classified as mild (10%) or moderate (2%). In 20% of the sessions, a slight mood shift was reported.

Table 2. Adverse effects during the stimulation sessions, expressed in percentage

Adverse Effect	Mild	Moderate	Severe	Total
Headache	0%	0%	0%	0%
Cervical pain	2%	0%	0%	2%
Scalp pain	2%	0%	0%	2%
Tingling	18%	5%	0%	23%
Pruritus	30%	18%	14%	62%
Burning sensation	10%	6%	0%	16%
Local flushing	44%	0%	0%	44%
Drowsiness	8%	0%	0%	8%
Concentration difficulty	10%	2%	0%	12%
Mood shift	20%	0%	0%	20%

DISCUSSION

The use of pediatric neuromodulation techniques still has an experimental character, given the lack of studies with scientific evidence on the effectiveness of its results in this audience. Regarding tDCS, there is still no Guideline that determines the ethical, legal and technical precepts of this practice. Although its risks associated with adverse effects are small, it is necessary to determine which configurations would be optimal for the stimulation of different cortical regions, taking into account the children's neuroanatomical model, cognitive modularity and ontogenetic neuroplasticity.[20]

In this sense, the objective of this study was to investigate the safety and tolerability of anodic tDCS for stimulation of brain areas associated with cognition based on the 10-20 EEG system. The area chosen for assembly was the right posterior parietal cortex (P4). This cortical site, as demonstrated by several studies, is involved in the processing of quantitative stimuli and non-symbolic quantities.[21-22]

Still regarding the assembly, it was important to determine where to place the anode and cathode, given the possible synergy of actions on the cerebral cortex involved with the position of the electrodes. We chose to position the anode on P4 and the cathode on the left deltoid muscle (contralateral), thus ensuring that only the excitatory effect would occur on the brain region of interest and no inhibitory effect would be manifested in the brain region. However, extracephalic assemblies make the permanence of the cortical changes promoted by tDCS less lasting than brain assembly, requiring greater current intensities for the effects of the first to be equivalent to the second. In addition to the fact that a higher voltage is required to maintain the supply of the desired current intensity during tDCS.[23]

The decision on the number of stimulation sessions was also a methodological challenge, first because we sought a number of sessions that was sufficient both to guarantee the expected changes in cortical excitability and the feasibility of the research, given that the participants were children or adolescents who could not miss school activities and whose parents, in their majority, worked 8 hours a day. The number of five stimulation sessions has already been demonstrated in other studies with children and adolescents as safe.[24-25]

Concerning the stimulation parameters, duration time and current intensity we opted for a low intensity current (1mA), considered safe for children and adolescents as demonstrated by computational modeling studies[6]. The chosen time was 20 minutes of stimulation, considering that they could increase the gain of cortical excitability.

Cognitive activity training is also an important methodological aspect. The type of training can be decisive for achieving results in studies with tDCS. The few studies involving the use of tDCS applied to CP, used training associated with the technique, treadmill gait training,[8-9] and balance therapy.[14] One of the challenges is that cognitive activity must be applied concomitantly or contiguously with the application of tDCS, so the duration of cognitive activity should be considered. The chosen activity lasted 20 minutes, starting with the application of active stimulation (anodic tDCS), totaling five cognitive training sessions (one per day). The cognitive activity proposed in this study was selected through a literature review, where evidence of results on the development of numerical skills using the Number Race software was found. The numerical skills developed by the software involve processing both symbolic and non-symbolic magnitudes. According to the triple code model, the cerebral site that preserves the non-symbolic processing of magnitudes is the posterior parietal cortex, specifically the region of the intraparietal sulcus, precisely the region stimulated in this study.[21] An advantage observed during the experiment was that cognitive activity increased the tolerance to the application of tDCS, encouraging participants to focus their attention on the activity that had a game format.

As proposed for tDCS, the development of consensus guidelines could help guide clinical research and meet requests from patients and parents for non-invasive brain stimulation.[26] A very important aspect is the safety and tolerability of the technique.

Andrade et al.[27] investigated the application of 30 min of 2 mA of tDCS over 10 days in 14 children (5-12 years) suffering from different neuropsychiatric disorders (expressive language disorder, dyspraxia, invasive developmental disorder, Asperger's syndrome). The main adverse effects were mood shifts, discomfort in skin perception (itching, tingling, burning), headache and drowsiness. The authors argue that some of these reported symptoms can be attributed to the disorder itself, not to stimulation.

The adverse effects of tDCS in children and adolescents were systematically reviewed by Krishnan et al.[28] and they found skin sensations (itching, tingling, redness, discomfort in the scalp, etc.) as the most frequent adverse effects, while the mood shift does not seem to be a critical problem.

Adverse effects were also investigated by Moliadze et al.[29] in 19 children (mean age 13.9 years, range 11-16 years) in a randomized controlled crossover trial with EEG and motor evoked potentials (MEP) before and after tDCS (10 min / 1 mA). Anodal, cathodic and sham assemblies (35 cm2 electrode) were applied over C3 with the reference electrode over the contralateral orbital region. Standardized questionnaires revealed the occurrence of side effects induced by well-known tDCS, such as itching, tingling and headache. The occurrence was not different between the stimulation conditions and the participants were unable to correctly guess the type of stimulation.

Brunoni et al.[19] reviewed study data using tDCS published until 2010. From 172 articles, 56% reported adverse effects and 63% reported at least one adverse effect. The authors showed that the rates of common adverse effects did not differ between active stimulation and sham: itching (39.3% vs. 32.9%, respectively), tingling (22.2% vs. 18.3%), headache (14.8% vs. 16.2%), burning sensation (8.7% vs. 10%) and discomfort (10.4% vs 13.4%).

In this study, the rates of pruritus (62%) and burning sensation (16%) were above the average percentage of these studies, while the adverse effects of tingling (23%) were close to what was reported, and headache was not reported by any participant. In our study, there were other adverse effects that were not reported in the review, such as mild drowsiness, concentration difficulties and mood shift.

In the review by Brunoni et al.[19], most of the reviewed studies did not systematically assess adverse effects. This is an important aspect, since most research does not systematically record adverse effects, failing to assess their intensity and frequency, even if they are mild or not observed.

In our study, no serious adverse effects were reported. According to the United States Food and Drug Administration (FDA), serious adverse events are those in which the result is death, life-threatening, hospitalization, permanent disability/damage, anomaly/birth defect, procedures necessary to prevent complications or permanent damage, and other serious events - for example, refractory seizures, cardiorespiratory arrest and anaphylactic reaction. There are no serious adverse events attributable to the use of tDCS.[19]

The adverse events reported by the participants were transient and classified as mild by the participants over the study period, which is consistent with the research that describes tDCS as safe and tolerable in its application to the pediatric population.[30]

Although anodic tDCS over the right PPC (P4) has not been tested before in children and adolescents with CP, in this study it was shown to be safe and tolerable, without serious adverse effects or additional discomfort beyond those already reported in the literature.[19]

CONCLUSION

The safety and tolerability of anodic tDCS for PPC was investigated and demonstrated promising clinical parameters for the investigated pediatric population. This study opens the way for future research that uses anodic tDCS in the right PPC as an experimental or clinical research method. It is a place of interest in the cognitive intervention of patients with learning difficulties in mathematics, such as children and adolescents with brain injury and/or dyscalculia.

This research has the small and convenience sample as a limitation, however the difficulties of conducting clinical studies with children and adolescents

with brain damage and normal IQ justify the reduced number of participants. If the results of this and other studies on tDCS safety and tolerability are confirmed in larger samples of subjects and the optimal parameters for use during stimulation are determined (i.e. intensity, duration, areas to be stimulated), tDCS may be included in the list of clinical tools for the treatment of different neurological and neuropsychiatric disorders, including persistent learning difficulties.

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