Combined effect of hydrotherapy and transcranial direct-current stimulation on children with cerebral palsy
A protocol for a randomized controlled trial

Xiao-Liang Chen, MD, Li-Ping Yu, MD, Ying Zhu, MD, Tie-Yan Wang, MD, Jing Han, MD, Xiao-Yan Chen, MD, Jia-He Zhang, MD, Jia-Li Huang, MD, Xiao-Ling Qian, MD, Bo Wang, MD

Abstract
Background: Cerebral palsy (CP) is a neurodevelopmental disorder caused by a brain injury resulting in poor coordination and motor control deficits, which is one of the most common physical disabilities in children. CP brings a heavy burden on families and society and becomes a significant public health issue. In recent years, hydrotherapy, and transcranial direct current stimulation (tDCS) as a physical therapy for CP is developing rapidly. When hydrotherapy and tDCS are used to treat separately, it has positive therapeutic effect in children with CP. The development of new therapies in combination with physical rehabilitation approaches is critical to optimize functional outcomes. tDCS has attracted interest in this context, because of significant functional improvements have been demonstrated in individuals with brain injuries after a short period of cerebral stimulation. Since the onset of this work, tDCS has been used in combination with constraint-induced therapy, virtual reality therapy to potentiate the treatment effect. Up to now, there are no studies on the effect of a combined application of hydrotherapy and tDCS in children with CP. We will conduct a 2-arm parallel clinical trial to investigate the effect of a combined application of tDCS and hydrotherapy.

Methods and analysis: This study is an outcome assessor and data analyst-blinded, randomized, controlled superiority trial during the period from October 2021 to December 2023. CP patients meeting the inclusion criteria will be allocated in a 1:1 ratio into the treatment group (hydrotherapy plus tDCS), or the control group (treatment as usual). All participants will receive 30 sessions of treatment over 10 weeks. The primary outcomes will be the difference in the Gross Motor Function Assessment and Pediatric Balance Scale during rest and activity. The secondary outcomes will be the difference in adverse effects between the control and treatment groups.

Conclusions: This study aims to estimate the efficacy of a combined application of tDCS and hydrotherapy in patients with CP.

Trial Registration: This study protocol was registered in Chinese ClinicalTrials.gov, ID: ChiCTR2100047946.

Abbreviations: CP = cerebral palsy, GMFM-88 = Gross Motor Function Measure 88, PBS = Pediatric Balance Scale, PEDI = The Pediatric Evaluation Disability Inventory, PT = physical therapy, RCT = randomized controlled trial, tDCS = transcranial direct current stimulation.

Keywords: cerebral palsy, children, hydrotherapy, transcranial direct current stimulation

This work was funded by Gansu Administration of Traditional Chinese Medicine Foundation (No. GZK-2017-59), Gansu Province Health Industry Scientific Research Project (GAWSKY2017-62 and GAWSKY2018-63).

The funders had no role in the following part: design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

At the time of submission, we will recruit patient for pre-experiment.

The authors have no conflicts of interest to disclose.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Department of Pediatrics, The Second Affiliated Hospital of Qiqihar Medical University, Qiqihar, Heilongjiang, China; Department of Nursing, Rehabilitation Center Hospital of Gansu Province, Lanzhou, Gansu, China; The Second Clinical Medical College, Lanzhou University, Lanzhou, Gansu, China; Department of Neurosurgery, The First Affiliated Hospital of Xi’an Jiaotong University, Xi’an, Shaanxi, China; School of Public Health, Lanzhou University, Lanzhou, Gansu, China; Department of Neurology, The Second Hospital of Lanzhou University, Lanzhou, Gansu, China.

Correspondence: Bo Wang, Department of Nursing, Rehabilitation Center Hospital of Gansu Province, No.53, Dingsi Road, Chengguan District, Lanzhou, Gansu 730000, China (e-mail: 2010580492@qq.com).

Copyright © 2021 the Author(s). Published by Wolters Kluwer Health, Inc.

This is an open access article distributed under the Creative Commons Attribution License 4.0 (CCBY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Chen XL, Yu LP, Zhu Y, Wang TY, Han J, Chen XY, Zhang JH, Huang JL, Qian XL, Wang B. Combined effect of hydrotherapy and transcranial direct-current stimulation on children with cerebral palsy: a protocol for a randomized controlled trial. Medicine 2021;100:49(e27962).

Received: 4 November 2021 / Accepted: 9 November 2021
http://dx.doi.org/10.1097/MD.00000000000027962
1. Introduction

Cerebral palsy (CP) is a neurodevelopmental disorder caused by a brain injury resulting in poor coordination and motor control deficits, which is one of the most widespread physical deformity in children.[1] This disorder commonly occurs in 2.11 cases per 1000 live births and are widely recognized for causing dystonia, motor, and movement dysfunction, and intellectual disability.[2,3] A previous meta-analysis demonstrated that the prevalence of CP among children aged 0 to 6 years in China is 0.23%,[4] The European surveillance of CP group described the motor type of CP as spastic, dyskinetic (dystonia, chorea, and athetosis), ataxic and mixed types involving the mentioned types.[5] Spastic cerebral palsy is the most common type of this movement disorder, which occurs in more than 80% in children.[6] CP is usually diagnosed in childhood, but its course can last into adolescence, adulthood, and has different severity. There are evidences that children with CP have a higher rate of deterioration of physical and mental function and a higher risk for secondary diseases.1-7 It is reported that the cost of care for each child is estimated at $921,000 in the US.[8] CP brings a heavy burden on families and society and becomes a significant public health issue.[9]

The conventional treatment for children with CP is made up of medical treatment, physical therapy (PT), occupational therapy, psychotherapy, surgical therapy, virtual reality technology, hyperbaric oxygen therapy, stem cell transplantation, and speech therapy.[10-12] Almost all these treatments are aimed at improving patient activity and functional participation, however, none of them can completely cure CP. In recent years, PT as a treatment for CP is developing rapidly, which is a special treatment method based on physical factors such as sound, electricity, light, force, water, magnetism, and thermal power. Owing to the risks of neurosurgery and side effects of pharmacological intervention, PT becomes the central part of rehabilitation for children with CP.[13,14] Among them, hydrotherapy promotes children’s voluntary and passive movement in the water through the resistance, buoyancy, static pressure, and warming effects of water, which is beneficial to improve human blood circulation and relax the muscles of the whole body, thereby promoting the alleviation of muscle spasm and the reduction of muscle tension, and then improves the children’s balance ability, expands the joint range of motion.[15] Numerous studies have pointed out that the potential of hydrotherapy programs have significant benefits for children with CP.[15,16] The result of a 10-week aquatic exercise training program is effective in the functional rehabilitation of children with spastic CP.[17] A previous systematic review published in 2017 suggested that evidence on aquatic interventions for children with CP is limited since only 2 used randomized control trial design, and the results were mixed.[18] Another systematic review published in 2021 showed that hydrotherapy can help improve the motor function and activities of children and adolescents with CP, and may improve their quality of life, which included 9 randomized controlled trials (RCTs).[19]

Noninvasive brain stimulation is one of PT which is under active investigation in childhood neurology and psychiatry, especially in disorders where focal cortical over- or under-activation is part of the pathophysiology.[20] Among them, 2 are developing rapidly, they are transcranial magnetic stimulation and transcranial direct current stimulation (tDCS). tDCS constant electrical currents are conducted to the brain via scalp electrodes, which is undergoing investigation as a credible treatment for a series of neuropsychiatric diseases. This technique shares a capacity to modulate regional cortical excitability, and well-tolerated by children and adults.[21,22] Now, active tDCS research is pushed in part by a favorable tDCS safety profile, the low cost of tDCS stimulator, and by fairly repeatable effects on the cortex, where (coarse) exposure to cathodal current brings about cortical suppression and exposure to anodal current brings about cortical activation.[23] tDCS has been tested as a treatment for several pediatric neurologic conditions.[20,22] Several RCTs also reported a beneficial effect of tDCS in patients with autism spectrum disorder,[24] attention-deficit/hyperactivity disorder,[25] epilepsy[26] and CP. The finding from a meta-analysis suggested that tDCS can improve the static balance in children with CP at follow-up and have a positive effect on gait velocity.[27] The heterogeneity of participant characteristics, dosing parameters, and outcome indicators makes it difficult to integrate citations and directly apply them to clinical practice. Caution must be taken when using this summary as an implementation guide.[27] The Commenter of this meta-analysis suggested that researchers could reduce heterogeneity, increase sample size, avoid unnecessary repetition of additional pilot studies as positive results have been confirmed, and establish a focus on immediate and longer-term participant-centered efficacy outcomes while closely monitoring safety, so that future research will be more meaningful to clinicians.[28]

To sum up, when hydrotherapy and tDCS are used to treat separately, it has positive therapeutic effect in children with CP. The development of new therapies in combination with physical rehabilitation approaches is critical to optimize functional outcomes. tDCS has attracted interest in this context, as significant functional improvements have been demonstrated in individuals with brain injuries after a short period of cerebral stimulation. Since the onset of this work, tDCS has been used in combination with constraint-induced therapy, gait and mobility training, virtual reality therapy to potentiate the treatment effect.[29-31] Up to now, there are no studies on the effect of a combined application of hydrotherapy and tDCS in children with CP. We will conduct a 2-arm parallel clinical trial to investigate the effect of a combined application of tDCS and hydrotherapy. We hypothesized that tDCS combined concurrently with hydrotherapy would result in the greater and long-lasting improvement in motor function.

2. Methods and analysis

2.1. Study design

This study is an outcome assessor and data analyst-blinded, randomized, controlled superiority trial and will be conducted at the Second Affiliated Hospital of Qiqihar Medical University, from October 2021 to December 2023. CP patients who meet the inclusion criteria will be allocated in a 1:1 ratio into the treatment group (hydrotherapy plus tDCS, n = 75, expected), or the control group (treatment as usual, n = 75, expected). All participants will receive 30 sessions of treatment over 10 weeks. The study design is presented in Figure 1.

2.2. Participants

Participants meeting the following inclusion criteria will be included: CP patients between 4 and 14 years old, CP was
The participants will be assessed for the first time, pre-intervention, and then randomly assigned to one of the 2 groups: combination treatment group (treatment with hydrotherapy and tDCS), control group (treatment as usual). The randomization sequence will be distributed by numerically sequenced and sealed opaque envelopes. This process will be completed by an independent researcher.[35] A second independent number performed the randomization. A series of numbered, sealed, opaque envelopes will be used to ensure concealed allocation. Each envelope will contain a card stipulating to which group the child will be allocated. This study will use the blind statistical analysis, where the statistical data will be analyzed by statisticians with unclear grouping and its meaning.

2.5. Evaluation and follow-up

Two experienced physical therapists who blind to which group each child belongs will evaluate the both group in the evaluation procedures. Four evaluations will be conducted:
- First evaluation: 1 week before intervention;
- Second evaluation: 1 week after the last intervention;
- Third evaluation: 4 weeks after the last intervention;
- Fourth assessment: 12 weeks after the last intervention.

These evaluations will be conducted on 2 nonconsecutive days.

2.6. Outcome measures

We will evaluate the CP children using questionnaires at the beginning of the treatment, within 1 week after 10weeks of therapy, 4 weeks, and 12 weeks after the last intervention. Descriptive measures and characteristics, such as age, gender, body weight, type of CP and the outcomes were recorded for all study participants. All patient related data will be safely collected and stored. Only researchers related to the study will be allowed to access to the trial dataset. The primary outcomes of this study are Gross Motor Function Assessment and Pediatric Balance Scale (PBS) between the treatment group and the control group. The secondary outcomes are the difference in Pediatric Evaluation Disability Inventory (PEDI), adverse effects between the control and treatment groups.

2.6.1. Primary outcomes measures. Gross Motor Function Measure 88 (GMFM-88): The GMFM-88 will be used to detect gross motor function change in this study.[36–38] The GMFM-88 is made up of 5 dimensions that can be analyzed separately or combined to produce a total GMFM-88 score. The 5 dimensions are as follows: lying and rolling, sitting, crawling and kneeling, standing, and walking, running, and jumping. All items are scored on a 4-point scale, the higher the score, the better the function.[36–38] The treating therapist, in collaboration with parents and children, will choose Gross motor goal dimensions while considering the age of children and gross motor function classification system level. All evaluation process will be recorded and later scored by a senior physiotherapist who is blind to group allocation. The results will be reported as percentage scores.

PBS: The same blinded researcher will administer the PBS before and after the intervention.[39–41] To assess balance, the PBS will be used, which is composed of 14 items. The items assess the functional activities which children could perform to function within the home, school, or community safely and independently. This scale has also been tested for children with CP and has good test–retest and interrater reliability when used assess participation of school-age children with mild to moderate movement disorder.[39–41]
2.6.2. Secondary outcome measures. The (PEDI, the PEDI is a questionnaire that quantitatively measures functional performance. This questionnaire includes 3 areas: self-care, mobility, and social function. The self-care part contains food, personal hygiene, toilet use, clothing, and toilet control. The functional items of mobility offered information about transfers, walking indoors and outdoors, and use of stairs. The social function part mirrors matters related to communication, problem solving, interaction with partner, amongst others. We will calculated total scores for each scale in each area, where each item has a score of 0 (the child is unable to play an activity) or 1 (the activity is part of the child’s repertoire), and the sum of the items generates the score for each field.\textsuperscript{[32,43]}

Adverse effects. We set this standard to refer to the specific details of previous study.\textsuperscript{[35]} Children with CP will be asked to answer on a 3-point scale: I did not feel unwell at any moment during the session; I felt unwell at some points during the session; I felt unwell throughout the session. The specific unwell are as follows: tingling sensation, burning sensation, headache, pain in the region where the electrodes were positioned, drowsiness, and mood swings. When participants pointed that they have specific adverse effect, in other words, the response is “2” or “3”, they will be instructed to quantify the intensity of perception (1, weak; 2, moderate; 3, strong; or 4, unbearable).

2.7. Intervention

2.7.1. Control group: usual care. Both groups of participants will continue to receive “usual care” during the 10-week intervention. Usual care refers to any therapeutic treatment or service that the child would normally receive outside of the intervention study. The researcher will evaluate children's condition, we expected that most participants in this study will not access additional therapy as possible.

2.7.2. Treatment group: hydrotherapy and tDCS. Our intervention plan is based on Akinola et al.\textsuperscript{[17]} research on hydrotherapy and studies about tDCS.\textsuperscript{[30,44,45]}

The participants in the treatment group will receive a treatment protocol which is about specific plans and measures during treatment. Participants will not receive exercise training in water, 2 times a week for 10 weeks, with the exercise area fully immersed in water. The water temperature will be controlled between 28°C and 31°C throughout the whole duration of intervention. Two physical therapists will be involved in the treatment of each participants in a treatment session. The exercise program contains 2 categories of exercises as follows.

Exercise 1 (manual passive stretching). This will include passively moving the joint involved in the spastic muscle group away from the direction of the main function and maintain this position for 60 seconds, where the muscle group is fully extended. This process will be repeated 5 times for each part, with a total duration of 5 minutes.

Exercise 2 (functional training). All children will receive 4 levels of functional training according to their dysfunction levels, and each level of training lasted 15 minutes. The 4 levels are the following:

- Level 1: 2-point kneeling exercise training
- Level 2: Sitting education/training
- Level 3: Standing education/training
- Level 4: Walking education/training

Two neurologists with ample experience in noninvasive cerebral stimulation will oversee the evaluations for the indication of tDCS. tDCS will be performed during the intervention sessions, it is reported that tDCS can promote behavioral changes through building a neural network that is conducive to the environment. Our study will employee the tDCS Transcranial Stimulation equipment produced by Soterix Medical Inc. The device works by 2 $5\times5\text{cm}^2$ nonmetallic sponge surface electrodes immersed in saline solution. The anodal electrode will be in the dominant brain hemisphere area over C3, following the internationally standardized 10 to 20 electroencephalogram system, corresponding to the primary motor cortex, and the cathode will be located in the contralateral supraorbital area.\textsuperscript{[45]} No stimulation will be provided throughout the rest of the session, which is a valid control procedure in studies involving tDCS. The current will be applied to the primary motor cortex for 20 minutes in the middle of each training session. The device has a button and the operator can control the intensity of the current. The stimulation will increase from 0 to 1 mA and gradually reduced in the final 10 seconds. The tDCS will be repeated once a day, 3 times a week, a total of 30 treatments.

We initially plan to carry out tDCS on Mondays, Wednesdays, and Fridays, and hydrotherapy on Thursdays and Sundays.

2.8. Statistical analysis

An experienced statistician will conduct the data analysis. When necessary, intention to treat analysis will be used with the data from the previous evaluation repeated to substitute missing data. We will use the Kolmogorov-Smirnov test to demonstrate normal data distribution. Thus, Parametric data will be presented as mean (standard deviation) as well as nonparametric data will be presented as median (inter-quartile interval). The effect size will be calculated by the difference between means of the pre-intervention and post-intervention evaluations and will be presented with the respective 95% confidence interval. The independent $t$ test and chi-square tests will be applied to assess and compare the baseline patient characteristics between the treatment and the control groups. Either 2-way ANOVA or the Kruskal-Wallis test will be used for the statistical analysis of the effects of control group or treatment group for parametric and nonparametric variables, respectively. The Bonferroni correction for multiple comparisons will be employed as the post hoc test. Statistical significance will be considered at a $P$ value of $<.05$. The data will be organized and tabulated using the Statistical Package for the Social Sciences (SPSS) version 19.0 (IBM, Armonk, NY, USA).

3. Discussion

According to incomplete statistics, there were about 5.3 million patients with CP in China in 2018, and it is increasing at a rate of about 50,000 per year. The investigation report of children with CP in 12 provinces in China pointed out that the incidence of CP in children aged 1 to 6 years was 2.48‰, and the most common type of CP was spastic CP, which accounted for 58.86% of children with CP. Children with spastic CP are unable to stand, sit up and walk normally due to rigid extension reflexes, overexcited reflexes, and abnormal muscle stiffness, which is the main cause of severe motor disability in children.\textsuperscript{[46]} Children with CP are a huge group, and their treatment and rehabilitation...
is an important task in our country. Rehabilitation therapy plays a key role in the management of CP in children. It can help children with CP to maximize their potential for physical independence and health, and minimize the impact of physical injury. At present, the rehabilitation treatment of CP is mainly based on PT, including exercise therapy, hydrotherapy, occupational therapy, and tDCS. Among the outcome indicators such as motor function and balance function, it has been proven that hydrotherapy and tDCS are effective for children with CP. This study protocol describes a RCT study design which will test the comparative effectiveness of combining hydrotherapy and tDCS. The outcome evaluations will include analyses of GMFM-88, PBS. If the combination of hydrotherapy and tDCS is proven to be superior to the other in some of these aspects, this evidence would permit professionals to recommend the ideal PT for patients with CP, which will minimize their incapacity and optimize their rehabilitation. It is hoped that findings from this research will be published and disseminated in an internationally recognized, peer-reviewed journal.

4. Conclusion
In conclusion, this protocol describes an outcome assessor and data analyst-blinded, randomized, controlled superiority trial that aims to investigate the efficacy of a combined application of tDCS and hydrotherapy in patients with CP. The results will ascertain whether tDCS combined concurrently with hydrotherapy would result in the greater and longer-lasting improvement in motor function. The findings will be of great significance for clinical practice about treating CP.

5. Ethics and dissemination
The trial will be commenced after ethical approval has been obtained from the Second Affiliated Hospital of Qiqihar Medical University. All study-related procedures will be performed only after obtaining written informed consent from children and their parents. Patients’ information will be collected, shared, and maintained in an independent closet to protect confidentiality before, during, and after the trial. The protocol has been registered at Chinese Clinical Trials Register, (http://www.chictr.org.cn/showproj.aspx?proj=128232, Identifier: ChiCTR2100047946).

Author contributions
Conceptualization: Xiaoliang Chen, Bo Wang, Xiaoling Qian.
Data curation: Xiaoliang Chen, Tieyan Wang, Ying Zhu, Jing Han, Jihe Zhang, Jiali Huang.
Formal analysis: Liping Yu, Xiaoliang Chen, Bo Wang, Xiaoling Qian.
Funding acquisition: Liping Yu, Xiaoliang Qian.
Investigation: Xiaoliang Chen, Tieyan Wang, Ying Zhu, Jing Han.
Methodology: Bo Wang, Xiaoling Qian.
Project administration: Bo Wang, Xiaoliang Chen, Xiaoling Qian.
Resources: Xiaoliang Chen.
Software: Liping Yu, Ying Zhu.
Supervision: Bo Wang, Xiaoling Qian.
Validation: Xiaoliang Chen, Bo Wang, Xiaoling Qian.
Visualization: Xiaoliang Chen, Xiaoling Qian.

Writing – original draft: Xiaoliang Chen, Liping Yu, Bo Wang, Xiaoling Qian.
Writing – review & editing: Xiaoliang Chen, Bo Wang, Xiaoling Qian.

References
[1] Bax M, Goldstein M, Rosenbaum P, et al. Proposed definition and classification of cerebral palsy, April 2005. Dev Med Child Neurol 2005;47:571–6.
[2] Oskoui M, Coutinho F, Dykeman J, Jetté N, Pringsheim T. An update on the prevalence of cerebral palsy: a systematic review and meta-analysis. Dev Med Child Neurol 2013;55:309–19.
[3] Patel DR, Neelakantan M, Pandher K, Merrick J. Cerebral palsy in children: a clinical overview. Transl Pediatr 2020;9(Suppl 1):S125–33.
[4] Feng Y, Pang W, Li X, Yang X, Liu S, Liu S. The prevalence of cerebral palsy in children aged 0-6 years in China: a meta-analysis. Chin Gen Pract 2021;24:603–7. (Chinese).
[5] Wimalasundera N, Stevenson VL. Cerebral palsy. Pract Neurol 2016;16:184–94.
[6] Smith KJ, Peterson MD, O’Connell NE, et al. Risk of depression and anxiety in adults with cerebral palsy. JAMA Neurol 2019;76:294–300.
[7] Whitney DG, Warschausky SA, Peterson MD. Mental health disorders and physical risk factors in children with cerebral palsy: a cross-sectional study. Dev Med Child Neurol 2019;61:579–85.
[8] Peck J, Urits I, Kassem H, et al. Interventional approaches to pain and spasticity related to cerebral palsy. Psychopharmacol Bull 2020;50(4 Suppl 1):108–20.
[9] Wang J, Pei J, Khiati D, et al. Acupuncture treatment on the motor area of the scalp for motor dysfunction in patients with ischemic stroke: study protocol for a randomized controlled trial. Trials 2017;18:287.
[10] Wang J, Shi W, Khiati D, et al. Acupuncture treatment on the motor area of the scalp for motor dysfunction in children with cerebral palsy: study protocol for a multicenter randomized controlled trial. Trials 2020;21:29.
[11] Vitrakis K, Dalton H, Breish D. Cerebral palsy: an overview. Am Fam Physician 2020;101:213–20.
[12] Gao C, Wu Y, Liu J, Zhang R, Zhao M. Systematic evaluation of the effect of rehabilitation of lower limb function in children with cerebral palsy based on virtual reality technology. J Healthc Eng 2021;2021:6625694.
[13] Talampas G, Kilbride C, Levin W, Lavelle G, Ryan JM. Interventions to improve or maintain lower-limb function among ambulatory adolescents with cerebral palsy: a cross-sectional survey of current practice in the UK. Phys Occup Ther Pediatr 2018;38:355–69.
[14] Colver A, Fairhurst C, Pharoah PO. Cerebral palsy. Lancet 2014;383:1240–9.
[15] Lai CJ, Liu WY, Yang TF, Chen CL, Wu CY, Chan RC. Pediatric aquatic therapy on motor function and enjoyment in children diagnosed with cerebral palsy of various motor severities. J Child Neurol 2015;30:200–8.
[16] Gorton JW, Currie SJ. Aquatic exercise programs for children and adolescents with cerebral palsy: what do we know and where do we go? Int J Pediatr 2011;2011:712165.
[17] Akinola BI, Gbiri CA, Odebiyi LE. Effect of a 10-week aquatic exercise training program on gross motor function in children with spastic cerebral palsy. Glob Pediatr Health 2019;6:2333794x19857378.
[18] Roostaei M, Baharlouei H, Azadi H, Fragala-Pinkham MA. Effects of aquatic intervention on gross motor skills in children with cerebral palsy: a systematic review. Phys Occup Ther Pediatr 2017;37:496–515.
[19] Cui Y, Xiao D, Ding L, Qiu F, Cong F, Qiu Z. Effects of aquatic therapeutic exercise on motor function and activities for children and youth with cerebral palsy: a systematic review and meta-analysis. Chin J Rehabil Theory Pract 2021;27:79–92. (Chinese).
[20] Hameed MQ, Dhamne SC, Gersner R, et al. Transcranial magnetic and direct current stimulation in children. Curr Neurol Neurosci Rep 2017;17:11.
[21] Rajapakse T, Kirton A. Non-invasive brain stimulation in children: applications and future directions. Transl Neurosci 2013;4:1–29.
[22] Palm U, Segmüller FM, Epple AN, et al. Transcranial direct current stimulation in children and adolescents: a comprehensive review. J Neural Transm (Vienna) 2016;123:1219–34.
[23] Rehmann R, Szczesny-Kaiser M, Lenz M, et al. Polarity-specific cortical effects of transcranial direct current stimulation in primary somatosensory cortex of healthy humans. Front Hum Neurosci 2016;10:208.

[24] Amatachaya A, Jensen MP, Patjanaasontorn N, et al. The short-term effects of transcranial direct current stimulation on electroencephalography in children with autism: a randomized, controlled crossover trial. Behav Neurol 2015;2015:928631.

[25] Bandeira ID, Guimarães RS, Jagersbacher JG, et al. Transcranial direct current stimulation in children and adolescents with attention-deficit/hyperactivity disorder (ADHD): a pilot study. J Child Neurol 2016;31:918–24.

[26] Auvichayapat N, Rotenberg A, Gersner R, et al. Transcranial direct-current stimulation for treatment of refractory childhood focal epilepsy. Brain Stimul 2013;6:696–700.

[27] Hamilton A, Wakely L, Marquez J. Transcranial direct-current stimulation on motor function in pediatric cerebral palsy: a systematic review. Pediatr Phys Ther 2018;30:291–301.

[28] Kelly N, Heathcock JC. Commentary on “Transcranial Direct-Current Stimulation on Motor Function in Pediatric Cerebral Palsy: A Systematic Review”. Pediatr Phys Ther 2018;30:302.

[29] Gillick B, Rich T, Nemanich S, et al. Transcranial direct current stimulation and constraint-induced therapy in cerebral palsy: a randomized, blinded, sham-controlled clinical trial. Eur J Paediatr Neurol 2018;22:358–68.

[30] Grecco LA, Duarte Nde A, de Mendonça ME, et al. Effect of transcranial direct current stimulation combined with gait and mobility training on functionality in children with cerebral palsy: study protocol for a double-blind, randomized controlled clinical trial. BMC Pediatr 2013;13:168.

[31] da Silva TD, Fontes A, de Oliveira-Furlan BS, et al. Effect of combined therapy of virtual reality and transcranial direct current stimulation in children and adolescents with cerebral palsy: a study protocol for a triple-blind, randomized controlled crossover trial. Front Neurol 2020;11:953.

[32] The Subspecialty Group of Rehabilitation, the Society of Pediatrics, Chinese Medical Association. Expert consensus on etiological diagnostic strategies for cerebral palsy. Chin J Pediatr 2019;57:746–51. (Chinese).

[33] Whitehead AL, Julious SA, Cooper CL, Campbell MJ. Estimating the sample size for a pilot randomised trial to minimise the overall trial sample size for the external pilot and main trial for a continuous outcome variable. Stat Methods Med Res 2016;25:1037–73.

[34] Saleem GT, Crasta JE, Slomine BS, Cantarero GL, Suskauer SJ. Transcranial direct current stimulation in pediatric motor disorders: a systematic review and meta-analysis. Arch Phys Med Rehabil 2019;100:724–38.

[35] Villalta Santos L, Benite Palma Lopes J, Almeida Carvalho Duarte N, Galli M, Collange Grecco LA, Santos Oliveira C. Effect of anodic tDCS over motor cortex versus cerebellum in cerebral palsy: a study protocol. Pediatr Phys Ther 2019;31:301–5.

[36] Lisa K, Kenyon . Gross motor function measure (GMFM-66 and GMFM-88) users’ manual. Phys Occup Ther Pediatr 2014;6:654–5.

[37] Oeffinger D, Bagley A, Rogers S, et al. Outcome tools used for ambulatory children with cerebral palsy: responsiveness and minimum clinically important differences. Dev Med Child Neurol 2008;50:918–25.

[38] Alotabi M, Long T, Kennedy E, Bavishi S. The efficacy of GMFM-88 and GMFM-66 to detect changes in gross motor function in children with cerebral palsy (CP): a literature review. Disabil Rehabil 2014;36:617–27.

[39] Franjoine MR, Gunther JS, Taylor MJ. Pediatric balance scale: a modified version of the berg balance scale for the school-age child with mild to moderate motor impairment. Pediatr Phys Ther 2003;15:114–28.

[40] Yi SH, Hwang JH, Kim SJ, Kwon JY. Validity of pediatric balance scales in children with spastic cerebral palsy. Neuropediatrics 2012;43:307–13.

[41] Chen CL, Shen IH, Chen CY, Wu CY, Liu WY, Chung CY. Validity, responsiveness, minimal detectable change, and minimal clinically important change of Pediatric Balance Scale in children with cerebral palsy. Res Dev Disabil 2013;34:916–22.

[42] Berg M, Jahnsen R, Frasile KF, Hassain A. Reliability of the pediatric evaluation of disability inventory (PEDI). Phys Occup Ther Pediatr 2004;24:61–77.

[43] Custers JW, Wassenberg-Severijnen JE, Van der Net J, Vermeer A, Hart HT, Holders PJ. Dutch adaptation and content validity of the ‘Pediatric Evaluation Of Disability Inventory (PEDI)’. Disabil Rehabil 2002;24:230–8.

[44] Ingugliai E, Bolognini N, Fiori S, Cioni G. Transcranial direct current stimulation (tDCS) in unilateral cerebral palsy: a pilot study of motor effect. Neural Plast 2019;2019:2184398.

[45] Collange Grecco LA, de Almeida Carvalho Duarte N, Mendonça ME, Galli M, Fregni F, Oliveira CS. Effects of anodal transcranial direct current stimulation combined with virtual reality for improving gait in children with spastic diparetic cerebral palsy: a pilot, randomized, controlled, double-blind, clinical trial. Clin Rehabil 2015;29:1212–23.

[46] Li X, Qiu H, Jiang Z, et al. Epidemiological characteristics of cerebral palsy in twelve province in China. Chin J Appl Clin Pediatr 2018;33:378–83. (Chinese).