Transcranial Direct Current Stimulation for Rehabilitation of Motor Disorders in Children with Cerebral Palsy: (Systematic Review).

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Abstract

Background: The use of Transcranial Direct Current stimulation (tDCS) in the motor rehabilitation of children with cerebral palsy is new, and thus the scientific evidence for its effectiveness needs to be evaluated through a systematic review. **Objective:** To provide updated evidence-based guidance for tDCS effects on functional motor skills of children with cerebral palsy**. Data sources:** Ovid, Medline, Cochrane, Pedro, Science direct, Web of science, EPSCOhost, PubMed and Google scholar website were searched from their earliest records up to August**. Data extraction:** Template was created to systematically code the demographic, methodological, and miscellaneous variables of each RCT. The Physiotherapy Evidence Database (PEDro) scale was used to evaluate the study quality. **Data synthesis:** Nine studies included 192 participants in total. Best evidence synthesis was applied to summarize the outcomes, which were balance ,gait parameters , spasticity and upper limb function .**Conclusions :** However researches on tDCS is still preliminary , the available data demonstrated the efficacy of tDCS as a new modality on rehabilitation of motor disorders in cerebral palsy children with immediate and long term effect on improving motor disorder. Further studies are still needed, especially those involving both neurophysiological and functional evaluations and to cover further domain on cerebral palsy.

Key wards: Transcranial Direct Current Stimulation-Motor Disorders – Rehabilitation- Cerebral Palsy- Systematic review.

Introduction

Cerebral palsy (CP) occupies a group of neurophysiologicalimpairments originatesfrom a wide-ranging reduction in subcortical activitythat compromises the activity of the both ofcorticospinal and somatosensorycircuits**[1].**CP results in reduction of the activation of the central nervous system during the carrying out ofmovements **[2].** A diminution in motor cortex excitability inCPchildren is associated with poor motor development **[3].Nevalainen et al[4]**reported that the neurophysiologicalanalyses in adolescents withhemiplegicCP have demonstrated global changes in cortexexcitability, even when the brain lesion isunilateral. Cerebral palsy children have postural problems resulting from spasticity, muscle weakness and impaired muscle coordination.These postural problems can also affect motor development, and resulting in a motor impairments leading to difficulties in performing basic functional activities, encompassing sitting, standing and walking abilities**[5,6].**

Transcranial direct current stimulation (tDCS) is considered as a non-invasive therapeutic method used to rehabilitate children with cerebral palsy in which the motor cortex is stimulated using a low-intensity (1–2 mA), monophasic, direct, electrical current through surface electrodes such intervention seems to be a promising new tool in the field of neuroplasticity**[7]**The advantages of transcranial direct current stimulation in comparison to other transcranial stimulation methods are the longer-lasting modulating effect on cortex function, simplicity of administration, and lesser fee. Furthermore, this type of intervention allows better placebo stimulation, thereby conferring greater precision to scientific findings **[8].**

Miranda et al[9].declared that the special effectsof using tDCS are accomplished by the movement of electrons due toelectrical charges. He added that the two poles are the anode (positive) andcathode (negative) electrodes. The electrical current floods from thepositive pole to the negative pole then, penetrating the skull andreachingthe cortex, producing different effects on biological tissues.Although most of the current is dispersing among the overlyingtissues, a sufficient amount reaches the structures of the cortex and altersthe membrane potential of the surrounding cells.

tDCS has short-term effects on cortex excitability when applied for short periods and longer-lasting effects related to plastic mechanisms when applied over a longer period **[10].Nitsche et al [11]**stated that polarized currents applied to the cerebral surface would augment unprompted firing and begin paroxystic activity when the anodal pole is used, whereas the cathode generally lowers these events.

Staggand Nitsche[12] reported that application of tDCS for longer than five minutes might persuade significant after-effects which probably are mainly due to changes in synaptic mechanisms, which could last many hours after the application.

Regarding the rehabilitation process, the aim of neuromodulation techniques is to increase local synaptic efficiency, thus changing the maladaptive plasticity pattern that emerges following a cortex lesion. The chance of combining physical therapy modalities is considered one of the advantages of transcranial direct current stimulation**[13].**tDCS sessions in combination with rehabilitation interventions leads to more improving in motor function which could reduce rehabilitation-related costs**[14]. Bolognini et al [15]**added that adding of tDCS to motor therapy will have more beneficial effect on neural plasticity than their use alone.

The evidence base of using tDCSin rehabilitation of children with cerebral palsy was studied by many recent researchers. Therefore the optimal effect of usingtDCSin rehabilitation of motor disorders in CP children needs to be systematically investigatedto be clearbeforetheir clinical use. Thus, The aim ofthis study was to provide physiotherapist with fundamental information about the evidence of the effect of transcranial direct current stimulation (tDCS) in motor disorders rehabilitation of children with cerebral palsy.

Subjects, Instrumentations and Methods

Subjects:

Search strategy:

This review included studies that examined the effect of Transcranial direct current stimulation on moter disorders in children with cerebral palsy. literature search was performed independently by the four authors using an electronic inclusive literature search of Cochrane Library, PubMed, Science Direct, Physiotherapy Evidence Database (Pedro) Web of Science, Ovid ,Medline, EPSCOhos and Google scholar databases from their earliest records to August 2017, using a number of key words:Transcranial Direct Current Stimulation, Noninvasive brain stimulation, Cerebral Palsy, Motor skills, Fine motor, Gross motor and Spasticity. These key words were used individually and/or were combined. All references from the selected articles were also cross-checked by the authors to identify relevant studies that may have been missed in the search. The reviewers also used the Science Citation Index (Science Direct) to conduct forward citation tracking of any eligible studies found, in order to identify additional articles relevant for the review.

Study selection:

Before the beginning of the study selection procedures, duplicated searches were excluded electronically by using Mendeley computer software. Thetwo reviewers.(S and M) independently reviewed the studies for eligibility based on title and abstract.Studies deemed potentially eligible by at least one reviewer then the full text versions were retrievedand independently screened by the two reviewers to determine whether they met inclusion criteria. Disagreement between the two reviewers in any stage was resolved by discussion until consensus was reached or, where necessary, the second reviewer (SH) made the final decision.

Eligibility criteria:

The inclusion criteria for studies to be included in this systematic review were as follows: participants in the study were children who had CP and were aged between 4 and 18 years old; the outcome measures used in the study were related to motor function, such as fine motor function, gross motor function in addition to level of spasticity and secondary out comessuch as strength or cortical excitability; the study design was an RCT; and the study was written in English. Studies were excluded if the research was animal, in vitro or computer model research or the study not published as a full text article.

Data-extraction and management:

Data were extracted by the reviewer (S) and checked by the reviewer (M) through a self-made extraction format designed by reviewer (SH and S). Disagreements between the two reviewers were resolved by discussion until consensus was reached.Key details of each study were extracted using the specific data extraction format .The format includes: research design,participants, eligibility criteria, intervention, and outcomes of interest and results of each study.

Assessment of methodological quality:

Two reviewers (S and M) independently assessed the methodological quality of the included RCTs, according to the Physiotherapy Evidence Data base (PEDro) scale**Appendix (1)**. The PEDro scale is a valid measure of the methodological quality of clinical trials and is based on the Delphi list developed by **Verhagenet al[16].**The scale is used to rate studies from 0–11 according to following 11 methodological criteria: specified eligibility criteria, random allocation, concealed allocation, baseline comparability, blinded subjects, blinded therapists, blinded assessors, adequate follow-up, intention-to-treat analysis, betweengroup comparisons, and point estimates and variability. Each item was scored as 1(yes) or 0(no). The studies were ranked as 'high quality' if their score is more than or equal 7, studies with a score of 5 or 6 were considered of 'moderate quality' and those with a score of 4 or less were deemed of 'poor quality' **[17, 18]** .PEDro scores were not used as inclusion/exclusion criteria, but rather as a basis for data-analysis and to discuss the strengths and weaknesses of studies.

Data synthesis and analysis:

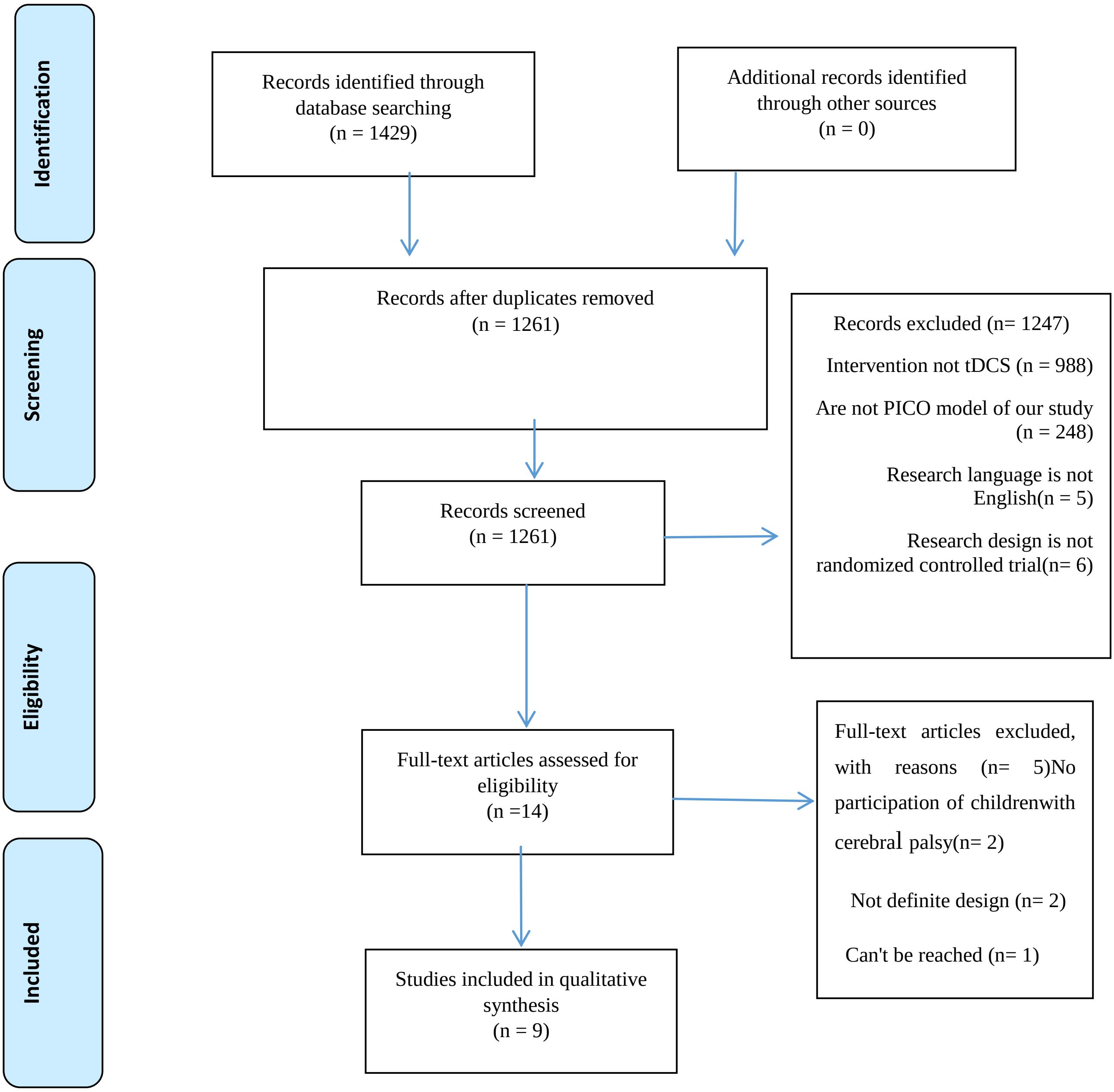
A meta-analysis was not practicable due to diverse outcome measures and other clinical heterogeneitybetween the included studies.Instead, the overall certainty of the evidence was assessed using a rating system (Modified Sackett Scale) approach **Appendix (2)** which consists of five levels of scientific evidence.For the purpose of this review, a simplified version of the categories used by **Sackett et al**. **(2000)** [19] was adopted. Instead of the original 10 scoring categories, to be a scoring system ranging from a level 1 evidence to a level 5 evidence, and added descriptions to each category to help designate the appropriate level of evidence based on the type of research design. In the Version 4.0 of this grading scheme used in this review, the evidence level of 1 category is further divided into 2 subcategories to distinguish between a single RCT with a PEDro score ≥ 6 (Level 1b), and 2 or more RCTs with PEDro scores ≥ 6 (Level 1a) .

RESULTS

Flow of studies through the review:

The literature search identified a total of 1429 potentially relevant articles. After theremoval of duplicates (n= 168), rejection based on title and abstract (*n*=1247), and inclusion andexclusion criteria (*n*=5).9 RCTs were included for the quality assessment and bestevidence synthesis. The selection procedure, including reasons for exclusion, is summarized in **figure(1).**

Figure (1) A PRISMA Flow chart showing the selection procedure for studies included in this systematic review



Description of Studies:

The data extracted from the 9 studies are summarized in **Table (1)**. There were 192 participants in the 9 studies. They were CP children their average age ranged from 4 to 18 years and they were all at levels (level I-IV) of the Gross Motor Function Classification Scale.

Methodological Quality and level of evidence:

The mean PEDro score of all studies was 7.4 (range5-9) **Table (2)**.(2 studies with a score of 9, 3 studies with a score of 8, 2 studies with a score of 7, 1 studies with a score of 6, and 1 studies with a score of 5), indicating that the quality of the RCTs included in thisresearch was high to moderate.All studies were randomized, 77.7% had below15% dropout rate and reported between-group difference, 78% group similarity at baseline andpoint estimate and variability. The majority of studies did notperform blinding of participant (65%) and therapist (100%),concealed allocation (88%), and blinding of assessor (77%). The level of evidence of eight studies out of the nine (88%) was 1b this means that the majority of the included studies had Good level of evidence for the recommendation to consider.

Interventions:

The intervention method, dose, duration and intensity varied across the studies. three studies used tDCS accompanied with treadmill training **(Duarte Nde et al. 2014; Grecco et al. 2017; Grecco, de Almeida, et al. 2014)** [23,24, 28]; three other studies used virtual reality in accompany with tDCS**(Collange Grecco et al. 2015; Lazzari et al. 2015; Lazzari et al. 2017)**[20 21, 25]; one study used tDCS with constrain induced motor therapy and motor training program to upper limb **(Moura et al. 2017)**[26];one study used tDCSwith traditional physical therapy**(Aree-uea et al. 2014)**[27]and the last one used tDCS only **(Grecco, Duarte, et al. 2014).**[22] The interventions mentioned in the previous literaturesranged from one to ten sessions in frequency. The time of tDCSapplication in each session was 20 minute on all reviewed studies.

Outcome Measures:

Studies also differed in the type of outcome measures used.One study used upper limb movement kinematics to measure the effect of single session of tDCS on upper limb movement kinematics**(Moura et al. 2017)**[26] while,**Aree-uea et al. (2014)** [27] usedpassive range of motion and modified Ashwar scale to measure spasticity changes after five days of application of tDCS. **Collange Grecco, et al. (2015), Grecco, Duarte, et al. (2014)(Grecco, de Almeida, et al.(2014)** [20, 22,24] used spatiotemporal gait variables to measure the effect of tDCS on gait of CP children. Moreover, **Lazzari et al. (2015 and 2017) andGrecco et al.(2017); Grecco, Duarte, et al.(2014) and Duarte Nde et al. (2014)**[21-23,25,28]used static balance variable to measure the effect of tDCS on balance in CP children. There were other varied secondary outcomes on some studies such as functional balance ,gross motor function measure,motor evoked potential and self-care**Table (2).**

Effect of transcranial direct current stimulation:

Moura et al. (2017) [26]reportedstatistically significant reductions in total movement duration and returning movement duration in both the paretic and non-paretic limbs in the group submitted to active tDCS. They added that no significant differences were found in the control group for any of the variables analyzed.

Aree-uea et al. (2014) [27]found thatparticipants assigned to active tDCS treatment evidenced significantly more pre- to immediately post-treatment reductions in spasticity than participants assigned to the shamtDCS and that these improvement in spasticity was maintainedfor at least 48 hours for wrist joints.

Collange Grecco, et al. (2015), Grecco, Duarte, et al. (2014)(Grecco, de Almeida, et al.(2014) [20, 22,24] declared thatthe experimental groups exhibited improvements in temporal functional mobility, gait variables (spatiotemporal and kinematics variables), accompanied by improvements in grossmotor function measure scale and enhanced motor evoked potential. They added that the results were maintained one month after the end of the intervention.

Several authors **(Lazzari et al. 2015, Lazzari et al. 2017, Grecco et al. 2017, Grecco, Duarte, et al. 2014, Duarte Nde et al. 2014)**[21-23,25,28]investigated the effect of tDCS on balance through assessing the area of oscillation of the COP in a group of CP children when standing on the force plate while their eyes open and closed.These authorsrecorded improvements on pediatric balance scale(PBS) which was sustained up to one month after intervention.

Grecco, et al.(2017) [28]studiedthe effect of combination of treadmill training and cerebellar anodal tDCS in six ataxic cerebral palsy children. They found thatthe experimental group showed significant reductions in oscillations of center of pressure (COP) with their eyes closed in comparison to control group. They added that the effects of treadmill training on functional balance and functional performance in mobility were observed on both groups but maintained in experimental group only.

Table (1) Data extraction sheet

Study	Study design	Population	Age Range (X—)	Eligibility criteria	Intervention	Outcomes	Results
Collange Grecco et al. (2015) [20]	RCT double blind	20 CP children	5- 10 years Mean age= 7.5	Spastic diparetic CP levels II or III of the GMFCS	RG (VR+ active anodaltDCS) CG(VR+ placebo tDCS) **Dosage** (20 minutes) (10 session)	-gait analysis, GMFCS-PEDI- -MEP	Better performance regarding gait velocity-cadence- gross motor function and MEP
Lazzari et al. 2015) ([21]	RCT double blind	12 CP children	4- 12 years Mean age= 8	Spastic CP levels I, II or III of the GMFCS	RG (VR+ active tDCS) CG(VR+ placebo tDCS) **Dosage** (20 minutes) (single session)	-Static balance)	significant improvement in sway velocity were found only in the mediolateral direction under both visual conditions (eyes open and eyes closed)
Grecco, Duarte, et al. (2014) [22]	RCT sham control study cross sectional	20 CP children	6-10 years Mean age= 8	Spastic CP levels I, II or III of the GMFCS	RG (active tDCS) CG(placebo tDCS) **Dosage** (20 minutes) (single session)	- Gait analysis -balance	Significant reductions in oscillations during standing in the anteroposterior and mediolateral directions with eyes open and eyes close. Significant improvements in gait velocity, cadence, and oscillation in the center of pressure during standing
Duarte Nde et al. (2014) [23]	RCT double blind	24 CP children	5-12 years Mean age= 8.5	Spastic CP levels I, II or III of the GMFCS	RG (treadmill training + active tDCS) CG(treadmill training + placebo tDCS) **Dosage** (20 minutes) (10 session)	- Static balance -PBS -PEDI	better results regardinganteroposteriorand mediolatera sway (eyes open and closedand the Pediatric Balance Scale.

Grecco, de Almeida et al. 2014)([24]	RCT double blind	24 CP children	5-12 years Mean age= 8.5	Spastic diparetic CP levels I, II or III of the GMFCS	RG (treadmill training + active tDCS) CG(treadmill training + placebo tDCS) **Dosage** (20 minutes) (10 session)	gait analysis, - -6minute walk test -Treadmill test GMFM- -MEP	Improvements in temporal functional mobility, gait variables (spatiotemporal and kinematics variables). There was a significant change in corticospinalexcitabilit
Lazzari et al. (2017) [25]	RCT double blind	20 CP children	4-12 years Mean age= 8	Spastic CP levels I, II or III of the GMFCS	RG (VR+ active tDCS) CG(VR+ placebo tDCS) **Dosage** (20 minutes) (10 session)	-Static Balance PBS- -Timed up and go test	Improvement of static andfunctional balance.
Moura et al. (2017) [26]	RCT sham control study	20 CP children	6-12 years Mean age= 9	Spastic hemiparetic CP, level I or II of the GMACS	RG (anodal tDCS) CG (sham tDCS). +functional training of the paretic upper limb **Dosage** (20-minute) (single session)	-Upper limb movement kinematics	Improvement in upper limb movement
Aree-uea et al. (2014) [27]	RCT sham control study	46 CP children	8-18 Years Mean age= 13	Spastic CP with levels II-IV of the GMACS	RG(anodal tDCS) CG (sham tDCS). Both group received routine physical therapy **Dosage** 20 min 5 days	-degree of spasticity -passive range of motion	reductions in spasticitand these improvement in spasticity maintainedfor at least 48 hours for wrist joints
Grecco et al. (2017) [28]	RCT Single-blind, sham-controlled, crossover,	6 CP children	5-11 years Mean age= 8	Ataxic CP with independent gait for at least6 month and complaints of daily falls	RG: (anodaltDCS over cerebellar region +treadmill training). CG:– (sham tDCS + treadmill training) **Dosage** 20 minute 10 sessions	-Static balance - (PBS) - (PEDI)	significant reductions occurred in oscillations of the center of pressure with eyes closed

RCT- randomized control trail ;cp- cerebral palsy ; RG-research group ; CG- control group; VR- virtual reality ;COP-center of pressure ; MEP-Motor evoked potential tDCS-transcranial direct current stimulation ;GMFCS – gross motor function classification scale ; PEDI- Pediatric Evaluation Disability Inventory ; PBS-Pediatric Balance Scale

Table (2).PEDro scores and level of evidence for included studies (n=9)

Study	Eligibility criteria	Random allocation	Allocation concealment	Baseline similarity	Blind subject	Blind therapist	Blind assessor	Adequate follow-up	Intention-to-treat	Between group comparison	Eligibility criteria	Total score	Levelof evidence
Collange Grecco et al. (2015) [20]	YES	YES	YES	YES	NO	No	NO	YES	YES	YES	YES	8	1b
Lazzari et al. (2015) [21]	YES	YES	YES	NO	YES	NO	NO	NO	NO	NO	YES	5	2
Grecco, Duarte, et al. 2014) [22](	YES	YES	NO	YES	YES	NO	YES	YES	NO	YES	YES	8	1b
Duarte Nde et al.(2014) [23]	YES	YES	YES	YES	YES	NO	YES	YES	NO	YES	YES	9	1b
Grecco, de Almeida, et al.(2014) [24]	YES	YES	YES	YES	NO	NO	YES	YES	YES	YES	YES	9	1b
Lazzari et al. (2017) [25]	YES	YES	YES	YES	NO	NO	YES	YES	NO	NO	YES	7	1b
Moura et al. (2017) [26]	YES	YES	YES	YES	NO	NO	YES	YES	NO	YES	YES	7	1b
Aree-uea et al. (2014) [27](	YES	YES	YES	YES	No	No	YES	YES	YES	YES	YES	8	1b
Grecco et al. (2017) [28]	YES	YES	YES	NO	NO	NO	YES	NO	NO	YES	YES	6	1b

DISCUSION

Transcranial direct current stimulation is probably beneficial for rehabilitation of motor disorders in children with cerebral palsy. The main objective of this review was to critically evaluate articles that demonstrate this assumption. As we selected only the randomized trials to meet the highest standard of evidence, a stiff conclusion cannot be achieved through this review with nine studies. Furthermore, there was large clinical heterogeneity presentedacross the studies.

Combining all outcome measures of all studies, transcranial direct current stimulation intervention generally demonstrated strong effects in improving motor functions in children with CP, comprising improvements in temporal functional mobility, gait variables(spatiotemporal and kinematics variables) in addition to reductions in spasticity , and improvements in grossmotor function measures scale and enhanced motor evoked potential .It helps in improvement offunctional balance and functional performance in mobility when comparing with conventional therapy or controls . epither used alone or in combination with other methods such as treadmill, virtual reality, constrain induced motor therapy and even with traditional physical therapy.**Kashi et al. (2012)** [29] demonstrated that anodal tDCSwas able to cause changes in motor cortex excitability, thereby improving motor control and lower limb movements.

Grecco, Duarte et al. (2014) [22]demonstrate that the combination of treadmill training and anodal stimulation of the primary motor cortex in the dominant hemisphere was capable of potentiating improvements in static and functional balance in the children with cerebral palsy. Moreover, anodal stimulation favored the maintenance of the gains one month following the completion of the intervention.

Conclusion:

Available data from nine reviewed studies demonstrated the efficacy oftranscranial direct current stimulation as anew modality in rehabilitation of motor disorders in children with cerebral palsy with immediate and long term effect on improving motor disorder including improve balance, gait variables,upper limb functions and modulate spasticity.

Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Appendix (1)PEDro scale

1. Eligibility criteria were specified no _ yes _ where:

2. Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received) no _ yes _ where:

3. Allocation was concealed no _ yes _ where:

4. The groups were similar at baseline regarding the most important prognostic indicators no _ yes _ where:

5. There was blinding of all subjects no _ yes _ where:

6. There was blinding of all therapists who administered the therapy no _ yes _ where:

7. There was blinding of all assessors who measured at least one key outcome no _ yes _ where:

8. Measures of at least one key outcome were obtained from more than 85%of the subjects initially allocated to groups no _ yes _ where:

9. All subjects for whom outcome measures were available received thetreatment or control condition as allocated or, where this was not the case,data for at least one key outcome was analysed by “intention to treat” no _ yes _ where:

10. The results of between-group statistical comparisons are reported for at least one key outcome no _ yes _ where:

11. The study provides both point measures and measures of variability for at least one key outcome no _ yes _ where:

Appendix (2) Modified Sackett Scale Version 4.0

Level	**Research Design**	**Description**
Level 1a	Randomized Controlled Trial (RCT)	More than 1 Higher RCT: Randomized Controlled Trial, PEDro score ≥ 6. Includes within subjects comparison with randomized conditions and cross-over designs.
Level 1b	RCT	1 Higher Randomized Controlled Trial, PEDro score ≥ 6
Level 2	RCT	Lower RCT, PEDro score < 6
	Prospective Controlled Trial (PCT)	Prospective Controlled Trial (not randomized).
	Cohort	Prospective Longitudinal study using at least 2 similar groups with one exposed to a particular condition
Level 3	Case Control	A retrospective study comparing conditions, including historical cohorts.
Level 4	Pre-Post	A prospective trial with a baseline measure, intervention, and a post-test using a single group of subjects.
	Post-test	A prospective post-test with two or more groups (intervention followed by post-test and no re-test or baseline measurement) using a single group of subjects.
	Case Series	A retrospective study usually collecting variables from a chart review.
Level 5	Observational	Study using cross-sectional analysis to interpret relations.
	Clinical Concensus	Expert opinion without explicit critical appraisal, or based on physiology, biomechanics or "first principles
	Case Report	Pre-post or case series involving one subject.

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