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Effect of transcutaneous spinal direct current stimulation on spasticity in upper motor neuron conditions: a systematic review and meta-analysis

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ABSTRACT

Study design: A systematic review and meta-analysis of clinical trials.

Objectives: To determine the effect of non-invasive transcutaneous spinal direct current stimulation (tsDCS) on spasticity, activity limitations and participation restrictions in various upper motor neuron diseases.

Methods: Six databases including CINAHL plus, Cochrane CENTRAL, Embase, MEDLINE, SCOPUS and Web of Science were searched for the relevant records from January 2008 to December 2022. Two reviewers independently selected and extracted data on spasticity, activity limitations and participation restrictions. The risk of bias was evaluated using the PEDro scale while the GRADE approach established the certainty of the evidence.

Results: Eleven studies were identified of which 5 (45.5%) were rated as having a low risk of bias and 8 (72.7%) were meta-analyzed. The meta-analyses did not show any significant differences between cathodal (SMD = -0.67, 95% CI = -1.50 to 0.15, P = 0.11, I^2 = 75%, 6 RCTs) or anodal (SMD = 0.11, 95% CI = -0.43 to -0.64, p = 0.69, I^2 = 0%, 2 RCTs) and sham tsDCS for spasticity. There was also no significant difference between active and sham tsDCS for activity limitations (SMD = -0.42, 95% CI = -0.04 to 0.21, p = 0.2, I^2 = 0%, 2 RCTs) and participation restrictions (MD = -8.10, 95% CI = -18.02 to 1.82, p = 0.11, 1 RCT).

Conclusions: The meta-analysis of the available evidence provides an uncertain estimate of the effect of cathodal tsDCS on spasticity, activity limitation and participation restriction. It might be very helpful, or it may make no difference at all. However, considering the level of the evidence

and the limitation in the quality of the majority of the included studies, further well-designed research may likely change the estimate of effect.

Registration: PROSPERO CRD42021245601

Keywords: Spasticity, Spinal cord stimulation, Neuromodulation, Neurological rehabilitation, Neuronal plasticity, Systematic review

INTRODUCTION

Spasticity is one of the cardinal signs of upper motor neuron (UMN) diseases such as stroke, spinal cord injury, multiple sclerosis, cerebral palsy, traumatic head injury, amyotrophic lateral sclerosis, brain tumor and spastic paraplegia. It is defined as 'disordered sensorimotor control resulting from an UMN lesion, presenting as intermittent or sustained involuntary activation of muscles [1]. This muscle over-activity is characterized by velocity and length-dependent hypertonia due to the hyperexcitability of tonic stretch reflexes [2]. The hyperexcitability of the stretch reflex results from adaptive changes in the spinal neural networks and intrinsic properties of spinal motor neurons following chronic lesions to descending spinal pathways, including the dorsal reticulospinal tract [3]. These changes lead to a decrease in disynaptic reciprocal inhibition, pre-synaptic inhibition of Ia terminals [4], post-synaptic inhibition, and/or autogenic Ib inhibition [5, 6] The net effect of the aforementioned changes is that the α-motor neurons will be uninhibited and discharge spontaneously to the extrafusal fibers of stretched muscles causing continuous contraction.

The prevalence of spasticity differs between disease conditions. It is said to be about 40% in stroke, 80% in multiple sclerosis, 65% in spinal cord injury, 17% to 50% in traumatic brain injury and 90% in cerebral palsy [7-9]. In addition, patients with spasticity experience pain, spasms, limb contracture and deformity. These can lead to impairment of dexterity, mobility, and self-care, and ultimately to limited functioning and restricted participation [10]. Furthermore, when spasticity is untreated or poorly managed, it can be a cause of physical and economic burden for patients and their Caregivers [11]. The cost of treatment for patients with spasticity has been

reported to be four times higher than for those without spasticity during the first 12 months after cerebral infarct [12]. As such, spasticity, together with other factors including pain, bladder problems, fatigue, and sleep, may have significant negative effects on health-related quality of life in patients with UMN conditions [13]. For instance, in an international survey of 427 patients with spasticity and their caregivers, 90% of the participants reported that spasticity affected at least one aspect of their quality of life [14].

There are many treatment approaches for spasticity including oral medications such as baclofen, tizanidine and dantrolene; focal injection of botulinum toxin, alcohol or phenol; baclofen delivered intrathecally through a pump; and surgical resection of selected dorsal roots of the spinal cord [15]. However, the surgical procedure is expensive and associated with complications such as sensory loss, urinary incontinence, low-back pain, and spinal deformity [16]. The medications are also not devoid of systemic side effects such as hyperthermia, hypotension, seizures, altered mental status and hallucination [17]. Other approaches such as physical management interventions do not treat the neuronal cause of spasticity [18]. They focus mainly on improving performance, relieving discomfort, and pain, and preventing secondary complications including contractures and pressure ulcers [19]. The optimal spasticity management has continued to elude practitioners. A relatively new form of intervention, transcutaneous spinal direct current stimulation (tsDCS), has been trialed.

The tsDCS has been established as a procedure to modulate spinal cord activity [20], and early experiments have indicated hope in its utilization as a tool to treat the neuronal cause of spasticity [21, 22]. The tsDCS consists of a constant direct current over the spinal cord through a

pair of sponge electrodes, cathode, and anode, one placed over the spinal cord and the other (the reference) over the right arm [23]. The direct current intensity is in the range of 1.5–2.5 mA which is below the perceptual threshold, and the effects last from minutes to hours [21]. Studies have shown that the electric fields induce differential polarization of the spinal motor neurons so that a persistent dendritic Ca2+ inward current modulates motor neuron excitability [24-26]. Several studies have already demonstrated the efficacy of this modality in reducing spasticity and improving α-motor neuron recruitment in patients with spinal cord injury [27-30], stroke, [31, 32] and hereditary spastic paraplegias [33]. However, this technique has been limited to the laboratory for research purposes only. It is also pertinent to note that there is no systematic review that primarily investigates the effectiveness of this novel technique in treating spasticity. This would better inform future studies and its clinical application.

As highlighted above, the pathophysiology of spasticity in all UMN diseases is the same and it is integrated in the transverse segments of the spinal cord [2]. It entails hyperexcitation of the stretch reflex arch following a period of shock or flaccidity and the absence of descending inhibitory drive due to the damaged dorsal reticulospinal tract [3]. Though the severity of the spasticity is higher when the affectation of the above extrapyramidal tract is at the spinal cord or brain stem level than at an internal capsule or cortex [34], the spinal segments are the targets of the stimulation, and the proposed mechanisms of action are the same for the two electrodes [21]. Thus, we aimed to carry out a comprehensive systematic review of the available evidence on the effectiveness of tsDCS in any condition leading to upper motor dysfunction including spinal cord injury, stroke, multiple sclerosis, cerebral palsy, traumatic head injury, amyotrophic lateral sclerosis, brain tumor and spastic paraplegia. Specifically, we sought to determine the

effectiveness of tsDCS in the reduction of spasticity, based on any valid and reliable outcome measure and the subsequent effects on activity limitations and participation restrictions.

METHODS

Eligibility criteria

PECOS structure (P-patients, E-exposure, C-comparison, O-outcome, and S-study design) was used to establish the following inclusion criteria: 1) patients with upper motor neuron diseases, (2) non-invasive spinal direct current stimulation was given as an intervention, regardless if there were other interventions provided (3) outcomes included assessment of spasticity, and (4) the studies were Randomized Controlled Trials (RCT) or Cross-over Clinical Trials (CCT). We excluded: (1) studies that used spasticity interventions together with tsDCS in the same group of participants without subjecting the sham group to similar intervention to cancel out its effect and (2) studies not reported in the English language including tables and abstracts. However, we included one study, (Savenkova et al., 2019) [35], reported in Russian language because both the abstract and the tables were comprehensively written in English.

Information Sources

An electronic search of titles and abstracts of articles was conducted in the following databases: CINAHL Plus, Cochrane CENTRAL, Embase, MEDLINE, SCOPUS and Web of Science. In addition, the following trial registers were searched: the Pan African Clinical Trial Registry, ClinicalTrials.gov, and the International Clinical Trials Registry Platform (ICTRP). Principal

investigators of the relevant completed trials were contacted for data where applicable. Finally, the reference lists of the included studies were manually searched for eligible papers.

Search Strategy

The following search terms were developed based on the titles of the relevant studies obtained: “trans-spinal cord stimulation” or “spinal direct current stimulation” or “non-invasive spinal stimulation” or “Transvertebral direct current stimulation” or “electrical spinal stimulation” or “neuromodulation” or “spinal cord stimulation” and “spasticity” or “hypertonia”. The aforementioned terms were entered into all databases and trial registries. To improve the precision and specificity of the search, we used three filters: “publication dates” (January 2008 to December 2022), “species” (Humans) and “Language” (English). Publication dates were used as a filter because tsDCS was first proposed in humans in 2008. The review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with a registration number: CRD42021245601. This report was written according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA).

Selection process

EndNote software (version 20.2) was used to remove duplicates among the identified records. The remaining records were imported into Covidence software for screening, quality assessment and data extraction. The software detected and removed more duplicates. Covidence was designed by researchers familiar with the systematic review process in order to make reviews more efficient [36]. It is the primary screening and data extraction tool for Cochrane authors. Two reviewers logged into the software and independently screened the titles and abstracts of

the remaining records for any evidence of non-invasive spinal direct current stimulation and/or assessment of spasticity. After the exclusion of the irrelevant records, the full-texts of the remaining records were retrieved and imported into the software. The two independent reviewers assessed the full-texts of the studies against the eligibility criteria of the review. The studies that qualified were moved to the next stage of data extraction and quality assessment. At each stage, the two reviewers discussed and reached a consensus on conflicts, with the help of a third reviewer (MSD), before moving ahead and the software assessed the level of inter-rater agreement using Cohen's kappa (ϰ) statistic [37].

Data collection process

The leading reviewer designed a customized data extraction template in Covidence software. Two independent reviewers extracted the required data from the included studies. In the case

of conflicts, a consensus was reached among the reviewers and the software assessed the level of the disagreement using Cohen's Kappa (ϰ).

Data items

In this review, based on the International Classification of Functioning, Disability and Health (ICF), spasticity was considered as an impairment that can lead to activity limitation and participation restriction in individuals with UMN disease conditions. For spasticity, we focused on clinical measures such as the Modified Ashworth Scale (MAS), Modified Tardieu Scale (MTS), and more objective tools such as Wartenberg's Pendulum Test (WPT) and Hoffmann's reflex (H-reflex) parameters. MAS entails grading the increased muscle tone on an ordinal scale of 0-4 (with an

additional grade of +1) based on resistance to passive movement across a relaxed joint [38]. MTS quantifies muscle tone at a specified speed, as slow as possible and as high as possible, to determine the dynamic component of the muscle contracture [39]. WPT of spasticity entails letting the lower leg swing freely under the influence of gravity while recording joint kinematics using an electrogoniometer [40]. H-reflex is an electrically induced reflex analogous to the mechanically induced spinal stretch reflex. The primary difference between the two is that H-reflex bypasses the muscle spindle [41] by activating Ia-afferent (sensory) fibers to reach the α-motor neuron pool of the corresponding muscle to the efferent (motor) fibers [42]. The efferent portion of the H-reflex pathway results from action potentials generated by the α-motor neurons, traveling along the efferent fibers until they reach the neuromuscular junction and produce a twitch response in the electromyography (EMG) (the H-reflex) corresponding to a synchronized contraction [43].

For activity limitation and participation restriction, generic measures that can be used for the general population such as Functional independence Measure, Barthel Index, Gross Motor Function Measure, 10-Meter Walk Test, 6-Minute Walk test, Short Form-36, WHO Quality of Life – BREF, etc, were considered. We also included disease-specific measures such as Spinal Cord Independence Measure III and Spastic Paraplegia Rating Scale. The main variable extracted for this review was the mean ± standard deviation of spasticity, activity limitation and participation restriction measures for study and control groups immediately after the last tsDCS session. Other variables extracted were study design, number of participants, patients' conditions, outcome measures, active and sham interventions, and parameters of stimulation, results and number of follow-ups.

Methodological Quality Assessment

The methodological quality (internal validity) of the included studies was assessed using Physiotherapy Evidence Database (PEDro) scale. The scale was developed by Verhagen et al. (1998) [44] based on the Delphi consensus technique to develop a list of criteria thought by the experts in the field to measure the methodological quality. The number of items in the scale and the design of the included studies were used to guide the scoring of the PEDro scale. Item 1 refers to the external validity of the included studies and thus, was not included in the total PEDro scores [45]. Items 2 - 9 are related to the internal validity of studies and items 10 and 11 refer to statistical analysis, ensuring sufficient data to enable appropriate interpretation of the results. Generally, studies scoring ≥ 6 out of 10 were considered high-quality, while studies scoring < 6 out of 10 were considered low-quality [46]. None of the included studies was available on the PEDro website. Hence, two independent reviewers performed the assessment and discussed their scores to reach a consensus.

Effect measures

For the meta-analysis, due to the variations in the scale of the outcome measures used in the included studies, we considered the standardized mean difference (SMD) of spasticity and activity limitations measures immediately after the intervention for the experimental sessions (anodal or cathodal tsDCS), compared to sham tsDCS sessions. Though many of the included studies assessed spasticity using MAS, a short ordinal scale, SMD as a summary statistic for continuous data was used for the analysis as recommended by Cochrane [47], because the authors expressed the data as Mean and SD. In addition, we used common standard deviations

of the control groups to calculate Cohen's d for the effect sizes because we pooled weighted mean difference from both RCTs and CCT [48].

Syntheses Methods

The data syntheses for the quantitative analysis were done by considering homogeneity among the studies in terms of active electrodes used in spinal cord stimulation. Meta-analysis was done for at least two homogenous studies. Five groups emerged: Group 1 consists of six studies; four assessed spasticity with Modified Ashworth Scale [35, 49-51] and the remaining two with pendulum test [52, 53] following cathodal stimulation. Group 2 consists of two studies [33, 54] that assessed spasticity with Modified Ashworth Scale following anodal stimulation. Group three consists of two studies [50, 51] that assessed activity limitations using the Spinal Cord Independence Measure III (SCIM III) and Gross Motor Function Measure (GMFM-88) following cathodal stimulation. Group four consists of one study [33] that assessed activity limitations using SPRS after anodal stimulation. Group five consists of one study [51] that assessed participation restrictions using WHO-QOL-BREF following cathodal stimulation.

The means ± SDs of the spasticity data were extracted for the analysis. When the data was not clear, the corresponding authors were contacted for clarification. We excluded studies [55-57] by authors that failed to reply to the emails sent to them. In one of the included studies,[41] the result was reported using Median (IQR). We calculated the mean using the following equation by Hozo et al. (2005) [58]: Mean = $\frac{a+2m+b}{4}$, where a = the smallest value (minimum); b = the largest value (maximum); n = the sample size; m = Median. According to the Cochrane guidelines, the standard deviation was calculated by taking a quarter (1/4) of the difference between the maximum and

minimum values of IQR [47]. Three studies presented results in terms of the standard error of the mean (SEM). Each was converted into standard deviation using the following equation: SD = SEM * ($\sqrt{n}$) [59].

Our meta-analysis included both within and between-subjects designed studies. Cross-over clinical trials are within-subject studies otherwise called repeated measure designs because all the participants were subjected to both experimental and control conditions, usually in random or counterbalanced orders to minimise carryover [48]. In such studies, there is a high correlation between the repeated measures due to the test-retest application of outcome measures [60]. As such, there is the possibility of overestimating effect size if the normal method of calculating effect size is used [51]. Therefore, the SD of the control group was used in the computation of the effect size [48].

Analysis

The result of the meta-analysis for each group was graphically presented using a forest plot containing each study's weighted effect size, 95% CI, and an overall pooled effect size depicted as a big diamond all in one concise table. From this plot, we can observe the distribution of effect sizes and determine crudely if there is variation between the studies. Review Manager Software (RevMan; version 20.2) was used to pool effect sizes for analysis. I^2-statistic was calculated to determine the proportion of heterogeneity among the studies and to guide the choice of statistical model for the analysis in accordance with Cochrane guidelines. Studies were considered to be homogenous when the ρ-value was greater than 0.05 and the heterogeneity index (I^2) is ≤ 50% and the fixed-effect model was used for the meta-analysis. Studies with

heterogeneity index (I^2) > 50 % and a p-value of less than 0.05 were considered to be heterogeneous and a random-effects model was used for analysis.

Certainty assessment

Grading quality of evidence and strength of recommendation (GRADE) criteria were employed to assess the certainty (confidence) in the body of evidence for each meta-analyzed outcome [61]. The quality of evidence was determined by considering four elements in each group: study quality, consistency, precision, and directness. The quality of the evidence was rated as either high-quality, moderate-quality, low-quality or very low quality (Appendix 1).

RESULTS

Study selection

A total of 890 records were obtained from the search in the databases; MEDLINE (56), Embase (398), Scopus (287), CINAHL (9), Cochrane CENTRAL (44) and Web of Science (96). In addition, a search in the trial registries and reference lists of the included articles yielded five and two records respectively. Endnote and Covidence software were used to remove 388 duplicates from the records. After screening the remaining 509 titles and abstracts, 453 were excluded based on the eligibility criteria. Cohen's Kappa revealed nonsignificant inter-rater agreement ($\kappa = 0.48$, $P > 0.05$). As pre-specified, differences were resolved through consensus. The full texts of the remaining 56 records were reviewed and 45 records were excluded for not fulfilling the eligibility criteria. One study [30], however, appeared to have fulfilled the criteria but was excluded because the subjects in the experimental group received tsDCS paired with peripheral nerve stimulation which compounded the result. Cohen's Kappa revealed significant inter-rater

agreement ($\kappa = 0.83$, $P < 0.05$) at this stage. A total of 11 eligible studies [33, 35, 49-57] were included in the review. Two studies [55, 56] that assessed spasticity and activity limitations using MAS and GMFM-88 reported incomplete data. Another study [57] reported a raw score of spasticity using MAS without assigning a score for the low muscle tone category. The corresponding authors of those three studies [55-57] were contacted for unpublished data or clarification but did not reply to the emails and subsequent reminders. Consequently, those studies were excluded from the meta-analysis. However, eight studies [33, 35, 49-54] provided sufficient data to be included in the meta-analysis (Figure 1).

Methodological Quality Assessment

The methodological quality assessment was conducted using the PEDro scale (Table 1). Overall, five studies were found to be of high quality (score of ≥ 6/10). The remaining six studies have a low quality (score of < 6/10). Specifically, most of the studies reported samples being randomized, but only 18% of the studies stated the method of concealed allocation to groups. Patients were not blinded to the treatment they received in 55% of the studies. As expected, no studies blinded those that administered the intervention to the patients' groups. Outcome assessors were also not blinded to the group of patients in 45% of the studies. Lastly, intention-to-treat analysis was performed in only 27% of the studies.

Study characteristics

The total study sample comprised 177 patients with various UMN disorders; 106 men and 71 women, and 41 participants where gender was not specified. The age of the patients ranged from 6 – 65 years. The majority of the patients (50.8%) had spinal cord injury, while the remaining had

cerebral palsy (30.5%), multiple sclerosis (19.8%), stroke (16.9%), and hereditary spastic paraplegia (6.2%) (Table 2).

Effects of stimulation

The cathode was used as an active electrode in 9 studies, while the anode was active in the other two studies. In the studies that sought to induce effects in the lower limb [33, 35, 49, 50, 52-54, 56, 57], the active electrode was placed at the lower thoracic (T10-T12) or upper lumber interspinous spaces (L1-2). For the purpose of effects on upper extremities, the active electrode was placed at the cervical spine (C5-C6) in three studies [35, 51, 55]. Among the studies that applied cathodal stimulation, seven studies assessed spasticity using MAS with three of them; Inanici et al. (2021) [51], Freyvert et al. (2018) [56], and Shapkova et al. (2020) [57], reported significant improvement in the score of the outcome measure in patients with SCI. The other four studies by Savenkova et al. (2019) [35], Picelli et al. (2015) [49], Solopova et al. (2017) [50], and Ikoeva et al. (2016) [56] reported no change in the outcome in SCI, CP, and stroke patients respectively. In the other two studies by Estes et al. (2017) [52] and Estes et al. (2021) [53], spasticity was assessed using the first swing excursion of the pendulum test in patients with SCI following cathodal stimulation and reported significant and nonsignificant improvement respectively.

Only two studies administered anodal stimulation and monitored spasticity using MAS. Ardolino et al. (2021) [33] reported Significant improvement, while Berra et al. (2019) [54] reported no change in patients with multiple sclerosis. Two studies assessed the excitability of α-motor neurons using Hoffmann's reflex (H-reflex) and reported varying findings. Ardolino et al. (2021)

[33] did not find a significant difference between sham and experimental conditions based on H-reflex amplitude and H-max/M-max ratio in their study on patients with hereditary spastic paraplegias. However, Shakpova et al. (2020) [57] reported an increase in excitation following stimulation in patients with SCI.

Concerning the activity limitations, Ardolino et al. (2018) [33] reported no improvement in SPRS scores with anodal stimulation. Conversely, Solopova et al. (2017) [50] and Ikoeva et al. (2016) [56] reported significant improvements in GMFM-88 scores following a combination of locomotive training and cathodal stimulation in cerebral palsy patients. Similar findings have been reported by Inanici et al. (2021) [51] in patients with SCI based on improvements in SCIM III scores following cathodal stimulation. Furthermore, this is the only study in this review that assessed participation restriction. They reported improvements in psychological well-being and physical health domains of WHO-QOL-BREF.

Meta-analyses comparisons

The first meta-analysis included six studies [35, 49-53] of 110 patients to determine the effect of cathodal tsDCS as an adjunct intervention to exercise on spasticity as assessed with the MAS and WPT. The outcome indicated no significant difference between the experimental and the control groups (pooled SMD = -0.67, 95% CI = -1.50 to 0.15, P = 0.11). There was also significant heterogeneity among the studies (I^2 = 75%) and a sensitivity analysis was conducted to find the source of the heterogeneity. The sensitivity analyses by removing Picelli et al. [49] and Savenkova et al. [35] supported the meta-analysis finding of no significant difference (pooled SMD = -0.03, 95% CI = -0.49 to 0.42, P = 0.89) with no observed heterogeneity (I^2 = 0%) (Figure 2).

Although the above result indicated that cathodal tsDCS does not have a statistically significant effect on spasticity and the 95% CI crosses the line of no effect, the outcome may not be without any clinical relevance. Firstly, SMD is reported in the units of the standard deviation of the Mean Difference (MD) rather than that of any of the measurement scales used in the studies; thus allowing direct interpretation. Generally, an SMD of zero (0) indicates that the intervention may not have had any effect. SMD above zero (+ve) indicates that the intervention increased the outcome, while that below zero (-ve) means the intervention reduced the outcome. Since the desired impact of the cathodal tsDCS was the reduction of spasticity, then an SMD of -0.67 indicated that the stimulation was moderately to largely effective in reducing the spasticity in the experimental group compared to the control by more than half of the Mean Difference (MD). This was more apparent when the SMD was converted to the units of the most predominant spasticity measure, MAS, by multiplying it with the pooled standard deviation of spasticity baseline scores in one of the studies as recommended by Cochrane [47]. We used an SD of 0.24 reported in a study by Picelli et al. (2015) [49] because it gives a higher positive outcome compared to other studies. We obtained an MD of -0.16 indicating that the MAS spasticity score in the intervention group was on average 0.16 lower than that in the control group. Considering the 95% CI = -1.50 to 0.15, it appears that the intervention will have some true clinical in the wider world population of people with spasticity. The lower arm of the 95% CI shows that the true effect might be double that moderate effect (150% SD or 1.5*0.24 = 0.36), though the upper arm indicates that it might have a weak or no effect or even a mildly harmful effect of increasing the spasticity (15% SD or 0.15*0.24 = 0.036).

The second meta-analysis comprised two studies, [33, 54] with 55 patients, investigating the effect of anodal tsDCS on spasticity as measured by the MAS. The outcome indicated no significant difference between the experimental and control groups (pooled SMD = 0.11, 95% CI = -0.43 to 0.64, p = 0.69), with no observed heterogeneity (I^2 = 0%) (Table 3). A positive SMD (0.11) indicates that the anodal tsDCS mildly increased spasticity in the intervention group by a value of 0.13 on MAS when we considered the SD of 1.2 in the study by Berra et al. (2019) [54]. In the world population, however, the 95% CI shows that the intervention may have worthwhile effects in either direction (-0.43 = moderate favourable effect, through to 0.69 = moderate unfavourable effect). Therefore, the true clinical impact is uncertain as it might be helpful, be harmful, or have negligible effect.

The third analysis involves two studies [50, 51] with 40 patients to assess the effect of cathodal tsDCS on activity limitations in patients with spasticity impairment. The outcome indicated no significant difference between the experimental and control groups (pooled SMD = -0.42, 95% CI = -1.04 to 0.21, p = 0.2), with no observed heterogeneity (I^2 = 0%) (Table 3). However, the negative SMD (-0.42) indicates that the cathodal tsDCS reduced the activity limitation in the intervention group by a value of 21.55 on GMFM-88 scale when we considered the SD of 51.3 in the study by Solopova et al. (2017) [50]. Based on the 95% CI, the decrease could be as much as 53.35 in the world population, but the limitation could also be marginally increased by 10.77. Thus, cathodal tsDCS may have some clinical impact on disability due to a reduction in spasticity, but with a slight risk of increase.

Single study comparisons

A single study comparison was conducted for studies that provided sufficient data. The outcome indicated no significant difference between the experimental and control groups for activity limitation in 22 patients following anodal stimulation (MD = -1.00, 95% CI = -11.32 to 9.32, p = 0.85) [33], and participation restriction in 12 patients following cathodal stimulation (MD = -8.10, 95% CI = -18.02 to 1.82, p = 0.11) (Table 3). The 95% CI indicated an inconclusive effect of the intervention on the outcomes. Cathodal stimulation might improve participation restriction in patients with SCI as measured using WHO-QOL-BREF or not be beneficial at all. Anodal stimulation might increase activity limitation or improve it in patients with Spastic Paraplegia as assessed using SPSS.

Certainty of evidence

We assessed the quality of evidence for each meta-analysis using the grading quality of evidence and strength of recommendations (GRADE). After discussion, we agreed that there was low-quality evidence for the relative effects of cathodal spinal cord stimulation compared to sham stimulation on spasticity, activity limitations and participation restrictions. However, the overall effects did not favor any intervention. For anodal spinal cord stimulation compared to sham stimulation, we agreed that there was moderate-quality evidence for the nonsignificant effects on spasticity and activity limitations (Table 3).

DISCUSSION

The present study systematically searched for and reviewed the effect of non-invasive direct current spinal stimulation on spasticity in various upper motor neuron conditions. Overall, there is respective low-quality and moderate-quality evidence that neither cathodal tsDCS (c-tsDCS) nor anodal tsDCS (a-tsDCS) was effective in the improvement of spasticity. The nonsignificant effects of tsDCS on spasticity in our review contradict the findings of a previous systematic review that included 13 studies to analyze the feasibility and efficacy of tsDCS on motor function in individuals with spinal cord injury [62]. The differences in the findings could be attributed to the fact that they included only three studies that examined the effects of the stimulation on spinal spasticity syndrome and the meta-analysis was not conducted due to the high degree of heterogeneity among the studies.

The results of our meta-analysis indicate that there is no enough evidence to support the effectiveness of tsDCS in reducing spasticity using any type of electrode. Nevertheless, the results of cathodal tsDCS applied by Picelli et al. (2015) [49], Savenkova et al. (2019) [35], Inanici et al. (2021) [51] and Estes et al. (2017) [52] showed high effect sizes favorable to tsDCS. Conversely, the studies by Ardolino et al. (2018) [33] and Berra et al. (2019) [54] that used anodal tsDCS showed inconclusive effect sizes. Thus, these outcomes have further supported the most prevailing theory that the modulatory effects of tsDCS on spinal segmental excitation are polarity dependent; [21] with cathodal and anodal tsDCS having different effects.

The effects of the c-tsDCS could be attributed to induced changes at both presynaptic and postsynaptic levels in the stretch reflex arc. At the presynaptic level, c-tsDCS reduces the

excitability of the Ia–αmotor neuron synapse by reducing the release of excitatory neurotransmitters [63]. The increase in excitation at these synapses has been implicated in the pathophysiology of spasticity [2]. Level of excitation at the synapse has been studied electrophysiologically using Hoffman's reflex (H-reflex), utilizing parameters such as H-reflex amplitude and homosynaptic depression (HD) [21, 22, 64-68]. In particular, HD, representing a reduced H-reflex amplitude within 8 – 12 seconds following activation of Ia–αmotor neuron, has been reported to decrease in spastic patients [63]. Thus, the ability of c-tsDCS to increase HD in normal individual supports its positive effects on spasticity [21]. On the other hand, a-tsDCS decreases HD in healthy individuals; which may explain its ineffectiveness in reducing spasticity. While c-tsDCS reduces the excitability of Ia–αmotor neuron synapse presynaptically, it increases the excitation of the motor neurons postsynaptically via direct inhibition of the spinal GABAergic system [69], and/or increases glutamate release at the spinal cord [70].

Apart from the effects of tsDCS on spasticity, we also analysed the subsequent changes in activity limitations and participation restrictions. We found low-certainty evidence that the stimulation did not improve the disability and handicap. However, only four studies assessed activity limitations and only those by Solopova et al. (2017) [50] and Inanici et al. (2021) [51] that used GMFM-88 and SCIM III following c-tsDCS provided enough data to be included in the analysis. Thus, future studies may change our confidence in the results since the analysed studies displayed high effect sizes in favour of stimulation. Only Inanici et al. (2021) [51] assessed participation restrictions after applying c-tsDCS. A single study comparison revealed nonsignificant improvement; even though the effect size favored the stimulation. These findings

indicate that reduction of spasticity alone without other factors such as pain, bladder dysfunction, fatigue and sleep problems may not improve disability and quality of life [13].

We used GRADE to assess the level of evidence supporting our findings [61]. There was low-quality and moderate-quality evidence for the lack of effects of cathodal and anodal tsDCS on spasticity respectively. Factors such as high heterogeneity among the studies, few studies with small sample sizes, and the use of subjective spasticity outcome measures might have reduced the quality of the evidence. We found substantial heterogeneity among the studies following the meta-analysis for the c-tsDCS group. As a result of the small number of studies, we did not calculate Q-statistic to determine whether the variation was due to sampling error alone or to some other yet unexplained factor. However, there is an indication that the different conditions of the patients in the studies might have caused the heterogeneity. This is because, among the six studies included in that group, four included spinal cord injured patients, [35, 51-53] while the remaining included those with stroke [49] and cerebral palsy [50]. After the analysis, we observed that the mean of one study [51] was an outlier because they summed up all the MAS scores of some selected muscles in the upper and lower limbs with a range from 0 to 40 points. In addition, the outcomes were measured using different scales. These variations, therefore, informed our choice for the standardized mean difference in the meta-analysis.

Generally, the decision to include any study that reported assessing spasticity in UMN conditions following tsDCS is a limitation in the review procedure since the level of severity of spasticity varies across the conditions. We did that in order to include many studies since the pathophysiological mechanisms of spasticity are similar in all conditions. Therefore, there is a

need for future reviews to be conducted for each condition. In the majority of the included studies, spasticity was assessed using the MAS. This tool is widely used to measure spasticity in the clinic due to ease of application and has been reported to be reliable [71]. However, it is not considered suitable to be used in mechanistic research due to its inability to differentiate the components of muscle tone (viscoelastic versus reflex activation of the contractile elements) [72]. In addition, the assignment of a score using this tool is subject to bias as it can be performed at different velocities and by different investigators. Nevertheless, few studies assessed spasticity using the preferred WPT which can objectively measure both the electrophysiological and biomechanical factors of spasticity. In addition, H-reflex was used to assess spasticity in two studies [33, 57], but these did not provide enough data to be included in the meta-analysis. Our review was further limited by the study design of the trials that were included. Some of the studies were cross-over designed trials with a small number of participants. Even the RCTs were not statistically powered to enable the generalization of their findings. Furthermore, we did not consider the variation in the stimulation protocol in the data synthesis due to the small number of eligible studies. A future review should cover that, as well as the possible persistence of the effects on follow-up since tsDCS can induce neuroplastic changes.

CONCLUSION

Overall, the meta-analysis of the available evidence provides an uncertain estimate of the effect of cathodal tsDCS on spasticity, activity limitation and participation restriction. It might be very helpful or it may make no difference at all. Therefore, the present evidence does not support the use of tsDCS in isolation or as adjuvant therapy in the management of spasticity. However,

considering the level of the evidence and the limitation in the quality of the majority of the included studies, further research may likely change the estimate of effect. Hence, there is a need for well-designed and statistically powered RCTs to assess the effect of this intervention in different UMN conditions using objective outcome measures.

DATA AVAILABILITY

The datasets analysed during this review are openly available within the article and its supplementary files.

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Author Contribution Statement: ABH conceived and designed the study with inputs from MSD, ATS and AA. ATS searched the literature and uploaded the records to Covidence. ABH and MAM screened the studies against the eligibility criteria, extracted the data and assessed the methodological quality of the included studies, while MSD settled the disagreements. ABH did the qualitative synthesis, and MSD and ATS did the meta-analysis. ABH wrote up the Manuscript which was critically reviewed by AA and MSD. The project was supervised by JM, HG and RYA. All authors contributed to the article and approved the submitted version.

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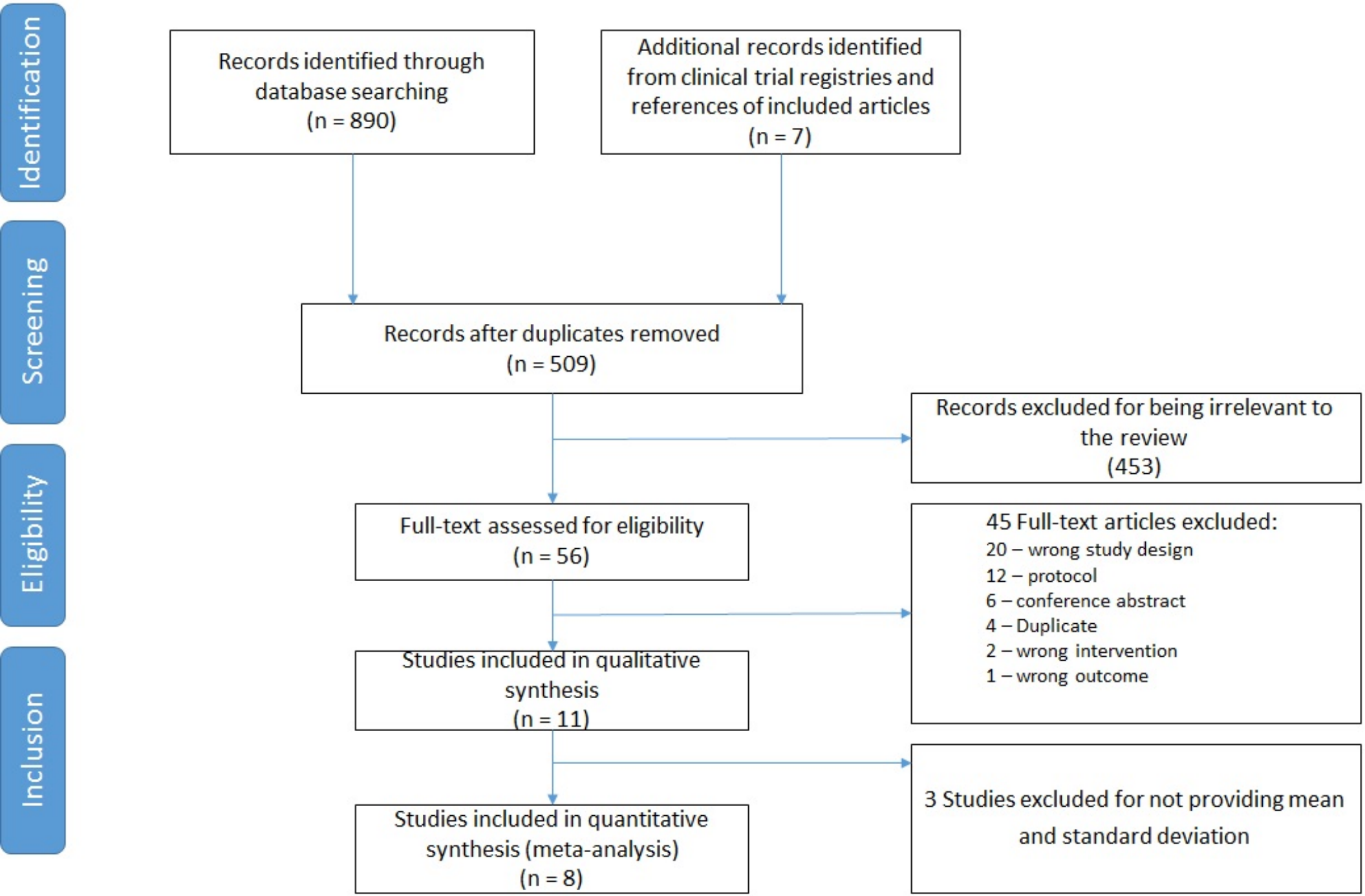
Figure 1: PRISMA Flow Chart

Figure 2: Sensitivity analysis

Table 1. Rating of trials on the PEDro methodological quality scale

Table 2: Characteristics of the included studies

Table 3: Assessment of quality of evidence using Grading Quality of Evidence and Strength of Recommendation (GRADE) criteria


Identification
Screening
Eligibility
Inclusion
Records identified through database searching (n = 890)
Additional records identified from clinical trial registries and references of included articles (n = 7)
Records after duplicates removed (n = 509)
Records excluded for being irrelevant to the review (453)
Full-text assessed for eligibility (n = 56)
45 Full-text articles excluded:
20 – wrong study design
12 – protocol
6 – conference abstract
4 – Duplicate
2 – wrong intervention
1 – wrong outcome
Studies included in qualitative synthesis (n = 11)
3 Studies excluded for not providing mean and standard deviation
Studies included in quantitative synthesis (meta-analysis) (n = 8)

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Estes 2017	-53.67	20.71	9	-47.7	20.71	10	25.2%	-0.28 [-1.18, 0.63]
Estes 2021	-54.9	56.68	8	-63.98	56.68	8	21.5%	0.15 [-0.83, 1.13]
Inanici 2021	6.3	9.2	6	9.3	9.2	6	15.9%	-0.30 [-1.44, 0.84]
Solopova 2017	1.7	0.7	13	1.6	0.7	15	37.4%	0.14 [-0.61, 0.88]
Total (95% CI)			**36**			**39**	**100.0%**	**-0.03 [-0.49, 0.42]**

Heterogeneity: Tau² = 0.00; Chi² = 0.83, df = 3 (P = 0.84); I² = 0%

Test for overall effect: Z = 0.14 (P = 0.89)

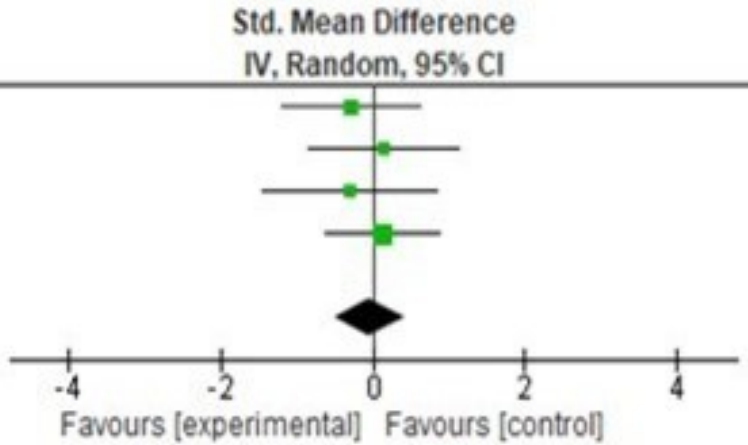


Table 1. Rating of trials on the PEDro methodological quality scale

Studies	1	2	3	4	5	6	7	8	9	10	11	Total
Ardolino et al. (2018)[33]	Y	Y	N	N	Y	N	Y	Y	Y	N	Y	6
Berra et al. (2019)[46]	Y	Y	N	Y	Y	N	Y	Y	N	Y	Y	7
Estes et al. (2017)[44]	Y	Y	N	Y	N	N	N	N	N	N	Y	3
Estes et al. (2021)[45]	Y	Y	N	Y	N	N	N	Y	N	Y	N	4
Freyvert et al. (2018)[47]	Y	N	N	Y	Y	N	Y	Y	N	N	N	4
Ikoeva et al. (2016)[48]	Y	N	N	Y	N	N	N	N	N	Y	Y	3
Inanici et al. (2021)[43]	Y	N	N	Y	N	N	N	Y	N	N	Y	3
Picelli et al. (2015)[41]	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9
Savenkova et al. (2019)[34]	Y	Y	N	Y	Y	N	Y	Y	N	Y	N	6
Shapkova et al. (2020)[49]	Y	N	N	N	N	N	N	Y	N	Y	Y	3
Solopova et al. (2017)[42]	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	7
Total	11	7	2	9	5	0	6	9	3	7	8	

Key: Y=Yes, N=No. PEDro = Physiotherapy evidence database. 1 = External validity; 2 = Random allocation to groups; 3 = Concealed allocation to groups; 4 = Baseline similarity; 5 = Blinding of subjects; 6 = Blinding of therapists; 7 = Blinding of assessors; 8 = Measures of at least one key outcome from > 85% of the subjects; 9 = Intention to treat analysis; 10 = Between group comparison; 11 = Point measures and measures of variability from at least one key outcome

Table 2: Characteristics of the included studies

Study	Design	Number of participants	Condition of the patients	Variables	Comparison	Intervention	Number of sessions	Follow-up	Results
Ardolino et al. (2021)[33]	CCT	11 (7 Female)	HSP	Spasticity: MAS and H-reflex Disability: SPRS	Sham tsDCS	Anodal tsDCS	2.0 mA, 20 min twice a day stimulation for five days	1 week, 1 month and 2 months	Anodal tsDCS group showed a significant improvement in MAS score while that of SPRS did not change
Berra et al. (2019)[46]	RCT	33 (25 Female)	MS	Spasticity: MAS	Sham tsDCS	Anodal tsDCS	20-mins of 2 mA stimulation , every working day for 2-weeks	4 weeks	There was no significant change in MAS
Estes et al. (2017)[44]	CCT	10 (2 Female)	SCI	Spasticity: FSE in a Pendulum Test	Sham tsDCS	Cathodal tsDCS	Single session of 30 minutes 50 Hz stimulation	45 minutes after intervention	tsDCS was associated with a significant mean change in FSE compared to sham-control
Estes et al. (2021)[45]	RCT	18 (4 Female)	SCI	Spasticity: FSE in Pendulum Test	Sham tsDCS + Locomotor training	Cathodal tsDCS + Locomotor training	2 weeks wash in locomotor training followed by addition of 30 minutes 50 Hz stimulation	_____	Neither group had significant changes in spasticity

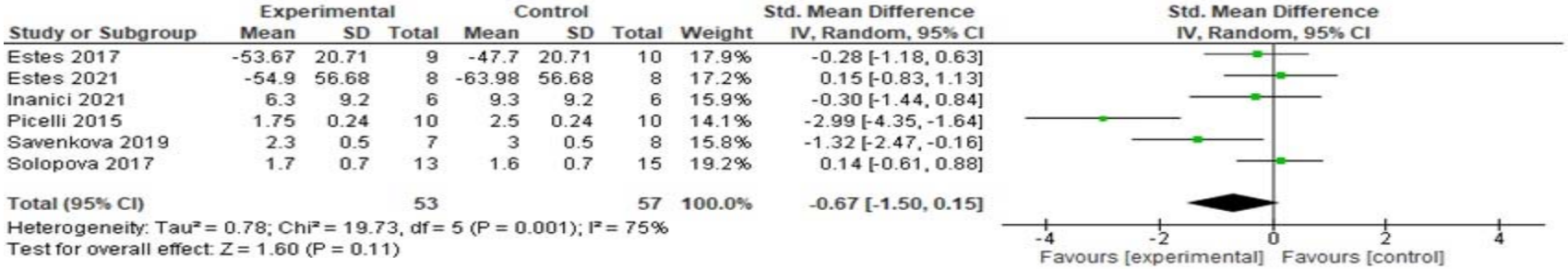
							, every day for 2 weeks		
Freyvert et al. (2018)[47]	CCT	6 (2 Female)	SCI	Spasticity: MAS	Sham tsDCS	Cathodal tSCS + Drug (buspirone) + Grip strength exercises	5–30Hz and 20–100mA stimulation NS/6 weeks	3-6 months	The aggregate MAS reduced with each study phase throughout the course of the study
Ikoeva et al. (2016)[48]	RCT	26	CP	Disability: GMFM-88 Spasticity: MAS	Sham tsDCS	Cathodal tsDCS Participants in both groups received robotic mechanotherapy	15 stimulations lasting 45 minutes each	_____	The gross motor functions and spasticity significantly improved in the experimental group compared to control
Inanici et al. (2021)[43]	CCT	6 (2 Female)	SCI	Spasticity: MAS Disablity: SCIM III Handicap: WHO-QOL-BREF	Functional task training	Functional task training and Cathodal tsDCS	30 Hz of stimulation for 120 minutes for 1 month.	3 months	tsDCS group showed significant improvement in MAS, SCIM III and WHO-QOL-BREF scores compared to control group
Picelli et al. (2015)[41]	RCT	30 (8 Female)	STR	Spasticity: MAS	Anodal tDCS + sham tsDCS	Anodal tDCS + cathodal tsDCS Participants in both groups received robot-assisted gait training	2.5mA for 20 min, five days a week, for 2 consecutive weeks	2 weeks and 4 weeks post-treatment	The MAS did not change significantly, but there was improvement in walking functions

Savenkova et al. (2019)[34]	RCT	15	SCI	Spasticity: MAS	Sham tsDCS	Cathodal tsDCS Participants in both groups received standard rehabilitation	Stimulation was given every working day for 2 weeks	_____	There was no significant improvement in MAS score.
Shapkova et al. (2020)[49]	RCT	35 (10 Female)	SCI	Spasticity: MAS, H-reflex	EWT	EWT + Cathodal tsDCS	3mA stimulation and EWT for 2 weeks	_____	There was significant improvement in spasticity in tsDCS group
Solopova et al. (2017)[42]	RCT	28 (13 Female)	CP	Spasticity: MAS Disability: GMFM-88	Sham tsDCS + Locomotor training	Cathodal tsDCS + Locomotor training	40 min 20-150 mA stimulation for 15 sessions	_____	No change in MAS in either group. The GMFM-88 score increased significantly in tsDCS group compared to control

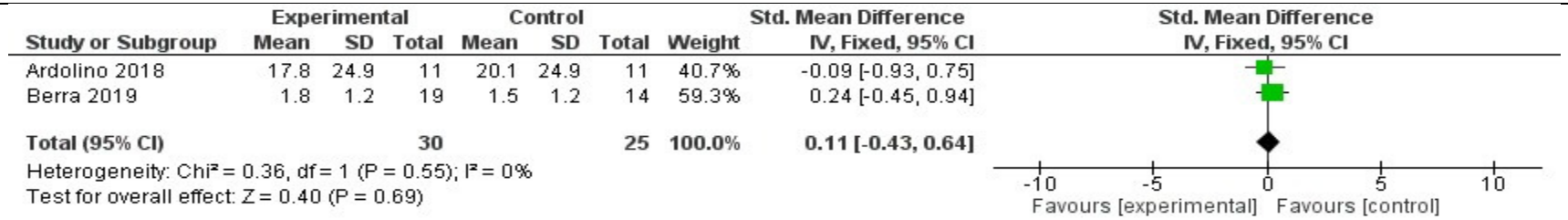
RCT = randomized controlled clinical trial, CCT = cross-over clinical trial, SCI = spinal cord injury, CP = cerebral palsy, tsDCS = transcutaneous spinal direct current stimulation, EWT = exoskeleton walk training, MAS = modified ashworth scale, GMFM-88 = gross Motor Function Measure scale, STR = stroke, FSE = first swing excursion, MS = multiple sclerosis, HSP = hereditary spastic paraplegia, SPRS = Spastic Paraplegia Rating Scale, SCIM III (Spinal Cord Independence Measure III); WHO-QOL-BREF (WHO Quality of Life – BREF)

Table 3: Assessment of quality of evidence using Grading Quality of Evidence and Strength of Recommendation (GRADE) criteria

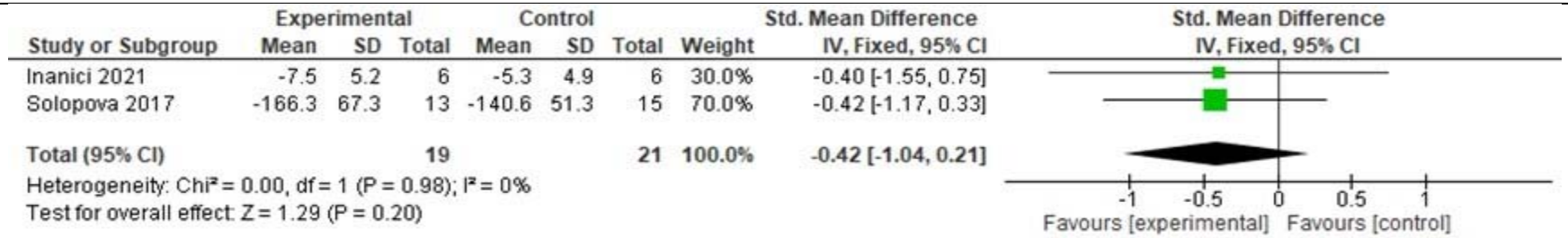
	Quality assessment				Summary of findings					
					No of patients		Effects			
No of studies	Quality	Consistency	Precision	Directness	Study	Control	Relative (95% CI)	Absolute	Quality	Comments
Cathodal spinal stimulation + exercise compared to sham stimulation for individuals with spasticity										
Estes et al. (2017)[44] Estes et al. (2021)[45] Inanici et al. (2021)[43] Picelli et al. (2015)[41] Savenkova et al. (2019)[34] Solopova et al. (2017)[42]	Serious limitations*	No important inconsistency	Imprecision of results†	None	53	57	SMD -0.67 (-1.50 to 0.15)	No difference	Low	Effect did not favour any intervention



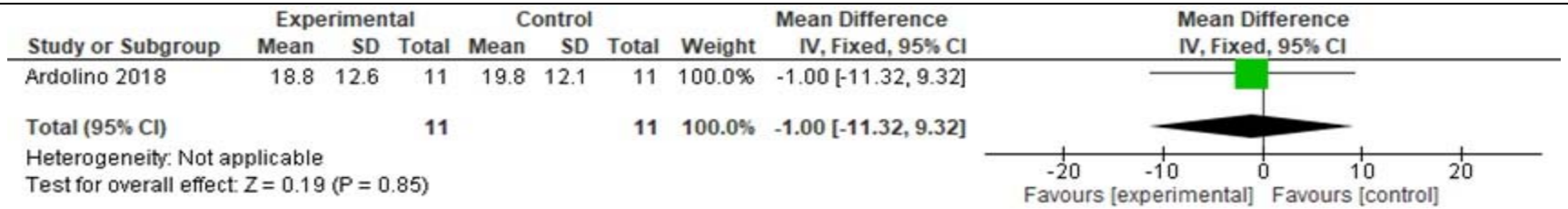
Anodal spinal cord stimulation compared to sham stimulation for individuals with spasticity										
Ardolino et al. (2018)[33] Berra et al. (2019)[46]	No serious limitation	No important inconsistency	Imprecision of results†	None	30	25	SMD 0.11 (-0.43 to 0.94)	No difference	Moderate	Effect did not favour any intervention



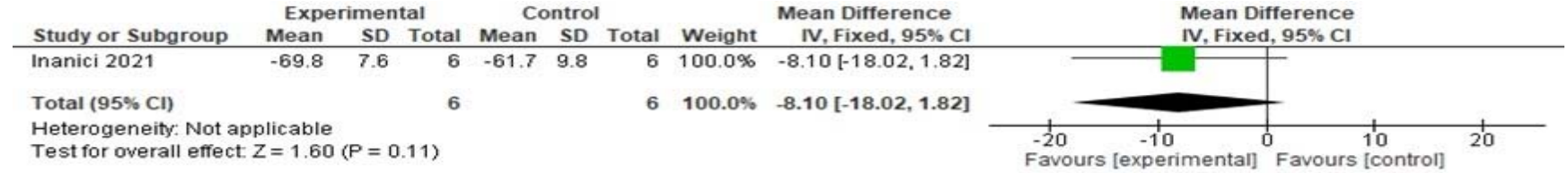
Cathodal spinal stimulation compared to exercise for activity limitations in individuals with spasticity										
Solopova et al. (2017)[42]	Serious limitations*	No important inconsistency	Imprecision of results†	None	19	21	SMD -0.42 (-1.04 to 0.21)	No difference	Low	Effect did not favour any intervention
Inanici et al. (2021)[43]										



Anodal spinal cord stimulation compared to sham stimulation for activity limitations in individuals with spasticity										
Ardolino et al. (2018)[33]	No serious limitation	No important inconsistency	Imprecision of results†	None	11	11	MD -1.00 (-11.23 to 9.32)	No difference	Moderate	Effect did not favour any intervention



Cathodal spinal stimulation compared to exercise for participation restrictions in individuals with spasticity										
Inanici et al. (2021)[43]	Serious limitations*	No important inconsistency	Imprecision of results†	None	6	6	MD -8.10 (-18.02 to 1.82)	No difference	Low	Effect did not favour any intervention



SMD = Standardized Mean Difference, MD = Mean Difference, *Less than 75% of trials scoring less than 6 on PEDro scale, †Sparse data of <400 participants per comparison.