THAMMASAT UNIVERSITY Mahidol University Chula Chulalongkorn University

PROCEEDINGS 2022

The International Physical Therapy Research Symposium (IPTRS)

Rehabilitation in new normal era

9 June 2022

Department of Physical Therapy,
Faculty of Allied Health Sciences
Thammasat University, Thailand

OP-5

CAN TRANSCRANIAL DIRECT CURRENT STIMULATION COMBINED WITH OVERGROUND GAIT TRAINING IMPROVE LOWER LIMB PERFORMANCE IN INDIVIDUALS WITH INCOMPLETE SPINAL CORD INJURY? : A PILOT STUDY

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Abstract

Introduction: Regaining lower limb performance, such as walking, is the primary goal of functional independence for individuals with incomplete spinal cord injury (iSCI). However, only rehabilitation may not promote full recovery. Transcranial direct current stimulation (tDCS) is a neuromodulation technology used in neurorehabilitation as a combination treatment. Previous meta-analysis found a trending of positive results of anodal tDCS in iSCI but still limited evidence of tDCS effect on lower limb function.

Objective: This study aimed to determine effects of 5 consecutive sessions of anodal tDCS combined with overground gait training on lower limb performance in iSCI.

Methods: Eighteen participants were allocated into the anodal group or sham group. They received 5 consecutive sessions of 2mA anodal tDCS or sham tDCS over leg motor area for 20 minutes followed by 40-minute of overground gait training. Lower limb performance was evaluated using 10-Meter Walking Test (10MWT), Timed Up and Go Test (TUG), and 5-times sit-to-stand test (5TSST) at pre-intervention, post-intervention, and 1-month follow-up.

Results: All outcomes of lower limb performance were improved in both groups ($p<0.05$). There was no significant difference between the groups.

Conclusion: Our pilot study found that 5 consecutive sessions of anodal tDCS combined with overground gait training induced non-superior improvement over gait training alone. Further study with a large sample is recommended to clearly investigate the effects.

Keywords: spinal cord injury; transcranial direct current stimulation; lower limb

Introduction

Spinal cord injury (SCI) greatly affects functional activity particularly lower limb function including, walking which was a primary goal of functional independence (Anderson, 2004). Previous study reported that people with incomplete spinal cord injury (iSCI) had a chance to regain their walking (Waters et al., 1994). Recent guideline has recommended overground gait training over other training for improving walking in iSCI, especially in chronic-onset (Hornby et al., 2020). However, only training might not promote full recovery (Hutson & Di Giovanni, 2019). To effectively promote recovery, the rehabilitation should be brief and efficient to minimize hospitalization that affects finances and causes infection. Recent study reported that combined training with neuromodulation techniques may be an option for enhancing recovery after SCI (Hofer & Schwab, 2019).

Transcranial direct current stimulation (tDCS) is a neuromodulation technique that currently used as an adjunctive treatment in neurorehabilitation. The tDCS applied over the primary motor cortex (M1) has been shown to modulate neural activity of both cortical and spinal levels (Nitsche & Paulus, 2000; Roche et al., 2009, 2011). It induced an after-effect excitability by modulating synaptic plasticity (Stagg et al., 2018). A recent review reported that the increasing stimulation intensity or duration within certain limits could enhance tDCS efficacy; anodal stimulation increased cortical excitability, while cathodal stimulation decreased cortical excitability (Stagg et al., 2018). Anodal tDCS has been shown to increase an expression of brain-derived neurotrophic factor (BDNF), which is essential for the recovery of damaged neuron (Podda et al., 2016). A study in rat with SCI found a growth of corticospinal axon termination in the spinal cord and increase of motor performance following 10 days of direct current stimulation over the motor cortex (Carmel et al., 2010). A previous study in people with SCI study found that 5 consecutive sessions of anodal tDCS could controlled central pain, and improve motor performance (Fregni et al., 2006). Previous meta-analysis reported a trend toward positive effect of anodal tDCS in iSCI (de Araújo et al., 2020), but there were limited evidences of tDCS with gait training in iSCI. Currently, there were only two studies that conducted in iSCI with severe motor deficits (i.e. non-ambulatory iSCI), in which patients received tDCS with robotic gait training (Kumru et al., 2016; Raithatha et al., 2016). The results of both studies showed non-superior improvement of lower limb performance over robotic gait training alone. Since corticospinal excitability may persist for 60 minutes after anodal stimulation (Jeffery et al., 2007), the time between tDCS and training is needed to be short for initiation of gait training rapidly (Raithatha et al., 2016). However, robotic device setting up is required time, therefore the overground gait training may probably more conveniently concerning this point.

This pilot study aimed to determine whether 5 consecutive sessions of applying anodal tDCS before immediately providing overground gait training can greatly improve lower limb performance in ambulatory iSCI compared to gait training alone or not.

Materials and methods

Participant

This study was a pilot double-blind randomized sham-controlled study. Eighteen participants were recruited following the inclusion criteria: 1) traumatic or non-traumatic motor iSCI (American Spinal Cord Injury Association Impairment Scale [AIS] C-D) (Kirshblum et al., 2020); 2) age between 18–70 years old; 3) onset post SCI during 1–30 months; and 4) able to walk at least 15 meters independently (with or without a walking device). They were excluded if they: 1) used a Knee-Ankle-Foot-Orthosis; 2) presented with a severe spasticity (Modified Ashworth Scale >2) 3) had moderate to high musculoskeletal pain (numeric pain score > 4/10) that affect walking; 4) had unstable clinical sign i.e., chest pain, resting heart rate > 100 bpm, systolic blood pressure ≥ 180 and/or diastolic ≥ 100 mmHg; and 5) had a contraindication to use tDCS, such as intracranial metal implant or cardiac pacemaker, scalp open wound, and history of epilepsy. Eligible participants were interviewed about demographic data and were assessed the severity of injury. They were stratified in pairs based on 2 confounders (Scivoletto et al., 2014); 1) level of injury (tetraplegia or paraplegia) and 2) chronicity (subacute < 12 months or chronic ≥ 12 months) (Fawcett et al.,2007; Wirth et al., 2008) before randomly allocated into 2 groups (anodal or sham group) by researcher 1. Participants provided written inform consent before participation. This study was approved by the Mahidol University Central Institutional Review Board (MU-CIRB 2021/407.1409) and the Sirindhorn National Medical Rehabilitation Institute Ethic Committee (No.64005).

Outcome measure

Researcher 2 who was blinded for the group allocation, performed outcome measurements for 3 times: pre-intervention (PRE), post-intervention (POST), and 1-month follow-up (F/U). The sequence of each testing was arranged by randomly selecting 4 separate opaque envelops. Each test was measured twice and the average was calculated. Between tests, there was a 2-minute rest time, or several minutes if needed to avoid exhaustion. The outcome measures were as follows.

10-meters walk test (10MWT)

The 10MWT was used for assessing walking speed. The participants instructed to walk with 1) their self-selected speed and 2) fast safe speed along 14-meters walkway. To reduce influence of acceleration and deceleration, the time was recorded only at the middle 10 meters (van Hedel et al., 2007). The time was converted to walking speed (m/s).

Time up and go test (TUG)

The TUG was used for measuring dynamic balance. The participants started from sitting on a chair with back against back rest. When researcher gave command “start”, they had to stand up and walk forward with fast safe speed to the 3-meter mark, then return to sit on the chair (Podsiadlo & Richardson, 1991). The entire duration was recorded in seconds (s).

5 times sit-to-stand test (5TSST)

The 5TSST was used for measuring lower limb strength and dynamic balance during changing position. The participants sat on a chair, with both hands by their sides or holding walking device if needed. After researcher gave command “start”, they had to fully stand up and sit for 5 times as quick as possible (Khuna et al., 2020). The total time was recorded in seconds (s).

Intervention

The tDCS was programmed by researcher 3 who was not involved in outcome measuring and intervention. Researcher 4 who was blinded from group allocation, performed tDCS administration. The stimulator (Ybrain, MINDD STIM, Korea) was used for delivering current through rectangular saline-soaked sponge-pad electrode size 35 cm^2 (5x7 cm). The international 10-20 EEG system was used to guide the electrode placement. The anodal electrode was placed at the vertex to stimulate the leg motor area of both cortices (Ghosh et al., 2019) and the cathodal electrode was placed over the right supraorbital region with a cap (Figure 1A). Participants in the anodal group received tDCS at 2.0 mA for 20 minutes with ramped up-down for 30 seconds as this intensity could stimulate the lower limb motor area (Ghosh et al., 2019). For the sham group, participants received delivered current only first 30 seconds before being automatically terminated, and the electrodes remained at the participants' head until 20 minutes. Participants were comfortably seated on chair during the stimulation. Adverse effects were recorded during and after stimulation.

After finish stimulation, all participants were given the overground gait training provided by researcher 4. The training protocol was adapted from the previous study (Pramodhyakul et al., 2016). Participants practiced walking along 10-meter walkway. Each round, they observed the target time countdown on the 22-inch display linked to the timer-program and placed at the end of walkway (Figure 1B). They attempted to complete their 10-meter walk within the target time, which were inferred from individual fast safe speed that was set at 25 % faster. The time given served as feedback and motivation for achieving the task which were elements of effective learning (Wulf & Lewthwaite, 2016). This adapted training protocol was previously shown to significantly improved walking speed, TUG, and 5TSST after post 5 day-intervention in iSCI (Pramodhyakul et al., 2016).

They were trained for 45 minutes including resting period. The intervention program was provided for 5 consecutive days. Participants were allowed to receive their regular rehabilitation programs or physical therapy (PT) during post-intervention to follow-up period. They received logbook and were asked to record their rehabilitation detail.

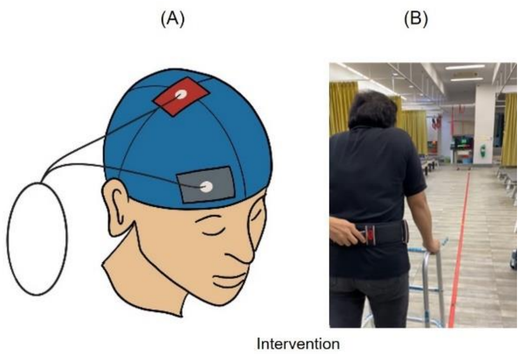

Figure1. Intervention (A) tDCS and (B) overground gait training

Statistical analyses

IBM SPSS software version 18.0 was used for statistical analyses. The independent t-test and Chi-square test were used to compare PRE data. The Shaprio-Wilk test was used to verify the normality. 10MWT and TUG was normally distributed while 5TSST was not. Two-way mixed analysis of variance

(ANOVA) with the Bonferroni correction was used for analyzing between-group or STIMULATION effect and within-group or TIME effect ([PRE], [POST], and [F/U]) of 10MWT and TUG. The Friedman test was used to analyze within-group comparisons and the Wilcoxon sign rank test was used for within-group pairwise comparisons, while the Mann Whitney U-test was used for between-group comparison of 5TSST. Statistical significance level was set at 0.05. The mean difference of outcome at POST was calculated as mean average of POST minus those of PRE, while the mean difference at F/U was calculated as mean average of F/U minus those of PRE. Continuous data were presented in mean ± standard deviation (SD). Categorical data were presented in number.

Results

There was no significant difference between-group of demographic and PRE data (Table 1).

Table 1 Demographics and PRE data

Variable	Anodal (n=9)	Sham (n=9)	p-value
Age (years)	41.89± 4.02	48.22 ± 4.28	0.297[a]
Onset of injury (months)	17.56 ± 3.563	14.89 ± 3.043	0.577[a]
Lower limb key muscle (motor scores)	39.67 ± 2.404	35.44 ± 3.078	0.296[a]
Gender (male/female)	7/2	6/3	0.599[b]
Etiology (traumatic/ non-traumatic)	7/2	4/5	0.147[b]
Severity of injury (AIS C/ D)	4/5	3/6	0.629[b]
Level of injury (tetraplegia/paraplegia)	5/4	4/5	0.637[b]
Chronicity (subacute/chronic)	4/5	4/5	1.000[b]
Using of walking device (non-use/use)	1/8	3/6	0.257[b]
10MWT (self-selected speed) (m/s)	0.42 ± 0.20	0.56 ± 0.35	0.312[a]
10 MWT (fast safe speed) (m/s)	0.59 ± 0.26	0.71 ± 0.42	0.459[a]
TUG (s)	28.36 ± 13.26	19.80 ± 8.67	0.125[a]
5TSST (s)	17.92 ± 0.45	19.97 ± 2.99	0.546[a]

[a] the independent t-test; [b] the Chi-square test

10MWT with self-selected speed

10MWT at PRE, POST, and F/U in the anodal group were 0.42 ± 0.20 m/s, 0.63 ± 0.31 m/s, and 0.65 ± 0.21 m/s respectively, meanwhile the values in the sham group were 0.56 ± 0.35 m/s, 0.66 ± 0.37 m/s, and 0.69 ± 0.40 m/s. Two-way mixed ANOVA showed a significant effect of TIME ($F_{2,32}$ = 18.163, p < 0.001); there was non-significant effects of STIMULATION and interaction effects ($F_{1,16}$ = 0.161, p = 0.698) and ($F_{2,32}$ = 2.672, p = 0.085), respectively.

10MWT with fast safe speed

10MWT at PRE, POST, and F/U in the anodal group were 0.59 ± 0.26 m/s, 0.83 ± 0.37m/s, and 0.85 ± 0.32m/s respectively, while the speed in the sham group were 0.71 ± 0.42 m/s, 0.84 ± 0.48m/s, and 0.84 ± 0.47m/s. Two-way mixed ANOVA showed a significant effect of TIME ($F_{2,32}$ = 27.308, p <

0.001); there was no significant effects of STIMULATION and interaction effects ($F_{1,16} = 0.052$, $p = 0.822$) and ($F_{2,32} = 2.956$, $p = 0.066$), respectively.

TUG

The TUG at PRE, POST, and F/U of the anodal group were 28.36 ± 13.26 s, 21.45 ± 9.09 s, and 19.33 ± 6.18 s respectively, while the values in the sham group were 19.80 ± 8.67 s, 15.00 ± 6.25 s, and 15.60 ± 6.18 s. Two-way mixed ANOVA showed a significant effect of TIME ($F_{2,32} = 11.571$, $p < 0.001$); there were neither non-significant effects of STIMULATION nor interaction effects (($F_{1,16} = 2.863$, $p = 0.11$) and ($F_{2,32} = 1.294$, $p = 0.288$), respectively.

5TSST

The 5TSST at PRE, POST, and F/U of the anodal group were 17.92 ± 1.45 s, 14.98 ± 0.82 s, and 14.65 ± 0.51 s respectively, while the values in the sham group were 19.97 ± 2.99 s, 16.80 ± 2.66 s, and 15.84± 1.98 s. The Friedman test showed within-group difference in both anodal group (p=0.009) and sham group (p=0.017) significantly. The Mann Whitney U-test showed non-significant difference of between group comparison at POST(p=1.00) and F/U (p=0.931).

The mean differences of outcomes are shown in Table 2.

Table 2 The mean difference of 10MWT (self-selected and fast safe speed), TUG and 5TSST

Variable	**Group**	**p-value (Within-group pairwise comparisons)**		**Mean difference**	
		PRE - POST	**PRE - F/U**	**At POST**	**At F/U**
10MWT (Self-selected speed)	Anodal	**0.009[a]**	**0.01[a]**	+0.21 ± 0.15	+0.23 ± 0.17
	Sham	0.105[a]	**0.037[a,]**	+0.10 ± 0.09	+0.13 ± 0.11
10 MWT (Fast safe speed)	Anodal	**0.001[a]**	**0.004[a]**	+0.24 ± 0.12	+0.26 ± 0.17
	Sham	**0.003[a]**	**0.025[a]**	+0.12 ± 0.07	+0.13 ± 0.11
TUG	Anodal	0.061[a]	0.053[a]	-6.91 ± 7.18	-9.03 ± 9.11
	Sham	0.069[a]	0.085[a]	-4.80 ± 5.13	-4.20 ± 4.72
5TSST	Anodal	**0.045[b]**	**0.003[b]**	-3.53 ± 8.87	-3.28 ± 3.70
	Sham	0.059[b]	**0.007[b]**	-3.17 ± 4.13	-4.13 ± 6.74

[a] the Bonferroni correction, [b] the Wilcoxon sign rank test, statistical significance differences were showed in bold style.

tDCS-related adverse effect

Participants in the anodal group reported itching sensations (33%), and tingling sensations (22%) only during stimulation period. Some participants in the sham group reported cutaneous sensations a moment after starting stimulation and it all disappeared after a few minutes (1-2 minutes) of stimulation.

Discussion

The purpose of this pilot study was to initially prove the effectiveness of combined anodal tDCS with overground gait training on lower limb performance compare with overground gait training alone. Our results demonstrated that participants in both groups increased their gait speed evaluated by 10MWT and reduced the duration to perform both TUG and 5TSST which revealed an improvement of lower limb performance, but no difference between the groups were found in all outcomes.

The result of 10MWT improvement in both groups were in agreement with the previous result that walking training with visuotemporal cue which is the same intervention in our present study significantly improved walking performances immediately after post 5 day-intervention in iSCI (Pramodhyakul et al., 2016). Previous tDCS studies in iSCI revealed that tDCS with gait training induced no superior results over training alone (Kumru et al., 2016; Raithatha et al., 2016). These are consistence with our current results. A recent systematic review of tDCS with gait training in neurological patients (including stroke, Parkinson's disease, and SCI) also reported inconclusive result to support that tDCS can promote gait performance (de Paz et al., 2019). Anodal tDCS over the leg motor area increased cortical excitability and also modulated the lumbar spinal network (Roche et al., 2011) that are involved in the central pattern generator (CPG) which was related to walking recovery after SCI (Guertin, 2013). However, tDCS after-effect was found in an only few spinal circuit following anodal stimulation (Roche et al., 2011). This might be a possible cause of non-significant improvement found here.

For TUG, our finding is compatible with Raithatha et al's study that anodal tDCS with gait training inducing no improvement of TUG over only gait training in iSCI (Raithatha et al., 2016). TUG is a clinical test of dynamic balance that consists of multiple subtasks, including sit-to-stand task, walking, and turning. A tDCS study in elderly people recommended placing an anodal electrode over the cerebellum to promote balance than the M1 area (Yosephi et al., 2018). The cerebellum helps to regulate anticipatory postural adjustment while changing positions, as in TUG (Marchese et al., 2020). There was an atrophy of cerebellar lobule after SCI that caused a decrease in cerebellar activity that might lead to balance impairment in iSCI (Lei & Perez, 2021). tDCS over the cerebellum could modulate cortico-cerebellar connectivity which is crucial for balance (Grimaldi et al., 2016). Our study selected the leg motor area aiming to improve motor performance, it may not fully give an advantage on balance effect. However, it should be noted that the decline of elderly cerebellar differ from iSCI. The tDCS responses can be also difference.

There was no SCI study about tDCS effect on sit-to-stand performance. 5TSST is clinical test that reflects leg strength especially knee strength which is the primary determinant of sit-to-stand ability. Our result resembled with Maeda et al.'s study that 7-sessions of anodal tDCS with exercise could not enhance knee strength in healthy people (Maeda et al., 2017). However, 5TSST was significantly improved after a single session of bilateral tDCS before physical therapy in individuals with subacute stroke (Klomjai et al., 2018). tDCS is used in neurorehabilitation as an additional treatment to maximize the results of the rehabilitation program (Klomjai et al., 2015). For greatly obtaining effect from tDCS, the main rehabilitation program should contain the factors that enhanced learning i.e. intensive repetition, task specificity (Schmidt et al., 2018). Our intervention was focusing on walking that may not directly promote 5TSST performance.

Regarding tDCS parameters, although 2mA anodal tDCS over the leg motor area has been shown to induce cortical and spinal excitability in healthy subjects (Ghosh et al., 2019; Roche et al., 2011), the responses in SCI people can be different. Previous studies have found that the severity of SCI can influence alterations in corticospinal excitability (Kumru et al., 2015). Murray et al.'s study concluded that to induce the altered corticospinal excitability in chronic iSCI with severe lesion, the magnitude of excitability changes depended on the amount of current intensity, up to 2 mA (Murray et al., 2015). In our anodal group, there were 44% of participants with severe lesion (AIS C). It is probable that our tDCS intensity might be insufficient for increasing corticospinal excitability. A few studies on the effect of intensity up to 4 mA were conducted but the results were inconclusion (Nitsche & Bikson, 2017). Since, individual factors is other factor that can alter intensity-induced excitability (Mosayebi-Samani et al., 2021), recommending of a fixed-dose intensity for iSCI is quite difficult.

Many mean differences (Table.2) achieved the smallest real difference (SRD) and the minimal clinically important difference (MCID) for people with SCI. The mean difference of 10MWT in both groups reached the SRD (SRD = 0.10 m/s) (Forrest et al., 2014) at POST and achieved the MCID (MCID = 0.13 m/s) (Lam et al., 2008) at F/U. Additionally, the mean differences of 10MWT in the anodal group obtained the MCID since POST, whereas the sham group can reach the MCID at F/U. The mean difference of 5TSST in both groups also attained the MCID (MCID=2.27 seconds) (Khuna et al., 2020). Nevertheless, only the mean difference of TUG in the anodal group achieved the SRD at F/U with change score of -9.03s or -31.84% (SRD%= 30) (Lam et al., 2008). Theses outcomes demonstrate that 5 days of overground gait training with cue not only showed common improvement, but provided a clinical difference for iSCI.

This study had limitations. First, the small sample was difficult to determine the tDCS effect clearly. Based on the mean difference in 10MWT with self-selected speed between the two groups of this study, a sample size of 20 participants in each group was suggested for further research. Second, participants still received their regular medication treatment. Two participants out of nine in the anodal group consumed 300mg of Gabapentin thrice a day for relief from neuropathic pain, which has been reported to reduced cortical excitability (Ziemann et al., 2015). Third, we did not sub-analyze data based on participants' chronicity. Their recovery rates would differ depending on chronicity. Fourth, this study was lacked of neurophysiological investigations. Lastly, we did not restrict the participants' rehabilitation until F/U that may affect the results. However, the logbooks showed no difference in type and amount of received rehabilitation in both groups. Eight participants in each group performed self-home exercise, while one participant in each group had 60-minute hospital PT once a week. Further studies should be performed with consideration of these limitations.

Conclusion

Our pilot study found that 5 consecutive sessions of anodal tDCS combined with overground gait training was safe in iSCI. However, it could not induce superior improvement over gait training alone. Further study with a large sample is recommended to clearly investigate the effects.

Declaration of interest statement

The authors have no conflicts of interest.

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