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Original article

Effect of single-session dual-tDCS before physical therapy on lower-limb performance in sub-acute stroke patients: A randomized sham-controlled crossover study

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ABSTRACT

Anodal stimulation increases cortical excitably, whereas cathodal stimulation decreases cortical excitability. Dual transcranial direct current stimulation (tDCS; anodal over the lesioned hemisphere, cathodal over the non-lesioned hemisphere) was found to enhance motor learning. The corresponding tDCS-induced changes were reported to reduce the inhibition exerted by the unaffected hemisphere on the affected hemisphere and restore the normal balance of the interhemispheric inhibition. Most studies were devoted to the possible modification of upper-limb motor function after tDCS; however, almost no study has demonstrated its effects on lower-limb function and gait, which are also commonly disordered in stroke patients with motor deficits. In this randomized sham-controlled crossover study, we included 19 patients with sub-acute stroke. Participants were randomly allocated to receive real or sham dual-tDCS followed by conventional physical therapy with an intervention interval of at least 1 week. Dual-tDCS was applied over the lower-limb M1 at 2-mA intensity for 20 min. Lower-limb performance was assessed by the Timed Up and Go (TUG) and Five-Times-Sit-To-Stand (FTSTS) tests and muscle strength was assessed by peak knee torque of extension. We found a significant increase in time to perform the FTSST for the real group, with improvements significantly greater than for the sham group; the TUG score was significantly increased but not higher than for the sham group. An after-effect on FTSTS was found at approximately 1 week after the real intervention. Muscle strength was unchanged in both limbs for both real and sham groups. Our results suggest that a single session of dual-tDCS before conventional physical therapy could improve sit-to-stand performance, which appeared to be improved over conventional physical therapy alone. However, strength performance was not increased after the combination treatment.

1. Introduction

Lower-limb functions are commonly disordered after stroke. However, despite classical rehabilitation techniques, the recovery of motor function after stroke is often incomplete. Transcranial direct current stimulation (tDCS) was introduced as a non-invasive tool to reversibly modulate brain excitability in humans. The use of tDCS has increased since the beginning of the 21th century. Its possible after-effects have led to increased interest in using tDCS for neurorehabilitation. A number of studies of stroke have reported that tDCS improved the performance of motor tasks and motor skills learning of the upper limbs [1,2]; however, only a small number of studies focused on lower-limb functions [1–3]. Using a higher current intensity (e.g., 2 mA) than that commonly used for the upper limb, 1 session of anodal tDCS over the M1 acutely enhanced the effect of motor practice of the paretic ankle [4], force production of the paretic knee extensors [5] and postural stability in patients with sub-acute stroke [6].

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After unilateral stroke, the excitability of the unaffected hemisphere is increased and an abnormally high interhemispheric inhibition drive from intact to lesioned hemisphere has been reported [7–9]. The enhanced neural activity of the contralesional motor areas prevents recovery of motor impairments during the subacute phase [10]. Anodal stimulation increases cortical excitability, whereas cathodal stimulation decreases cortical excitability. Dual-tDCS with anodal over the lesioned hemisphere and cathodal over the non-lesioned hemisphere has been used in unilateral stoke to restore brain excitability. Dual-tDCS seems to be a promising tool to enhance motor learning [11], with even greater ability to improve motor performance than unihemispheric tDCS in healthy adults [12,13]. In an imaging study, the corresponding tDCS-induced changes were reported to involve interhemispheric interactions [14]. One recent study reported improved walking speed immediately after a single session of dual-tDCS in sub-acute stroke patients [15].

Studies combining tDCS and training have found improved motor function over training alone [11,13,16–18]. However, the tDCS impact on motor performance varies widely, mostly because of differences in design/task/stimulation methods etc. Hence, meta-analyses did not report a significant improvement in motor performance with tDCS after stroke [19].

Little is known about the effects of dual-tDCS on the lower limb after stroke. The aim of the present study was to examine whether 1 session of dual-tDCS before conventional physical therapy (PT) modified clinical outcomes of lower-limb functions and how this compared to PT alone. The ability to transfer from sit-to-stand and to walk are the most commonly performed tasks of daily living and these are goals for rehabilitation after stroke. Our clinical outcomes were muscle strength and functional assessments that related to sit-to-stand and walking.

2. Methods

2.1. Participants

All included patients were first-ever diagnosed with cerebral infarction, confirmed by CT or MRI, with an onset of less than 6 months (mean [SD]: 3.2 [0.4] months). They had lower-limb weakness but were able to perform sit-to-stand independently and walk without physical assistance for at least 3 m. Participants were screened for exclusion criteria including the presence of intracranial metal implants, cochlear implants, cardiac pacemaker, history of seizures, no clear neurological antecedent history or psychiatric disorder, or excessive pain in any joint of the lower limb. A description of the study was provided to all participants and written informed consent was obtained from all before the experiments. The study protocol was approved by the local ethics committee of Mahidol University and registered at ClinicalTrials.gov (NCT03035162).

2.2. Experimental protocol

The study was conducted as a double-blind crossover sham-controlled trial. Each participant completed 2 sessions of experiments (real or sham) with an intervention interval of at least 1 week [17]. The 2 experiments were performed in random order for each participant. The experimental procedure is outlined in Fig. 1. Participants received PT for 1 h after dual-tDCS. In fact, the ideal timing for applying tDCS to maximize neuroplasticity and evoke behavioral changes has not been determined [19]. Even though a "during" training paradigm tends to have a better effect, we selected the "before" training paradigm for practical reasons because PT is much easier without the tDCS setup and tDCS before training has been shown to promote motor performance [20].

To determine lower-limb function, we examined strength and functional performance. Knee extensor strength was chosen because it is primarily required for performing sit-to-stand and walking. Strength was measured by using a Biodex system while participants comfortably sat in the position of knee flexed at 60° on the attached arm support. Participants performed 3 rounds of maximum voluntary contraction (MVC) of the knee extensor for 5 s separated by 2-min rests. The largest MVC was used for analysis. The data were observed in both deficient and normal limbs.

For functional assessments, the TUG and FTSST tests were chosen. The TUG, a simple and quick functional mobility test [21], was reported to be reliable and valid and correlated well with gait performance and walking endurance in stroke [22]. Participants were asked to sit on the chair and place their back against the chair. Timing began at "GO", the participants walked for 3 m, turned, walked back and sat down. Timing ended when the back was against the chair again. The FTSST test is commonly used to assess mobility and lower-limb acceleration [23]. It has also been introduced as an outcome measure for strength training and functional performance in stroke [24,25] and was reported to be reliable [26]. Participants were asked to stand up with the legs fully extended and sit down 5 times as quickly as possible. Timing began at "GO" and ended when the patient's buttocks touched the seat after the fifth sit-to-stand. Times were recorded in seconds. These outcome measures were evaluated before and after the intervention by a researcher who was blinded to the intervention.

2.3. Intervention

2.3.1. Transcranial direct current stimulation

Patients were seated with their arms comfortably supported to receive the stimulation. Skin preparation was required before applying the stimulation electrodes. A DC portable stimulator (HDC stim, Magstim, Wales, UK), programmed by an LCD touch screen (HDC prog), delivered a direct current through 2 rectangular saline-soaked sponge-pad electrodes with 35 cm^2 surface. An electroconductive gel was applied under the electrodes to reduce contact impedance. A 10–20 electroencephalography system [13] was used to apply anodal tDCS over the M1 of the affected hemisphere and cathodal tDCS over the M1 of the unaffected hemisphere, with the medial border of each electrode placed 5 mm lateral from the vertex. The current flowed continuously for 20 min during the real condition. For the sham condition, to provide stimulus sensation to participants, only 120 s was chosen because a duration of at least 3 min was previously found required to induce after-effects [27]. Current intensity was fixed at 2 mA because this was reported to induce changes in the excitability of deeper cortical structures innervating lower-limb muscles [28] and lower-limb spinal networks [29] and modulate the activity of the supplementary motor area involved in lower-limb performance, as explored by functional MRI [30]. tDCS was applied by a researcher who was blinded to the outcome assessment and data analysis.

Participants were asked about their feelings during tDCS. Eleven (58%) participants reported cutaneous sensations during real tDCS (3 itching and 8 tingling) and 3 (16%) reported tingling during the sham procedure. However, these sensations disappeared after tDCS removal. One participant experienced mild headache after tDCS, which resolved without any treatment within 24 h.

2.3.2. Conventional physical therapy

Participants received PT for 1 h under the guidance of a physical therapist with 10 years experience in stroke rehabilitation, with blinding to the tDCS intervention. PT was administered to improve strength of the affected limbs including hip flexor, hip extensor,

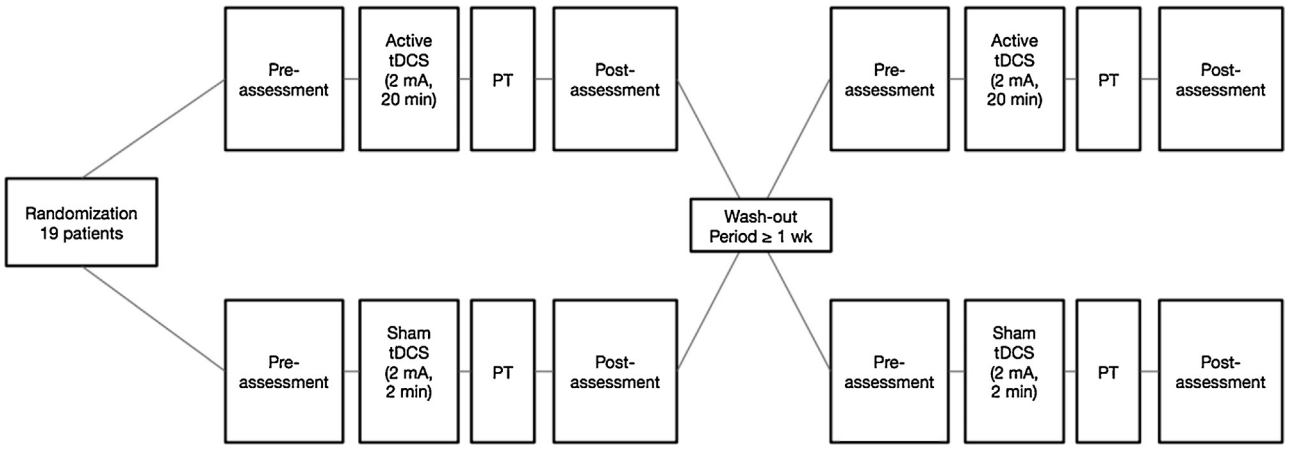

Fig. 1. Experimental procedure. Baseline assessment was performed before the experiment. Then, participants were randomly allocated to receive the real or sham experiment for their first experiment. After transcranial direct current stimulation (tDCS), each participant received PT for 1 h and post-assessment was performed immediately after the PT session. At least 1 week after the first experiment, the second experiment was performed in the same participant. The procedure was the same as the first experiment except for stimulation type (real/sham).

knee flexor, knee extensor and ankle dorsiflexor. The sequence and repetition of exercises were the same for all participants.

3. Statistical analysis

Data are reported as mean [SEM]. Data were compared between Stimulation (real vs sham) and Time (PRE (baseline) vs. POST) by two-way repeated measures ANOVA. One-way ANOVA was used to compare Time (PREreal, POSTreal, PREsham) to check for the carryover in participants who received real tDCS during their first session ($n = 10$) and the recovery effects for those who received sham tDCS during their first session ($n = 9$) (PREsham, POSTsham, PREreal). Tukey's post-hoc analysis was applied if a significant main effect was found. Paired t-test was used to compare data within groups (PRE vs POST). Significance was set at $P < 0.05$. Statistical analyses involved use of Sigma Plot.

4. Results

We included 19 patients with hemiparesis after sub-acute ischemic stroke (5 females, mean [SEM] age: 57.2 [2.8] years, range: 20–74 years) (Table 1).

4.1. Strength performance

Affected side: for the real group, mean [SEM] MVC at PRE was 50.49 [5.1] and at POST was 54.48 [5.3]. For the sham group, MVC at PRE was 50.23 [4.9] and at POST was 51.71 [5.3]. Two-way repeated-measures ANOVA showed no significant main effect for Stimulation ($F_{(1,18)} = 0.339$, $P = 0.568$) or Time ($F_{(1,18)} = 2.823$, $P = 0.110$), with no significant interaction observed between these factors ($F_{(1,18)} = 0.894$, $P = 0.357$) (Fig. 2A).

Unaffected side: for the real group, MVC at PRE was 71.11 [5.7] and at POST was 74.79 [5.4]. For the sham group, MVC at PRE was 73.11 [6.2] and at POST was 74.11 [6.0]. Two-way repeated-measures ANOVA showed no significant main effect for Stimulation ($F_{(1,18)} = 0.0121$, $P = 0.914$) or Time ($F_{(1,18)} = 1.018$, $P = 0.326$), with no significant interaction observed between these factors ($F_{(1,18)} = 0.910$, $P = 0.353$) (Fig. 2B).

4.2. Functional performance

TUG: for the real group, TUG score at PRE was 21.4 [2.9] s and at POST was 17.8 [2.0] s. For the sham group, TUG score at PRE was 20.1 [2.2] s and at POST was 18.7 [2.2] s. Two-way repeated-

Table 1
Participant characteristics.

Participant	Sex	Age (years)	Handedness	Paralysis	Post-stroke (months)	Type of stoke	Lesion	MMT score (LL)	Underlying disease
P01	M	20	Right	Left	5	Ischemic	Subcortical	III+	–
P02	M	50	Right	Left	2	Ischemic	Subcortical	IV	HT
P03	F	52	Right	Right	4	Ischemic	Pons	III	DM, DVT
P04	M	60	Left	Left	3	Ischemic	Cortical, subcortical	III	HT
P05	M	55	Right	Left	5	Ischemic	Cortical, subcortical	III+	HT
P06	M	69	Right	Left	1	Ischemic	Subcortical (lacunar), pons	III+	HT
P07	F	55	Right	Right	5	Ischemic	Subcortical (lacunar)	III	HT, AF
P08	M	74	Right	Left	3	Ischemic	Subcortical, medullar	III+	HT, DM, DLP, CVD, renal stone
P09	F	41	Right	Left	2	Ischemic	Subcortical	III+	HT
P10	M	72	Left	Left	4	Ischemic	Subcortical	III	HT, DLP, BPH
P11	F	57	Right	Right	3	Ischemic	Subcortical	III	HT, DM, DLP
P12	M	64	Right	Right	5	Ischemic	Subcortical (lacunar)	III+	HT
P13	F	62	Right	Right	5	Ischemic	Subcortical (lacunar)	III	HT, DLP
P14	M	68	Right	Left	4	Ischemic	Subcortical	III+	HT
P15	M	66	Right	Left	1	Ischemic	Subcortical	IV	HT
P16	M	58	Right	Left	1	Ischemic	Cortical, subcortical	III	HT, DLP, cardiomegaly
P17	M	56	Right	Right	1	Ischemic		IV	HT, DLP
P18	M	48	Right	Right	6	Ischemic	Subcortical	III+	HT, DM
P19	M	60	Left	Left	1	Ischemic	Subcortical	IV	HT, DLP

AF: atrial fibrillation; BPH: benign prostatic hyperplasia; CVD: cardiovascular disease; HT: hypertension; DLP: dyslipidemia; DM: diabetes mellitus; MMT: manual muscle test; LL: lower limb.

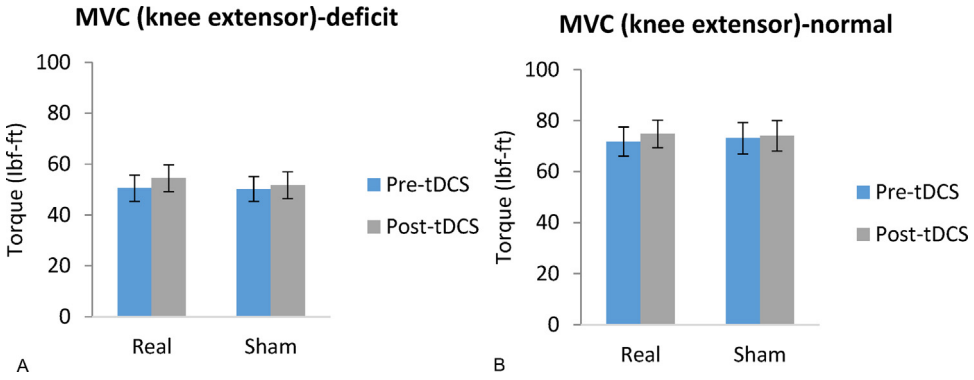

Fig. 2. Raw data for maximum voluntary contraction (MVC) of knee extensor of the affected limb (A) and normal limb (B) in pound-foot units (lbf-ft) pre- and post-tDCS. Data are mean (SEM).

measures ANOVA revealed only a significant main effect for Time ($F_{(1,18)} = 16.099$, $P < 0.001$), but the effect of Stimulation and interaction effects were nonsignificant ($F_{(1,18)} = 0.022$, $P = 0.883$; $F_{(1,18)} = 2.408$, $P = 0.138$, respectively). Real and sham groups did not differ at PRE (real: 21.4 [2.9] vs sham 20.1 [2.2] s, $P = 1.000$), which indicates that TUG scores at baseline were comparable (Fig. 3).

FTSST: for the real group, FTSST score at PRE was 16.7 [1.2] s and at POST was 13.7 [0.9] s. For the sham group, FTSST score at PRE was 16.1 [1.4] s and at POST was 15.0 [1.1] s. Two-way repeated-measures ANOVA revealed significant main effects of Time ($F_{(1,18)} = 13.594$, $P = 0.002$) and an interaction between Time and Stimulation ($F_{(1,18)} = 8.88$, $P = 0.008$), which suggests that real dual-tDCS led to greater improvements than sham treatment over time. FTSST scores at baseline were comparable because we found no significant difference between real tDCS and sham at PRE (real:16.7 [1.2] vs sham 16.1 [1.4] s, $P = 1.000$) (Fig. 4).

In addition, we performed the analysis separately for only the first session (real/sham). Ten patients received real tDCS on their first session and 9 patients for sham tDCS. For MVC, we found no significant difference between PRE and POST for both real and sham groups ($P > 0.005$). For TUG, we found a significant difference between PRE (24.0 [4.7 s] and POST (18.5 [3.0 s], $P = 0.004$ for only the real group, with no difference for the sham group ($P > 0.005$). For FTSTS, paired t-test revealed a significant difference between PRE (18.3 [1.2 s] and POST (15.1 [1.2 s], for only the real group ($P = 0.003$), with no difference for the sham group ($P > 0.005$).

4.3. Carryover effect

We did not initially design our study to follow up the carryover effect. However, the carryover effect could be checked at 1 week after tDCS in 10 participants who received real tDCS during their first session. We used the data from PREreal, POSTreal and PREsham for analysis. For FTSST, one-way ANOVA revealed a significant difference ($F_{(2,27)} = 3.652$, $P = 0.039$); post-hoc comparisons showed a significant difference between PREreal (18.3 [1.2] s) and PREsham (14.5 [1] s) ($P = 0.047$, Tukey test), which indicates a significant increase in FTSST performance within 1 week after 1 session of tDCS. No significant difference was found for TUG scores and MVC ($P > 0.005$).

4.4. Recovery effect

Because participants were in the sub-acute phase after stroke, their performance over time could change. The results from our 9 patients who received sham tDCS for their first session were analyzed by using the data from PREsham, POSTsham and PREreal. One-way ANOVA revealed no significant difference for all outcomes ($P > 0.005$), which indicates that no recovery effect appeared within 1 week after sham tDCS.

5. Discussion

The purpose of this study was to investigate whether a single session of dual-tDCS before PT could immediately improve lower-limb function and if the improvement would be greater than PT alone. We compared the effect of real and sham tDCS on the MVC of knee extensors and TUG and FTSST scores in the same participants. All baseline data were the same for both groups. No improvement in MVC was found within or between groups. For the performance tasks, we found only a significant interaction for FTSST, indicating greater sit-to-stand performance after tDCS plus PT than PT alone, with no significant improvement in TUG over PT alone. We

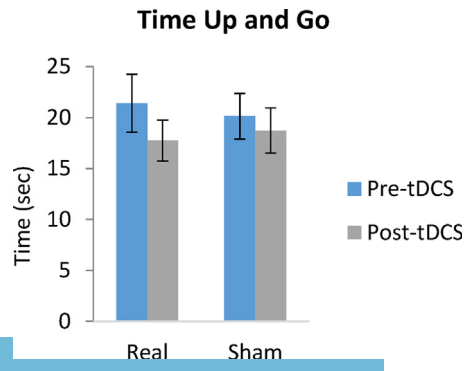

Fig. 3. Time Up and Go data in seconds pre- and post-tDCS. Data are mean (SEM).

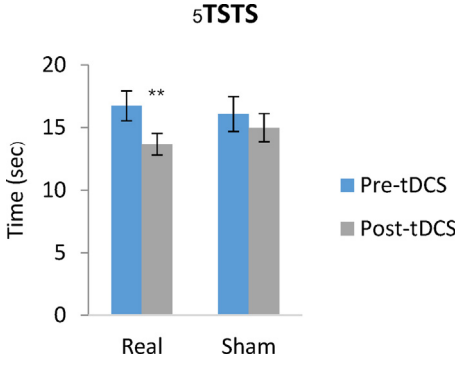

Fig. 4. Data for Five-time sit-to-stand (FTSST) in seconds pre- and post-tDCS. Data are mean (SEM). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

additionally performed the analysis for the first session for each participant. In comparing before and after the intervention, we found no significant difference in both real and sham groups for strength performance. The real group showed a significantly greater performance in TUG and FTSST, with no difference found for the sham group. Hence, for the first session, with no involvement of recovery and/or testing effect, real tDCS could increase functional performance. The carryover effect was tested in patients who received real tDCS during their first session. We found a significant difference for FTSST but no difference for TUG or MVC. A recovery effect during 1 week was checked in patients who received sham tDCS during their first session and revealed no significant difference for all outcomes, thus indicating no recovery effect.

Many tDCS studies in stroke have reported positive results of motor function after a combination of tDCS and training as compared with training alone [11,13,18,31]. Here, we also observed that the FTSTT score was significantly improved in the real versus sham group. An after-effect was found at approximately 1 week for FTSTS, but we do not know the precise duration of the effect. Studies of the upper limb have reported that the after-effect after tDCS plus training remained for at least 20 to 25 min [17,32] or 1 day after the stimulation ended [33] but not until day 10 [32].

One session of dual-tDCS over the M1 at rest could immediately improve TUG performance in subacute stroke [15]. This finding agrees with our observations for the groups of participants and tDCS technique used; however, no training was performed in the previous study. The authors observed that participants with subcortical lesions showed a greater change in TUG than did other participants. However, our 13 participants with pure subcortical lesions showed heterogeneous responses. Although TUG performance was improved, we found no significant difference between the real and sham groups. This finding agrees with a study of an early phase of stroke showing that multiple sessions of cathodal tDCS over the unaffected M1 with rehabilitation induced a significant clinical improvement of upper and lower extremities including TUG performance but did not lead to higher functional improvement than traditional rehabilitation alone [34]. A possible explanation for the lack of non-superior improvement in TUG we found could be the similarity in trends for both groups and probably not different with our current sample size. Regarding functional performance evaluation, 4 participants could perform the TUG within 10 s. The TUG test is sufficiently sensitive to detect small changes in patients with stroke including mild chronic stroke; however, the ceiling effect was seen in patients with relatively good walking ability [35]. For the FTSST, cut-off scores of 12 s were found to be discriminatory between healthy older people and those with stroke [26]. Five participants performed the FTSST in 12 s or less, which is considered relatively good performance. A ceiling effect may also explain in part some of the limited changes in functional performance, especially in these participants.

We found no improvement in MVC. Our results contradict the pioneering finding by Tanaka et al. in subcortical stroke, showing an increase in knee extensor MVC immediately after anodal tDCS over the M1 [5]. This contradiction could be due in part to differences in methodology because we used dual-tDCS. Our data agree with the study of Montenegro et al., who reported that one session of dual-tDCS was unable to improve knee extensor MVC in stroke [36]. The low focality of dual-tDCS to leg muscles may have attenuated effects on peak torque. Multiple sessions of anodal tDCS with training did not produce significantly greater increases in knee extensor MVC in healthy participants as compared with training alone [37]. tDCS effects on motor unit recruitment induced via the descending volleys were relatively small as compared with physiological adaptation in healthy participants. tDCS is probably of more benefit to motor performance modulation in people with more severe motor impairment than those with mild impairment [38]. This situation might explain the lack of strength improvement found here, because some of our participants had relatively mild motor impairment. Moreover, we did not evaluate possible confounding effects such as fatigue. Our PT program was developed specifically to target lower-limb strength including knee extensors, but no trend of improvement appeared in either group. Muscle fatigue after training may affect MVC because it was measured immediately after PT. In addition, we observed no changes in MVC for the non-paretic leg in either group. This finding could support in part the idea that dual-tDCS montage over the M1 does not lead to worsening in the non-paretic leg; however, multiple tDCS sessions are required to prove this.

5.1. Limitations

The first limitation is that a transcranial magnetic stimulation localization (TMS) of the leg hotspot could give a better-individualized localization. This limitation could explain the lack of effect we found. Several tDCS studies have used the 10–20 system to target the M1 [15,34,36]. Although in children with stroke, the 10–20 system and the TMS-derived motor hotspot location differed to some degree in each individual, this distance discrepancy also relied on the electrode size. However, there was no association between the distance and function [39]. The second limitation is a lack of a neurophysiologic test. A systematic review showed that tDCS does not generate a reliable neurophysiologic effect beyond motor-evoked potentials [40].Nevertheless, Madhavan et al. reported improved lower-limb performance induced by tDCS over the M1 with non-significant changes in corticomotor excitability evaluated by motor-evoked potentials [41]. This was also found with other tDCS studies, finding behavior measurably enhanced with non-significant or lack of changes in corticomotor excitability [16,38]. The third limitation is the timing of the effect: the maximum effect on motor performance is probably not immediately after but is delayed. A 1-session dual-tDCS induced maximum improvement in dexterity of the paretic fingers at 20 min after the stimulation ended [17] and facilitated maximum consolidation of thumb movements at 24 h later [33]. The fourth limitation is that applying tDCS at different times such as during PT would have been a better option because a "during"training paradigm tends to have a better effect [19]. The final limitation is that measuring strength of other lower-limb muscles (i.e., hip, ankle muscles) should be addressed in future study.

6. Conclusion

A single session of dual-tDCS before PT in people with sub-acute stroke immediately improved lower-limb function but not strength. Such improvement was greater than with PT alone for the FTSST but not TUG. Observations of later after-effects or evaluation of multiple sessions of tDCS on long-term performance are needed to further investigate the benefits of its use in rehabilitation.

Disclosure of interest

The authors declare that they have no competing interest.

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