Original Article

Effects of Transcranial Direct Current Stimulation on Motor Activity of Lower Limb Muscles in Chronic Stroke†

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Background: Anodal transcranial direct current stimulation [tDCS] enhances cortical excitability and increases lower limb force in healthy volunteer and stroke patients. Effects of tDCS on motor activity of lower limb muscle and gait performance in chronic stroke patients was not explored.

Objective: To study the effects of tDCS on motor activity of lower limb muscles and gait performance in chronic stroke patients.

Materials and Methods: Ten chronic stroke patients participated in a single-blind, crossover, and sham-controlled pilot study. Each patient participated in two stimulation conditions applied to the lower limb motor cortex area of affected hemisphere, i.e., anodal stimulation (2 mA, 10 minutes) and sham stimulation (2 mA, 30 seconds). The sequence of stimulation was randomly assigned. Wash-out period between stimulation is at least 48 hours. Root mean square [RMS] amplitude and median frequency [MF] of the vastus medialis oblique [VMO] and tibialis anterior [TA] muscles of the paretic limb and the Timed Up & Go test [TUG] were measured before and immediately after stimulation.

Results: The average RMS amplitude of the VMO muscle of the paretic limb increased by 13.6% and 7.7% after anodal tDCS and sham stimulation, consecutively. The average RMS amplitude of the TA muscle decreased by 2.3% and increased by 9.1% after tDCS and sham stimulation. The average MF of the VMO muscle of the paretic limb decreased by 1.9% and 2.9% after anodal tDCS and sham stimulation, consecutively. The average MF of the TA muscle decreased by 2.4% and increased by 2.9% after tDCS and sham stimulation. The TUG was decreased by 1.2% and increased by 1.7% after tDCS and sham stimulation, consecutively. RMS, MF, and TUG were not statistically different between tDCS and sham stimulation (ANCOVA test, $p>0.05$).

Conclusion: Single session of anodal tDCS at ipsilesional hemisphere could not enhance motor activity of lower limb muscles in chronic stroke patients.

Keywords: Transcranial direct current stimulation, Stroke, Rehabilitation, Motor cortex

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Weakness of lower limb is commonly found in chronic stroke patients. The strength of the paretic lower limb correlates with gait performance in stroke patients[1]. Knee muscle strength predicts walking ability in mild to moderate severity chronic stroke patients[2]. Strength of paretic ankle and hip muscles also correlates with gait performance. Any strategy to increase motor learning and strength of lower limb muscles, especially knee extensor, may facilitate walking and reduce functional limitation.

Transcranial direct current stimulation [tDCS] is one type of non-invasive brain stimulation. It delivers weak electrical current to the cortex. Anodal tDCS facilitates cortical excitability and cathodal tDCS inhibits cortical activity. Previous study demonstrated that single session of anodal tDCS increases motor evoked potential [MEP] amplitude of the leg motor cortex area in healthy volunteers[3,4]. Cathodal tDCS cannot decrease MEP amplitude of leg motor cortex. There was early evidence of modulation effect by anodal tDCS on lower limb muscle in healthy volunteer. Toe pinch force of healthy volunteer also increases after single session of anodal tDCS[5]. Before February 2009, at the time we started the present study, only one study showed a benefit of single session of anodal tDCS to enhance cortical excitability of lower limb motor cortex in chronic stroke patients[6]. There is no clinical trial confirming an effect of single session of tDCS on lower limb motor activity and

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gait performance in stroke patients.

The aim of this study is to test whether single session of anodal tDCS affects motor activity of paretic lower limb and gait performance in chronic stroke patients. If tDCS can enhance lower limb motor activity and gait performance, it may combine with lower limb strengthening and ambulation training to augment gait performance and functional mobility in stroke patients.

Materials and Methods

Participants

Stroke patients were recruited from the outpatient rehabilitation medicine services of a University Hospital. The study was approved by the institutional ethical committee. The research was conducted in accordance with the Declaration of the World Medical Association. All participants gave written, informed consent before the experiment. Inclusion criteria include the first episode of hemiparesis caused by an ischemic stroke, onset longer than six months, age at onset older than 18 years, normal consciousness, stable neurological status, muscle power of the knee extensor and ankle dorsiflexor of paretic limb were grade 2 to 4 (Medical Research Council System), and stage 4 to 6 of Brunnstrom recovery stage of the lower limb. Exclusion criteria include seizure, fixed contracture of knee or ankle joint, modified Ashworth scale [MAS] score of 2 or greater of the knee or ankle, the Thai Mental Status Examination score lower than 23, currently using sodium- or calcium-channels blockers and N-methyl D-aspartate [NMDA] receptor antagonist, and have a contraindication for electrical stimulation.

Forty-eight stroke patients were initially recruited. Thirty-one patients met the inclusion criteria. Twenty-one patients were excluded because they were currently using the calcium-channels blockers at the time of recruitment (n = 19), or had severe spasticity of the knee or ankle of the paretic limb (n = 2). Ten patients participated in the study.

Experimental procedure

A patient-blind, crossover, sham-controlled pilot study was conducted. A sample size was not calculated. Participants underwent two stimulation sessions (anodal tDCS and sham stimulation) separated by at least 48 hours to wash out a carry-over effect of tDCS. The sequence of stimulation was randomly assigned by a computerized generated randomization program with counterbalance among them. Root mean square [RMS] amplitude and median frequency [MF] of the vastus medialis oblique [VMO] and tibialis anterior [TA] muscles of the paretic limb and the Timed Up & Go test [TUG] were measured before (pre-stimulation) and immediately after each stimulation session (post-stimulation) (Figure 1).

Transcranial direct current stimulation

The tDCS device (Phoresor II Auto Model PM850, IOMED, Inc., Salk Lake City, Utah 84120, USA) was used to deliver the direct current through the cranium. Anodal electrode (TransQE, IOMED, Inc., USA, active surface area 10.1 cm^2) with saline soaked was placed over the ipsilesional leg motor cortex area (1 cm posterior and 1 cm lateral to Cz according to a 10 to 20 EEG system). Self-adhesive cathode surface electrode (TransQE, IOMED, Inc., USA, surface area 25 cm^2) was placed over the contralateral supraorbital area. Elastic Velcro strap was used to secure the anode. The tDCS at an intensity of 2 mA was applied for 10 minutes with 10 seconds ramped up and 10 seconds ramped down[3]. The current density at the electrode was 0.20 mA/cm^2. For the sham stimulation, the authors applied 10 seconds of 2 mA stimulation with 10 seconds ramped up and 10 seconds ramped down[7]. The tDCS device remained out of the eyesight of the participants during the experiment. Participants of both tDCS and sham stimulation felt a tingling and burning sensation on the scalp that disappeared within seconds. Participants could stop the stimulation if they decided to leave the study or experienced any intolerable adverse effects.

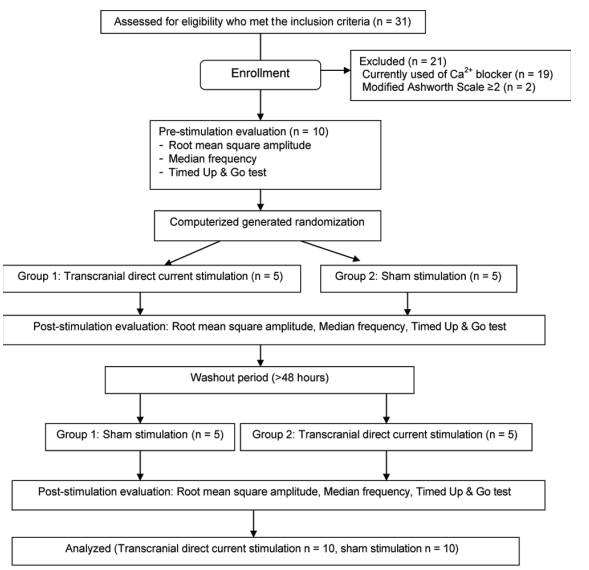

Figure 1. Experimental design of randomized single-blinded crossover sham-controlled study.

Measurement of motor activity of lower limb

RMS amplitude and MF of the VMO and TA muscles were used for measuring motor activity of the paretic limb[8]. RMS represents the number of motor unit activities and levels of effort intensity[9]. MF represents motor unit discharge frequency and muscle fiber conduction velocity[10]. Increased RMS and MF represents increased motor activity and improvement of motor control. The electrodiagnostic machine with power spectrum analysis software (Medelec Synergy, Medelec Inc., UK, bandwidth 10 Hz to 10 kHz, amplified with sensitivity 500 μV per division, sweep speed 100 ms per division) was used for measuring RMS amplitude and MF. The electromyographic [EMG] signals of the VMO and TA muscles were recorded using a 4 mm disc electrode with standard technique[11]. The measurement was repeated 10 times for each muscle. An average RMS amplitude and MF of each muscle was used for analysis.

In the VMO muscle, an active electrode was placed over the motor point superomedial to the patella. A reference electrode was placed 4 cm proximal to the active electrode. Participants sat in a comfortable chair with trunk lean on the backrest, arm on the armrest, and feet flat on the floor. The author told them to extend their knee from 90° flexion starting position to full extension then maximally hold in this position for five seconds.

In the TA muscle, an active electrode was placed over the motor point on the lateral side of tibial crest, four fingerbreadths below the tibial tuberosity. A reference electrode was placed 4 cm distal to the active electrode. The author told them to dorsiflex the ankle from a neutral position to 20° dorsiflexion then maximally holds in this position for five seconds.

The Timed Up & Go test (TUG)

The TUG correlates with dynamic balance and level of mobility[12,13]. The TUG was measured before and immediately after stimulation session. Participants were instructed to walk at a comfortable speed along a 3-meter walkway. The time was measured from rising from an armchair, walk for three meters, turning, walking back to the chair, and sit down. Each participant performed the TUG two times. The mean time was used for analysis.

Statistical analysis

Demographic data were reported by a number and mean ± standard deviation, range, and proportion. According to the main outcome, motor activity and gait performance, we presented a standard error of mean instead of standard deviation because we randomized small number of subject from large population of stroke patients. Standard error estimates the variability between means of multiple samples from the same population. Thus, standard error represents precise estimation of mean in small random sample from the whole population. Analysis of co-variances [ANCOVA] was used to test the effect of anodal tDCS and sham stimulation on the RMS amplitude and MF of the VMO and TA muscles and TUG. The significant change between the two methods of stimulation was accepted if p value was smaller than 0.05. The SPSS statistic program (version 13.0 SPSS Inc., Chicago, IL, USA) was used to analyze the data.

Results

Ten chronic ischemic stroke patients participated in the study. The mean age was 57.1± 12.2 (range 24 to 65) years. Five patients were left hemiparesis. The mean onset was 34.1±18.9 (14.3 to 70.4) months. Nine patients have right-legged predominant according to an interview. Most of them could walk without walking aids. The characteristics of the patients are shown in Table 1.

Table 1. Patient characteristics

Characteristics	Subjects (n = 10)
Age (years), mean ± SD (range)	57.1±12.2 (24 to 65)
Gender	
Male:female	6:4
Time after onset (months), mean ± SD (range)	34.1±18.9 (14.3 to 70.4)
Paretic side	
Right:left	5:5
Walking aid	
Use:not use	1:9
Rehabilitation program	
Day treatment:home program	1:9
Motor power of paretic limb (MRC grading)	
Knee extensor (grade 0:1:2:3:4:5)	0:0:0:0:10:0
Ankle dorsiflexor (grade 0:1:2:3:4:5)	0:0:2:3:5:0
MAS score	
Knee extensor (grade 0:1:1+:2:3:4)	6:3:1:0:0:0
Ankle dorsiflexor (grade 0:1:1+:2:3:4)	2:7:1:0:0:0
Brunnstrom stage of recovery of lower limb	
Stage 1:2:3:4:5:6	0:0:0:5:2:3
TMSE score, mean ± SD (range)	27.3±2.7 (24 to 30)

MRC = Medical Research Council scale; MAS = modified Ashworth scale; TMSE = Thai Mental Status Examination

Table 2. Motor activity and gait performance before and after tDCS and sham stimulation

	Anodal tDCS, mean (SE)		Sham stimulation, mean (SE)		*p*-value*
	Pre	Post	Pre	Post	
RMS amp (μV)					
Vastus medialis	88.2 (20.5)	100.2 (23.3)	87.4 (19.8)	94.1 (20.4)	0.40
Tibialis anterior	148.4 (32.0)	145.0 (31.5)	131.6 (24.4)	143.7 (29.6)	0.05
MF (Hz)					
Vastus medialis	80.6 (5.4)	79.1 (4.9)	83.8 (4.6)	81.4 (3.5)	0.99
Tibialis anterior	101.1 (8.6)	98.7 (8.8)	90.6 (7.9)	93.3 (7.4)	0.16
TUG (seconds)	16.0 (2.0)	15.8 (2.1)	15.5 (2.2)	15.7 (2.3)	0.39

tDCS = transcranial direct current stimulation; RMS amp = root mean square amplitude; MF = median frequency; TUG = Timed Up & Go test

* *p*-value show statistic significant level comparing an effect of anodal tDCS with sham stimulation

The average RMS amplitude of the VMO muscle of the paretic limb increased by 13.6% and 7.7% after anodal tDCS and sham stimulation, consecutively. The average RMS amplitude of the TA muscle decreased by 2.3% and increased by 9.1% after tDCS and sham stimulation. The average MF of the VMO muscle of the paretic limb decreased by 1.9% and 2.9% after anodal tDCS and sham stimulation, consecutively. The average MF of the TA muscle decreased by 2.4% and increased by 2.9% after tDCS and sham stimulation. The TUG decreased by 1.2% and increased by 1.7% after tDCS and sham stimulation, consecutively. RMS, MF, and TUG were not difference between tDCS and sham stimulation (ANCOVA test, $p>0.05$). Results are shown in Table 2. No major adverse effect was found after tDCS and sham stimulation.

Discussion

The RMS and MF of the VMO and TA muscles of an affected side do not improve after single session of anodal tDCS (2 mA, 10 minutes) and sham stimulation (2 mA, 30 seconds). The present study does not show an enhancing effects of tDCS on number of motor unit activity, motor unit discharge frequency, and muscle fiber conduction velocity. Thus, the results are not confirming a benefit of single session of anodal tDCS on motor activity and gait performance. We propose two hypotheses. First, the tDCS method activates many different populations of neurons in cortex such as inhibitory, excitatory, interneurons and projection neurons. These may show opposite result and response differently to previous study. Small electrode may decrease spread of current, thus, provide more focus on the stimulation site than with a large electrode. Although the anodal electrode used in the present study is smaller than the usual size, the result is not improved. Second, an effect of tDCS protocol depends on the state of ongoing activity in the brain. The authors did not use an EEG monitor brain state to apply tDCS in appropriate state. Therefore, a variation of tDCS effect may depend on individual brain state during stimulation. This hypothesis is supported by recent study. An anodal tDCS increases motor excitability of the paretic TA muscle during on-brain stage such as walking in stroke patients[6]. The tDCS during training may be better than pre-training stimulation in the present study. Motor cortex excitability of the TA muscle of healthy volunteer increases after the anodal tDCS using the same parameters[3,4]. Besides the two hypotheses suggested above, the current density used to excite motor cortex of stroke patient may be higher than of healthy volunteer.

An anodal tDCS transiently enhances knee extensor force of chronic stroke patients after stimulation in a previous study[14]. Force may increase from a neural adaptation, facilitation of motor learning, and neural plasticity via increased secretion of activity dependent brain-derived neurotrophic factor [BDNF] to optimize motor unit activation[15-17]. The present study did not measure knee extensor force. Therefore, we cannot compare the result. However, that study did not measure correlation of increased knee extensor force with gait performance.

Gait performance test was not observed in the previous studies. The authors measured the TUG before and immediately after stimulation. The TUG after anodal tDCS and sham stimulation were not significantly changed. Single session of anodal tDCS did not improve gait performance. TUG of all participants is longer than 12 seconds, a cut-off point for faller[18]. Although they can walk independently, they needed further training to reduce fall risk.

The anodal tDCS modulates the activity of sodium- and calcium-channels and NMDA receptor[19,20]. Use of the sodium- and calcium-channels blocker and NMDA receptor antagonist may inhibit the neural

membrane depolarization effect of tDCS. The authors excluded all participants who currently use these medications to eliminate this effect. Some participants had an itching sensation during stimulation and fatigue after stimulation. They disappeared after a short period. No major adverse effect was found. The present study has limitations such as small sample size, patient blinded only, and single session of tDCS stimulation. Double blinded randomized controlled trial in larger sample size is needed to confirm these results. Repeated stimulation may enhance motor activity of lower limb muscle and gait performance in stroke patients. Before February 2009, at the time we started this study, there is no clinical trial confirming an effect of repeated tDCS on lower limb motor activity and gait performance in stroke patients. In 2015, cortical excitability and lower limb motor recovery of subacute stroke patients improved after 10 sessions anodal tDCS. However, gait performance, balance, and ambulatory level were not improved[21]. Further study is needed to prove an advantage of tDCS in this aspect.

In conclusion, our results indicate that a single session of anodal tDCS (2 mA, 10 minutes) at ipsilesional motor cortex area would not enhance motor activity of VMO and TA muscles and TUG in chronic stroke patients.

What is already known on this topic?

Previous study demonstrated that single session of anodal tDCS enhances cortical excitability of the leg motor cortex area and increases toe pinch force in healthy volunteers. In chronic stroke patients, anodal tDCS transiently enhances cortical excitability and increases knee extensor force of the paretic limb. As the authors known, neither motor activity nor gait performances were observed in stroke patients after a single session anodal tDCS.

What this study adds?

In the present study, it was shown that a single session of anodal tDCS (2 mA, 10 minutes) at ipsilesional lower limb motor cortex area could not enhance motor activity of VMO and TA muscles and TUG in chronic stroke patients.

Acknowledgment

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Potential conflicts of interest

None.

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ผลของการกระตุ้นสมองด้วยไฟฟ้ากระแสตรงผ่านกะโหลกศีรษะต่อการทำงานของกล้ามเนื้อขาในผู้ป่วยโรคหลอดเลือดสมองระยะเรื้อรัง

สิรินุช อุดรภิชาติ, วสุวัฒน์ กิติสมประยูรกุล

ภูมิหลัง: การกระตุ้นสมองด้วยไฟฟ้ากระแสตรงผ่านกะโหลกศีรษะด้วยขั้วอาโนด ช่วยเพิ่มการทำงานของสมอง และเพิ่มแรงของขาในอาสาสมัครสุขภาพดี และผู้ป่วยโรคหลอดเลือดสมอง ยังไม่มีการศึกษาผลของการกระตุ้นสมองด้วยไฟฟ้ากระแสตรงผ่านกะโหลกศีรษะต่อการสั่งการทำงานของกล้ามเนื้อขา และค่าประเมินการเดินในผู้ป่วยโรคหลอดเลือดสมองระยะเรื้อรัง

วัตถุประสงค์: เพื่อศึกษาผลของการกระตุ้นสมองด้วยไฟฟ้ากระแสตรงผ่านกะโหลกศีรษะด้วยขั้วอาโนดต่อการสั่งการทำงานของกล้ามเนื้อขา และค่า Timed Up & Go test [TUG] ในผู้ป่วยโรคหลอดเลือดสมองระยะเรื้อรัง

วัสดุและวิธีการ: ผู้ป่วยโรคหลอดเลือดสมองระยะเรื้อรัง 10 ราย เข้าร่วมการศึกษานำร่องแบบไขว้ปกปิดด้านเดียวและมีการควบคุมด้วยกลุ่มหลอก ผู้ป่วยได้รับการกระตุ้นที่สมองส่วนสั่งการของขาด้านที่เป็นรอยโรค 2 แบบ ได้แก่ การกระตุ้นด้วยขั้วอาโนด ใช้ไฟ 2 มิลลิแอมแปร์ นาน 10 นาที และกระตุ้นหลอกใช้ไฟ 2 มิลลิแอมแปร์ นาน 30 วินาที มีการสุ่มลำดับของการกระตุ้นก่อน-หลัง วัดค่า root mean square [RMS] amplitude และ median frequency [MF] ของกล้ามเนื้อ vastus medialis oblique [VMO] และ tibialis anterior [TA] และค่า TUG ก่อนและหลังกระตุ้นทันที

ผลการศึกษา: ภายหลังการกระตุ้นสมองด้วยไฟฟ้ากระแสตรงผ่านกะโหลกศีรษะด้วยขั้วอาโนด และกระตุ้นหลอก พบว่าค่าเฉลี่ยของ RMS amplitude ของกล้ามเนื้อ VMO ข้างที่อ่อนแรงเพิ่มขึ้นร้อยละ 13.6 และ 7.7 ตามลำดับ และค่าเฉลี่ยของ RMS amplitude ของกล้ามเนื้อ TA ในกลุ่มที่กระตุ้นด้วยอาโนดลดลงร้อยละ 2.3 และเพิ่มขึ้นร้อยละ 9.1 ในกลุ่มกระตุ้นหลอก ค่าเฉลี่ยของ MF ของกล้ามเนื้อ VMO ภายหลังการกระตุ้นสมองด้วยไฟฟ้ากระแสตรงผ่านกะโหลกศีรษะด้วยขั้วอาโนดและกระตุ้นหลอกลดลงร้อยละ 1.9 และ 2.9 ตามลำดับ ส่วนค่าเฉลี่ยของ MF ของกล้ามเนื้อ TA ในกลุ่มที่กระตุ้นด้วยอาโนดลดลงร้อยละ 2.4 และเพิ่มขึ้นร้อยละ 2.9 ในกลุ่มกระตุ้นหลอก ค่า TUG ลดลงร้อยละ 1.2 ภายหลังกระตุ้นด้วยขั้วอาโนด และเพิ่มขึ้นร้อยละ 1.7 ภายหลังกระตุ้นหลอก ค่า RMS, MF และ TUG ไม่แตกต่างกันเมื่อวิเคราะห์ด้วย ANCOVA ($p>0.05$)

สรุป: การกระตุ้นสมองด้วยไฟฟ้ากระแสตรงผ่านกะโหลกศีรษะด้วยขั้วอาโนดที่สมองด้านเดียวกับรอยโรค 1 ครั้ง ไม่เพิ่มการสั่งการทำงานของกล้ามเนื้อขาและค่า TUG ในผู้ป่วยโรคหลอดเลือดสมองระยะเรื้อรัง