Original Research

Effect of Short Period Simultaneous Stimulation of Transcranial Direct Current Stimulation (tDCS) on Occupational Therapy to Motor Function of Upper Extremity in Stroke Subjects

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ABSTRACT

Background: Stroke causes upper extremity motor function disturbances that may affect quality of life. The affected brain has an ability to recover by way of neuroplasticity. Transcranial direct current stimulation (tDCS) is a non-invasive modality that could induce brain neuroplasticity.

Aim: To determine the effect of tDCS stimulation on recovery of upper extremity motor function in subacute ischaemic stroke patient.

Material and Methods: Twenty two stroke patients enrolled according to inclusion criteria, divided into 2 groups, control group and intervention group. Control group had occupational therapy for 5 days consecutively and intervention group had occupational therapy and tDCS stimulation simultaneously for 5 days consecutively. Upper extremity motor function was evaluated with *Fugl-Meyer Assessment* (FMA) before and after intervention.

Result: Significant improvement of FMA score on control group ($p=0.018$) and intervention group ($p<0.001$). Comparison of the result after the treatment revealed that the intervention group showed more significant improvement in FMA score than the control group.

Conclusion: Application of tDCS stimulation on occupational therapy simultaneously showed better improvement of upper extremity motor function in subacute ischaemic stroke patient, compared with occupational therapy only.

Keywords: *transcranial direct current stimulation, tDCS, occupational therapy, Fugl-Meyer assessment, motor function, subacute ischemic stroke*

Introduction

Stroke, according to World Health Organization, is a cerebrovascular event with rapidly developing clinical signs of focal or global cerebral function disturbance with signs lasting 24 hours or longer or leading to death, with no apparent cause other than vascular origin. The American Heart Association estimated that there are 795,000 strokes

How to cite this article : Utomo A, Wardhani IL, Pawana IPA. *Effect of short period simultaneous stimulation of transcranial direct current stimulation (tdcs) on occupational therapy to motor function of upper extremity in stroke subjects*. SPMRJ. 2020;2(2):66-72

annually with 610,000 new cases and 180,000 recurrent cases. Stroke causes the highest level of disability compared to any other disease. National Stroke Association stated that 10% stroke survivors recovered completely without any disability, 25% recovered with mild disability, 40% suffered moderate to severe disability requiring long term care.[1,2]

Stroke incidence rate according to 2013 Indonesian Basic Health Research or Riskesdas showed an increased number, from 8.3 per 1000 people in 2007 to 12.1 per 1000 people in 2013. East Java Province had the fourth highest prevalence of stroke in Indonesia. The number of stroke patients treated in Dr Soetomo hospital, Surabaya increases every year. There were 750 patients every year in 1990-2000, that increased to 1000 patients every year in 2001-2010, and to 1600 patients per-year in 2011.[3] Many studies showed that upper extremity impairment occur in 85% of stroke patients, and that most of stroke patients with initial upper limb impairment still have significant functional problems five years after the acute event.[4]

Stroke causes damage and dead to neurons due to ionic imbalance in the membrane and oxygen deprivation. This condition leads to loss of the brain function, depending on the stroke area which doesn't show enhanced activity. The area surrounding the stroke, peri-infarct zone, shows excitatory or inhibitory activity in which that activity will stimulate neuroplasticity. Recovery of brain function after stroke depends on neuroplasticity activation. Neuroplasticity is an ability of neurons or brain structures to adapt and adjust the nervous system at functional and structural levels when exposed to new experiences. Many exercises and modalities had been developed to stimulate neuroplasticity. Transcranial direct current (tDCS) has been developed in this last decade as a non-invasive modality to modulate the cortex. Transcranial direct current stimulation delivers weak sub-threshold electrical current stimulation, through scalp and bone, directly to a targeted brain area, modulating the excitability of the brain and inducing neuroplasticty. Previous research showed that tDCS has an effect on nitrosodimethylamine/N-methyl D-aspartat (NMDA) receptor efficacy and on brain derived neurotrophic factor (BDNF) which are both important factors of neuroplasticity.[5]

The mechanisms of action are still poorly understood. A hypothesis stated that a sub-threshold stimulation from anodal tDCS will enhance excitability of the targeted brain area which alters the chance of neuron to fire and resulting in more activity. A sub-threshold stimulation will cause depolarization on neuron's membrane and cause the NMDA receptor density to be fragile. As the result, the intracellular Ca^{2+} concentration will increase and stimulates activity dependent BDNF-secretion that will induce neuroplasticity.[6]

An evidence-based guideline on the therapeutic use of tDCS on motor stroke in 2017 stated "no recommendation" for the tDCS use. "No recommendation" means the absence of sufficient evidence to date, but not the evidence for an absence of effect. This should encourage for more researches to further the knowledge of tDCS on motor function in stroke patients. Some studies showed that tDCS which simultaneously applied with physical therapy brought faster recovery in stroke patient.[7]

Many studies have been done and no serious side effects have occured. Slight itching under the electrode, fatigue, nausea, and headache have been reported in minor cases from a series of more than 550 subjects. Retinal phosphenes can be perceived at the start and end of stimulation especially with frontopolar electrode position.[8]

This study was performed to know whether there was any difference in motor function improvement between tDCS stimulation on occupational therapy simultaneously and occupational therapy only after 5 days tDCS stimulation.

Material and Methods

This study was an experimental study on subacute ischemic stroke patients with a randomized control two group design. The subjects of this study were 22 subacute ischemic stroke patients, from Dr. Soetomo Academic General Hospital Rehabilitation Medicine Outpatient Clinic, appropriate with the inclusion criterias. Inclusion criterias were subacute ischemic stroke, hemiparesis, could understand instruction, manual muscle test 0-4, no severe cardiac disease, good static and dynamic sitting balance, agreed to be study subjects and to follow the protocol by signing the informed consent. Exclusion criterias were uncontrolled hypertension, visuospatial disturbance, hemineglect, aphasia, apraxia, using metal implant, pace maker or hearing aid device and presence of head skin lesion. Drop out criterias of the subject were discontinuing the programs once and unwilling to continue the programs. Subjects were randomized to determine whether the subject enrolled into the control or intervention group. Subjects were divided into 2 groups, the first group as the intervention group, had occupational therapy and tDCS with 2 mA current for 5 days consecutively and the second group as the control had occupational therapy only for 5 days consecutively. The outcome of this research was evaluated with Fugl Meyer Assesment (FMA) of Upper Extremity score before and after the treatment. Fugl Meyer Assesment of Upper Extremity scale was performed (score range from 0 to 66) to assess upper extremity motor improvement. Transcranial direct current stimulation (2 mA, 20 min) was delivered by a constant current electrical stimulator (Caputron Activa Dose II, Gilroy, USA) connected to a pair of saline-soaked sponge electrodes (5 cm x 5 cm). The active anodal electrode was placed on premotor cortex area (PMC) (Figure 1). Premotor cortex area was defined as being 2.5 cm anterior to M1 motor area. M1 is primary motor cortex area (C3 or C4) according to the international 10-20 electroencephalogram (EEG) system. The anode was placed on the affected hemisphere and the reference electrode on the supraorbital region in the contralateral hemisphere.[9]

Statistical analysis was conducted using the Statistical Package for Social Sciences (SPSS 20.0). The characteristics baseline were compared using Fisher’s exact test and independent sample t test. Researcher evaluated the differences of FMA Score level before and after the treatment of both groups, using paired t-test (if the data were normally distributed) or Wilcoxon test (if the data were not normally distributed). The differences (delta) FMA score was also compared between-groups using independent t test. The differences were considered statistically significant if *p value* < 0.05. All subjects had signed the informed consent form and this study had ethical clearance from the ethical committee of Dr. Soetomo Academic General Hospital.

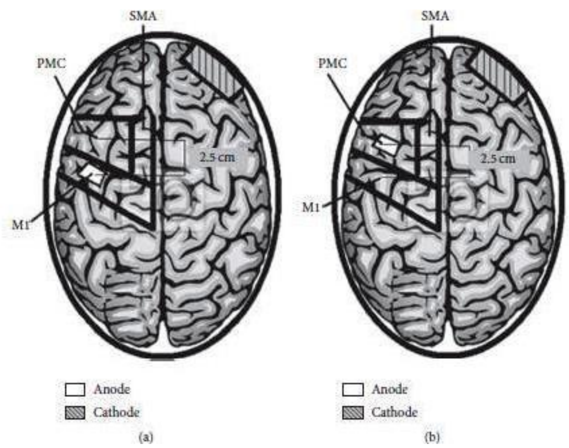

Figure 1. Electrode montage of 5 tDCS sessions. (a) M1 position. (b) PMC position. SMA: Supplementary Motor Area.[10]

Result

All 22 subjects completed the sessions and study protocol, with no losses throughout the study. None of the subjects reported any adverse effects during or after the electrical stimulation. The homogeneity test of subjects' characteristics whether age, sex, manual muscle test (MMT) and spasticity before treatment between control and intervention group found no significant differences (Table 1), so they did not influence the result of the study. There were significant improvement ($p<0.05$) of FMA score before and after treatment both in control group and intervention group (Table 2). Comparison of the delta FMA revealed that the intervention group showed more significant improvement in FMA score than the control group (p<0.001) (Table 3).

Discussion

The average age of subjects in both groups was 55 years old, with the number of male subjects more than female subjects (Table 1). Those data suited the theory, stating that male and age more than 55 years old are some of the non-modifiable risk factors of stroke events. There are many descriptive studies supporting this theory. Wardhani and Martini (2015) showed the prevalence of stroke patient at PMR outpatient clinic in Haji General Hospital Surabaya was 63.6% for male and 36.4% for female while in Neurology outpatient clinic according to investigation of Rahayu (2016) was 69.7% for male.[10,11]

Table 1. Sociodemographic characteristic of subjects at baseline

Characteristics	Control group	Intervention group	p value
Age (year)			
(Mean ± SD)	54.73 ± 6.25	55.00 ± 10.64	0.94*
Sex			0.66**
Male (n)	8	6	
Female (n)	3	5	
MMT (Pre)			0.51***
Spasticity			0.22***

* Independent t-test; ** Fisher's Exact test; ***Mann Whitney test

Table 2. FMA score of control and intervention group before and after treatment

	Control (*Mean*±SD)	*p value*	Intervention (*Mean*±SD)	*p* value
Before	22.27 ± 19.75	0.02*	26.91 ± 19.69	<0.001**
After	25.36 ± 22.18		39.36 ± 22.01	

***** Wilcoxon test; **Paired t-test**,** Sig: *p* < 0,05

Table 3. Comparison of delta FMA between control and intervention group

FMA	n	Mean± SD	p value
Intervention	11	12.46± 6.08	<0.001*
Control	11	3.09± 3.86	

***** Independent t-test; Sig: *p* < 0,05

This study showed there were significant improvement of FMA score after the treatment in both groups. The principle of stroke rehabilitation is sensory and motor reeducation exercise thus specific functional exercise for affected limb followed by compensated exercise of non-affected limb to do activity daily living optimally.[1] Occupational therapy used many modalities to do exercise. Exercise can enhance the process of neuroplasticity by increasing angiogenesis, neurotropic factors, the blood brain barrier integrity, brain vasomotor activity, and mitochondria biogenesis, also by moderating apoptosis and inflammation occuring on the brain.[12] Exercise increases expression of angiogenic growth factor such as vascular endothelial growth factor (VEGF) and caveolin-1, playing major parts in neovascularization and improvement of vascular density, it also increases BDNF, nerve growth factor (NGF), and insulin-like growth factor (IGF-1).[13]

Mandal and Mokashi (2009) studied 26 stroke subjects that divided into 2 groups. Control group had only Bobath's neurodevelopmental therapy while intervention group had Bobath's neurodevelopmental therapy combined with task oriented occupational therapy with the outcome evaluated were FMA and functional independence measure (FIM). The treatment was performed for 6 weeks. Intervention group had better improvement on FMA and FIM compared to pre and post treatment than control group.[14] Carr and Shepherd advocated that task oriented exercise improved functional performance of daily activities, such as walking and reaching to grasp objects in stroke patient.[15] A randomized control trial (RCT) study by Jannette et al showed that additional task related practice improved mobility and upper limb function on stroke patient faster.[16]

This study compared between tDCS stimulation on occupational therapy simultaneously (intervention) and occupational therapy only (control). The result was the intervention group had better improvement in motor function than control group. This finding is consistent with previous studies. A meta-analysis by Butler and friends from 8 RCT of chronic stroke subjects made a conclusion that anodal tDCS on affected M1 brain area significantly improved motor recovery of upper extremity compared with control group (no treatment, sham tDCS, and placebo). The outcomes were Jebsen-Taylor Hand Function Test (JTHFT), Reaction Time (RT), Pinch Strength (PS), Box and Block Test (BBT), and FMA.[17]

Andrade and friends made a pilot RCT to 60 stroke patients that were divided to 3 groups. Group 1 had a constraint induced movement therapy (CIMT) and sham tDCS, group 2 had CIMT and anodal tDCS on primary motor area and group 3 had CIMT and anodal tDCS on premotor cortex area. The current intensity was 0.7 mA, 10 minutes, 5x/week for 2 weeks. The result was the third group has better improvement on FMA and BBT than two others group.[9] An RCT, double blind, sham controlled study of 26 chronic stroke patients by Ilic et al. showed significant result on improvement of Modified Jebsen Taylor Hand Function Test (MJTHFT) but not significant for FMA and handgrip dynamometer.[18]

Those studies results happened through the effect of anodal tDCS stimulation, although mechanisms on molecular basis are not well identified yet. Anodal tDCS depolarizes the neuronal membrane and glutamate is released by pre-synaptic neuron and binds in NMDA and AMPA receptors. Despite the depolarization, there is increase of intracellular Ca^{2+} in post synaptic neuron, which can activate protein kinase, such as Calcium/calmodulin-dependent kinase (CaMK). In a long-term mechanism CaMK activate cAMP-response element binding protein (CREB) which binds with BDNF promoter. This binding caused BDNF gene transcription to increase the BDNF secretion, as a neuroplasticity factor.[19]

This study has several limitations. First, the subjects were only subacute ischemic patients, so it is difficult to generate the results to all stroke patients. Second, the assesment of FMA was done by researcher himself, that the result may be influenced by subjectivity of the researcher. It is better to do double blind study for the further study.

Conclusion

Application of tDCS stimulation on occupational therapy simultaneously to subacute ischemic stroke patients for 5 days consecutively increased upper extremity motor function better than only occupational therapy.

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