Entomology and Applied Science Letters
Volume 5, Issue 3, Page No: 13-20

Available Online at: www.easletters.com

ISSN No: 2349-2864

Impact of Anodic Transcranial Direct Current Stimulation (TCDS) on Changes in Movement and Life–Related Functions in Patients with Chronic Ischemic Stroke: A Clinical Trial

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ABSTRACT

Stroke is one of the main causes of death; stroke survivors may suffer several neurological impairments. They typically show pathological enhanced neural activity in a number of areas in both hemispheres. Transcranial direct current stimulation (tDCS) can be applied to modify cerebral excitability, which has recently been applied for treatment of neurological disorders.

In this study, 100 patients with chronic ischemic stroke were divided into four groups of control, sham, anodic and cathodic tDCS (n=25). They took routine treatment, and received the same tDCS protocol (three times a week for 30 min per session during one month). Movement and cognitive functions were examined by the National Institute of Health Scale (NIHSS), Barthel index, and Rey test, before and 1 and 3 months after running tDCS sessions. The evaluation of changes in movements and cognitive functions in the chronic ischemic stroke patients was performed using anodic and cathodic tDCS. The results showed that 0-1 month after tDCS, 1-3 months after tDCS, and 0-3 months after tDCS, the NIHSS score and Barthel index significantly increased in the anodic with control, sham and cathodic groups, respectively (P<0.001). Moreover, the Rey test score in 0-1 month after tDCS and 0-3 months after tDCS significantly decreased in the cathodic with control, sham and anodic groups. In sum, anodic and cathodic tDCS have advantageous effects on movement and cognitive rehabilitation in stroke patients; however, this helpful effect was not equal in one domain. Future studies are needed to acknowledge this difference and represent precise treatment protocols.

Keywords: tDCS, life–related functions, chronic ischemic

HOW TO CITE THIS ARTICLE: Seyed Ahmad Hosseinzadeh, Shahrzad Mazhari, Kiomars Najafi, Meysam Ahmadi, Iraj Aghaei, Masuumeh Niazi, Mohammad Shabani*, Impact of anodic transcranial direct current stimulation (TCDS) on changes in movement and life–related functions in patients with chronic ischemic stroke: A clinical trial, Entomol Appl Sci Lett, 2018, 5 (3): 13-20 ,

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Received: 12/02/2018
Accepted: 28/07/2018

INTRODUCTION

Stroke is one of the main causes of death worldwide. It has high economic costs, and is the principal reason of incapacity. Stroke survivors may hurt numerous neurological impairments such as hemiparesis, communication disorders, and cognitive deficits in visuospatial perception. Approximately 50-60 percent of patients with stroke still practice several degrees of gross motor impairment [1,2]. It has been proven that a stroke which disturbs the cerebral cortex can cause broad spectrum of effects contingent upon the lesion site [3]. Today, the preferred options to treat the stroke usually encompass maintenance of the patient, preservation of

function in the brain area, and patient adaptation to reduced function. In this sense, new therapeutic modalities have been developed for monitoring patients after a stroke. In the acute phase of a stroke, a significant proportion of patients reveal motor signs including hemi-paresis or lower dexterity. After acute ischemic injury, retrieval from motor debits in the first few weeks and months after the stroke is mainly determined by neural organization. Nevertheless, most of stroke patients display an enduring motor discrepancy that impacts their everyday activities in spite of severe medical and physical therapy. Functional neuroimaging trials by means of PET or functional MRI have confirmed irregular cortical activation forms. In language domain, pathological activation patterns after stroke also reveal aphasia and impaired visuospatial attention network in patients with neglect [4]. In the motor domains, stroke patients naturally display pathologically improved neural activity in numerous areas both in the lesioned (ipsilateral) and healthy (contralesional) hemispheres [5]. The membrane polarization alter may, in turn, cause various variations in single-neuron synaptic and network activity, which might eventually be revealed in behavioral and cognitive variations [6]. In recent years, tDCS has been used to remedy neuropsychological and neurological impairments.

The use of tDCS affects the engagement of direct existing, which is a continual current of charged particles in one direction. Two surface electrodes are generally applied in contemporary tDCS protocols; one serving as the anode and the other as the cathode [7-9]. The direction and intensity of the current determine the current flows from the anode to the cathode, some being directed through the scalp and some moving through the brain leading to increase or decrease in cortical excitability [10-12].

The primary aim of anodal stimulation is up-regulation of excitability in the affected hemisphere. Anodal tDCS is delivered to M1 lesioned hemisphere. Behavioral improvements were along with the increased cortical excitability and decreased intracranial inhibition within M1 lesioned hemisphere, indicating the participation of glutamatergic and GABA ergic neurotransmission as the likely operating mechanisms [6,13]. Based on the lesion site, stroke-induced failure of a brain area can extent to undamaged regions linked to that node in both hemispheres. Enhanced inter-hemispheric coupling between homological areas seems to be a common feature of recognized resting-state networks after stroke, but it is often parallel to a reduced network efficiency in these patients [5]. Under the cathode, there will be extra positive ions such as sodium ions and their combination with water. Under the anode, however, there will be a corresponding accumulation of negatively charged ions such as chloride ions. The combination of these ions with water ions may produce basic (alkaline) reactions which are called electrochemical effects of direct current. Anodal motivation raises cortical excitability, when cathodal stimulation has the reverse effect [14,15].

The results and effects of tDCS application on stroke patients are controversial in related papers. Some studies have shown the positive effects of anodal tDCS on corticospinal excitability [16], upper limb motor recovery [16], enhanced motor skill learning after stroke [17], improving precision grip and dexterity of the paretic hand [18], increasing knee extensor force [19], facilitating motor recovery [20], performing motor sequence tasks after chronic stroke [21], and improving motor function [22]. On the other hand, some studies have shown the positive effects of cathodic tDCS, for example, neuroprotective effect of cathodal tDCS in a rat stroke model [14], improving hand dexterity and selective attention [23], and positive impacts on post-stroke unilateral visuospatial neglect [4]. Therefore, using well-known motor and cognitive criteria, the current research was designed to provide a better understanding of the anodic and cathodic tDCS functions in improving motor and cognitive functions in chronic stroke patients.

2. MATERIAL AND METHODS

2.1. Participants

The study population included 100 patients (male and female; aged between 41-75 years) who were divided into four groups. All of the subjects were patients with chronic ischemic stroke (between 3 weeks to 3months after stroke) in the subcortical ischemic of the middle cerebral artery territory who were admitted at the Tolou Clinic, Rasht, Iran. Magnetic resonance imaging (MRI) was performed to confirm lesion locations. Patients with other types of stroke were not included in order to reduce the heterogeneity of the study population.

Patients with heart pace maker or metal implants, seizure or drug-resistance epilepsy, and those who use neuroactive or psychoactive drugs, implant pumps, stimulators or shants and patients with brain tumors, dementia, drug

abuse and severe cognitive deficits were excluded.

All the patients took routine drugs and medications (such as physiotherapy), and were divided randomly into four groups: 1) control (taking routine treatment only) (N=25); 2) sham (N=25); 3) anodic tDCS (N=25); and 4) cathodic tDCS (N=25).

2.2. Transcranial direct current stimulation (tDCS)

TDCS was applied three times a week in 1month for 30 min per session by a battery-powered constant current electrical stimulator (at2-mA intensity using a pair of surface saline-soaked35 cm^2sponge electrodes (5×7cm). At 2mA, tDCS was considered a safe brain-stimulation technique that is associated with relatively minor adverse effects.

Two different electrode montages including an anode and a cathode were used. In anodal tDCS, the anode electrode was placed over the left superior temporalgyrus, while the cathode was placed over the contralateral superior region (cp5).

The current was flown through the brain and other tissues of the head from the anode to the cathodal electrode. In cathodal tDCS, the cathode was used for placing symmetrical to the left gyrus (cp6), while the anode was placed in the contralateral supraorbital region. In sham tDCS, the anode was placed over the left superior temporalgyrus and the cathode was placed on the contralateral supraorbital region, but no current was exerted (Fig. 1) [24,25].

All the patients received the same protocol three times a week, for 30 min per session in one month. Then, the evaluation tests were applied for the patients three months later after stopping the tDCS sessions.

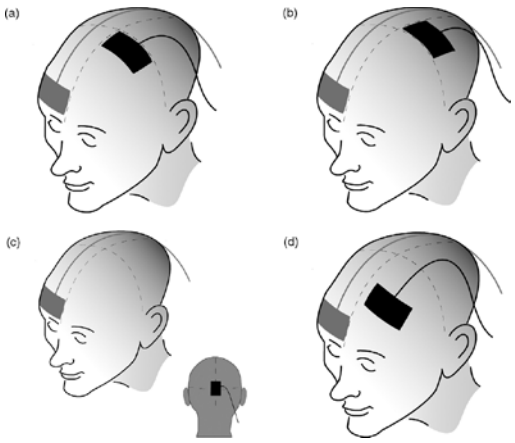

Fig1. Four typical tDCS electrode locations on the skull surface

The four figures illustrate the typical placement of anode and cathode during stimulation of the A) primary motor cortex; B) somatosensory cortex; C) primary visual cortex; and D) anterior language cortex. Note that in Fig. 1(C) one electrode is placed at the back of the head (see small image of the head), while the other electrode is placed at the right supra-orbital area. One electrode is placed on the area of the skull covering the target structure and the other electrode is typically placed either over the supraorbital area of the other hemisphere or over the corresponding area of the contralateral hemisphere. Note that other stimulation positions have been investigated as well [24].

2-3. Experimental procedure

All the participants were measured by two movement function scales (NIHSS & Barthel ADL index) and one cognitive function test (Rey test) for the evaluation of visual-executive memory before the tDCS sessions, one month and three months after the tDCS sessions.

2.3.1. National institute of health stroke scale (NIHSS)

Healthcare providers use The National Institute of Health Scale or NIHSS Stroke Scale (NIHSS) in order to measure the stroke-caused impairments objectively. The NIHSS consists of 11 items, each of which scores a specific ability between 0 and 4. For each item, a score of 0 typically indicates normal function in that specific ability, while a higher score shows some level of impairment. The singular scores from each item are summed for calculating a patient's total NIHSS score; the maximum possible score and the minimum score are 42 and 0, respectively [26].

2.3.2. Barthel index scale

To assess performance in daily life activities, the Barthel scale or Barthel ADL index which as an ordinal scale, is used. Each performance item is rated on this scale with a given number of points assigned to each level or ranking. It uses ten variables describing AD and with a degree of independence after discharge from the hospital [27].

2.3.3. Rey test

The Rey test is a neuropsychological assessment in which the examinees are asked to reproduce a complicated line drawing first by copying versus freehand (recognition) and then by drawing from memory (recall). Many different cognitive abilities are needed for a correct performance, and therefore the test permits the evaluation of different functions such as visuospatial abilities, memory, attention, planning and working memory (executive memory). Moreover, it is frequently used to further explain any

secondary effect of brain injury in neurological patients to test the presence of dementia, or study the degree of cognitive development among children [28].

2.4. Statistical analysis

All data was expressed as mean ± SEM and analyzed using SPSS software (version 18. IBM, USA). Two-way repeated measures ANOVA was applied for assessing difference between the groups, time of treatment and group interaction × time of treatment. Individual comparisons were made by Tukey's test. A value of P<0.05 was considered to be significant statistically. The result of the two-way repeated measures ANOVA showed that there was significant difference between the groups before the initiation of tDCS protocol and within the groups or treatment time (P<0.0001). Furthermore, the group interaction ×treatment time was significant (P<0.0001) suggesting that the effects of the groups in different times were significant on rehabilitation of chronic stroke. Therefore, applied repeated measures ANOVA test was applied for assessing time difference between 0-1 month after tDCS, 1-3 months after tDCS, and 0-3 months after tDCS protocol between the groups.

3. Results

The demographic characteristics of the study analysis showed that the four groups did not differ in age, sex, time of post stroke treatment and lesions region (Table 1).

Table 1. Biographical information and distribution of groups

	Control	Sham	Anodic	Cathodic	P Value
Age, Mean ± SE	59.4±1.62	59.1±1.43	57.96±1.56	60.4±1. ±34	0.72
Time of post stroke treatment Mean ± SE	39.13±3	33.88±1.27	33.56±1.11	33.21±1.27	0.074
Gender, Female (%)	13 (52%)	13	12	13	0.98
Right Lesion side, number (%)	10 (40)	11	11	11	0.98

4.1. The effects of anodic and cathodic tDCS on NIHSS test

The result of the two-way repeated measures ANOVA followed by Tukey HSD test showed that there was a difference in the NIHSS score between the three times: 0-1 month after tDCS, 1-3 months after tDCS, and 0-3 months after tDCS. The difference significantly increased in the anodic tDCS group with the control, sham and cathodic tDCS groups (P<0.001). However, comparing the cathodic tDCS group with the sham group showed that the difference in the NIHSS score significantly decreased between the two times 0-1 month after tDCS and 0-3 months after tDCS (P<0.05 and 0.001), respectively (Fig. 2).

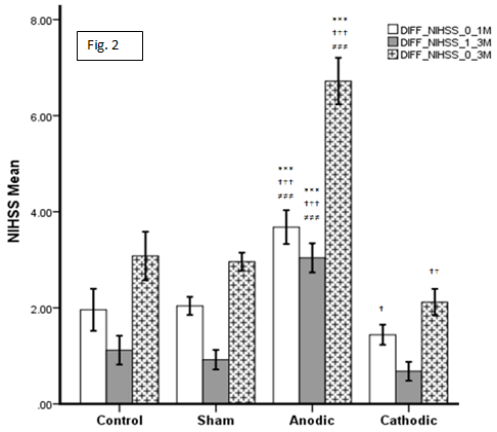

Fig 2 . The effects of anodic and cathodic tDCS on the difference changes of NIHSS score among the groups in the three times: before - 1 month after tDCS , 1 - 3 months after tDCS , before - 3 months after tDCS treatment;. ***p<0.001 as compared to the control group; †p<0.05, ††p<0.01and ††† p<0.001 as compared to the sham group; ###p<0.001 as compared to the cathodic tDCS group. ANOVA was followed by Tukey's post-hoc test.

4. 2. The effects of anodic and cathodic tDCS on Barthel index test

The result of the two-way repeated measures ANOVA followed by Tukey HSD test showed that there was a difference in the Barthel index test result between the three times: 0- 1 month after tDCS, 1-3 months after tDCS, before - 3 months after tDCS treatment. The difference significantly increased in the anodic tDCS group with control, sham and cathodic tDCS groups (P<0.001). Furthermore, the difference in the Barthel index test's results between the cathodic tDCS group and the sham group significantly decreased 0-1 month after tDCS and 0-3 months after tDCS (P<0.01 and 0.05, respectively; Fig. 3).

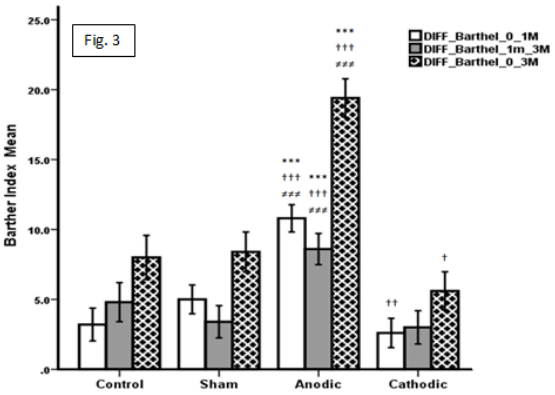

Fig 3. The effects of anodic and cathodic tDCS on the difference changes of Barthel index among the groups in the three times: before - 1 month after tDCS, 1 - 3 months after tDCS, and before - 3 months after tDCS treatment; ***p<0.001 as compared to the control group; †p<0.05††p<0.01and ††† p<0.001 as compared to the sham group; ###p<0.001 as compared to the cathodic tDCS group. ANOVA was followed by Tukey's post-hoc test.

.3 The effects of anodic and cathodic tDCS on Rey test

The result of the two-way repeated measures of ANOVA followed by Tukey HSD test showed that there was a difference in the Rey test score 0-1 month after tDCS. Accordingly, the test score significantly decreased in cathodic tDCS group as compared to the control, sham and anodic tDCS groups (P<0.05, P<0.001, P<0.001, respectively). While 0-3 months after tDCS, the difference significantly decreased between the groups equally (P<0.001). However,1-3 months after tDCS, the decrease in cathodic tDCS was significant in the control group (P<0.001) (Fig. 4).

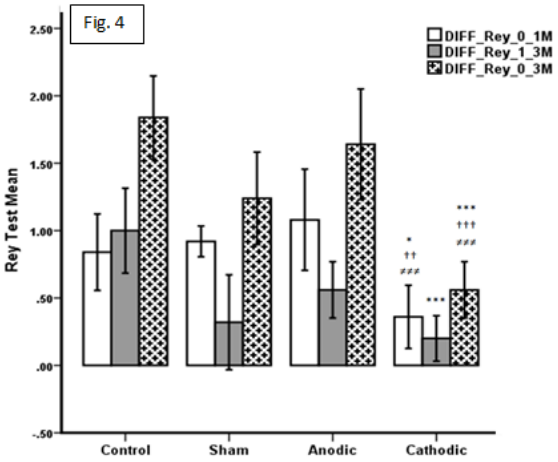

Fig 4. The effects of anodic and cathodic tDCS on the difference changes of Rey test among the groups in the three times: before - 1 month after tDCS, 1 - 3 months after tDCS, and before - 3 months after tDCS treatment; *p<0.05 and ***p<0.001 as compared to the control group; ††p<0.01 and ††† p<0.001 as compared to the sham group; ###p<0.001 as compared to the anodic tDCS group. ANOVA was followed by Tukey's post-hoc test.

5. DISCUSSION

The aim of the current study was to investigate the potential therapeutic effects of anodic and cathodic tDCS protocol in chronic stroke patients. The results showed that anodic tDCS application led to positive improvements in movement (based on the NIHSS scores) and life related functions (based on the Barthel index scores). However, on the executive memory, based on the Rey test, cathodic tDCS had a positive effect. Although the cause of tDCS effects on movement, life-related and executive functions could not be found, the findings of this study showed that this procedure had multiple positive facets on rehabilitation of chronic stroke patients.

A number of studies, like the present research, have shown that anodic tDCS had positive effects on stroke. Anodic tDCS may help motor function of the paretic upper limb in patients suffering from chronic stroke [16]. Another study on stroke survivors showed that anodic tDCS can improve selective attention [23], motor skill learning, long term retention [29] and the behavioral gains[30].

Dual tDCS was used during motor skill learning with a paretic upper limb and resulted in extended shaping of brain activation, which helped behavioral improvements in stroke patients [18]. Moreover, dual-tDCS enhanced the motor control of precision grip and digital dexterity beyond the time of stimulation [17]. These studies have suggested that dual-tDCS

should be tested in longer protocols for neurorehabilitation of moderately and severely impaired patients [17]. [19] indicated that single session of tDCS transiently increased knee extensor force in patients with hemiparetic stroke. In two other studies, it was distinguished that tDCS application had a potential for enhancing the effectiveness of gait training in chronic stroke [31,32].These studies were similar to the present study in terms of the obtained findings.

Moreover, the advantages of tDCS for movement training were proved in many studies. In a pilot study, the tDCS combined with robot-assisted gait training indicated positive changes in chronic stroke [33,34]. Other studies revealed that the combination of bihemispheric tDCS and peripheral sensorimotor activities improved motor functions [20], motor sequence task and reaction time in patients with chronic stroke [21,22,35,36].

On the other hand, our results showed that cathodic tDCS improved the Rey test score. Similar to the present study, there have been some studies indicating the beneficial effects of cathodic tDCS on stroke, like improved hand dexterity and selective attention [23] and positive effects on post-stroke unilateral visuospatial neglect [4]. However, some other studies have revealed that anodal tDCS makes a long-term beneficial effects on aphasia improvement, and improves post-stroke unilateral visuospatial neglect and has good impacts on motor perception in subjects with occipital stroke [37].

According to the results of the present research and other studies mentioned above, it can be said that although tDCS has not been used for so long in the neurology and treatment of diseases such as stroke, based on the few papers available, it can be declared that using this method in the near future would offer promising prospects to researchers.

It seems that the increasing use of this method and its cost-effectiveness would have significant effects on reducing the cost of treatment. Ease of use and very high safety for patients can be mentioned as some of the other benefits of this method for reducing disabilities of people with stroke.

Finally, the results of the present study demonstrated that anodic tDCS was a helpful and safe method for increasing the rehabilitation of movement and life-related functions in chronic stroke patients. However, cathodic tDCS was observed to enhance executive memory. The capability of anodic tDCS to modulate cortical excitability becomes useful; however, further investigation is required to explore which one (anodic tDCS or cathodic tDCS) is preferred.

6. Conflict interest

The authors declare no conflict of interest.

7. ACKNOWLEDGEMENT

This work was supported by the Kerman Neuroscience Research Center, Kerman, Iran and the Kavosh Research Center for Behavioral-Cognitive Sciences and Addiction, the Guilan University of Medical Sciences, Rasht, Iran. The authors also thank Professor Sheibani, Dr. Shabani and Dr. Esmaeilpour for their kindness, assistance and considerations (ethics code number IR.KMU.REC.1395.234).

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