Enhancement of Motor Recovery through Left Dorsolateral Prefrontal Cortex Stimulation after Acute Ischemic Stroke

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Background: Two previous studies, which investigated transcranial direct current stimulation (tDCS) use in motor recovery after acute ischemic stroke, did not show tDCS to be effective in this regard. We speculated that additional left dorsolateral prefrontal cortex (DLPFC) stimulation may enhance poststroke motor recovery. *Methods:* In the present randomized clinical trial, 20 acute ischemic stroke patients were recruited. Patients received real motor cortex (M1) stimulation in both arms of the trial. The 2 arms differed in terms of real versus sham stimulation over the left DLPFC. The motor component of the Fugl-Meyer upper extremity assessment (FM) and Action Research Arm Test (ARAT) scores were used to assess primary outcomes, and nonlinear mixed effects models were used for data analyses. *Results:* Primary outcome measures improved more and faster among the real stimulation group. During the first days of stimulations, the sham group's FM scores increased by 1.2 per day, while the real group's scores increased by 1.7 per day ($P = .003$). In the following days, FM improvement decelerated in both groups. Based on the derived models, a stroke patient with a baseline FM score of 15 improves to 32 in the sham stimulation group and to 41 in the real stimulation group within the first month after stroke. Models with ARAT scores yielded nearly similar results. No significant adverse effect was reported. *Conclusion:* The current study results showed that left DLPFC stimulation in conjunction with M1 stimulation resulted in better motor recovery than M1 stimulation alone. **Key Words:** Transcranial direct current stimulation—acute ischemic stroke—function recovery—rehabilitation.

Introduction

Transcranial direct current stimulation (tDCS) has been useful in enhancing motor recovery after stroke in the subacute and chronic stages.[1] However, only 2 studies have investigated tDCS use in recovery from acute ischemic stroke.[2,3] Rossi et al showed that 5 daily sessions of anodal primary motor cortex (M1) stimulation were safe among acute ischemic stroke patients but did not improve patients' motor impairment.[3] Di Lazzaro et al used bihemispheric (anodal stimulation of ipsilesional M1 and cathodal stimulation of contralesional M1) M1 stimulation instead of anodal stimulation.[2] Although they did not find any clinical benefits, real stimulation increased long-term potentiation–like plasticity of M1 after 1 week and M1 excitability after 3 months.[2] They postulated that clinical outcomes were not sensitive enough to capture tDCS benefits.

Functional imaging has shown that the use of tDCS results not only in the activation of its target brain area but also in the activation of other cortical and subcortical brain areas.[4,5] Vaseghi et al showed that the anodal

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stimulation of the dorsolateral prefrontal cortex (DLPFC) resulted in the activation of the M1 in healthy volunteers.[6] They also showed that dual-site costimulation of the DLPFC and the M1 increased motor evoked potentials (MEPs) of the right first dorsal interossei muscle 50% more than when first dorsal interossei MEPs were measured after stimulating the M1 (usual tDCS anodal stimulation).[7]

Left DLPFC stimulation also has cognitive and behavioral effects. Its stimulation has been used in the treatment of depression,[8] and depression is more common among stroke survivors than elderly individuals without a history of stroke.[9] Cognitive impairment is another major problem after stroke. Even after minor strokes, about half of stroke patients illustrate impairment in at least 1 cognitive test,[10] and DLPFC stimulation improves learning[11] and decision making.[12] Thus, stimulation of the left DLPFC in addition to the M1 may enhance motor recovery through other pathways such as improved learning and reduced depression symptoms.

The first goal of the present study was the evaluation of the efficacy and safety of extending conventional M1 stimulation by the addition of DLPFC stimulation in motor impairment recovery after acute ischemic stroke. The second goal was the evaluation of the feasibility of tDCS use in acute ischemic stroke treatment in a developing country.

Methods

Patients

Acute ischemic stroke patients who were admitted to an academic hospital and had upper extremity paresis were recruited in this study. Their brain lesions were confirmed through diffusion-weighted imaging sequences of magnetic resonance imaging. Muscle forces of shoulder abduction and finger extension of the paretic upper extremity were scored using the UK Medical Research Council scoring system. Patients were recruited if the summation of the scores of their shoulder abduction and finger extension forces in the paretic arm was more than 0 and less than 9. The exclusion criteria consisted of decreased level of consciousness, Global or Wernicke's aphasia due to stroke, prestroke dementia, any metal head implants, any severe comorbidity such as severe kidney or renal impairment, and inability to return for follow-up visits (i.e., referral patients from rural areas).

Twenty patients were recruited and randomized to the real and sham groups through blocked randomization using the sealed envelope website. All of the patients or their families signed the consent forms, and the study was approved by the ethics committee of the Tehran University of Medical Sciences, Iran.

tDCS

The current, generated by DC stimulators made in Iran, was delivered through saline-soaked sponges $4 \times 4\ cm^2$ in size. The real stimulation was 2.0 mA for 30 minutes with 30 seconds of fade in and fade out, while the sham stimulation was 2.0 mA for 10 seconds with the same fade-in and fade-out duration.

In both real and sham groups, patients received real stimulation at the M1 with the anode and cathode over C3/C4 of the affected and unaffected hemispheres, respectively. Then, the left DLPFC was stimulated by real/sham tDCS, with the anodes over F3 and the cathodes over the right supraorbital ridges. Each patient received the treatment for 10 sessions over 2 weeks.

Outcome Assessment and Statistical Analysis

The motor component of the Fugl-Meyer upper extremity assessment (FM) and Action Research Arm Test (ARAT) scores were used to assess the primary outcomes. A blinded investigator (H.O.) performed the stimulations and assessments. Outcome assessment was conducted at baseline, after 10 sessions of stimulation, and 1 month and 2 months after the stimulations.

Mixed effect models were used to study FM and ARAT changes during the days after the stroke, and maximum likelihood was used for the estimation of parameters. First, the linear model was fitted to the changes. Then, nonlinear components were added by the addition of quadratic, cubic, and quartic components to the linear model. The deviance statistics of the models were compared using the chi-square test to select the best-fitting model.

After the selection of the best model, the stimulation type (true versus sham) was added to the model to determine whether it would make the model fit parameters better. First, stimulation type was added to the linear growth component (interaction between time and stimulation type) and the initial level of the outcome variable (i.e., FM score). Then, stimulation type was added to other components of the model (quadratic and cubic time components). Ultimately, other variables of interest, such as sex and affected hemisphere, were added to the model to determine whether the stimulation effect would change across prespecified strata. SPSS software (version 20.0; SPSS Inc., Chicago, IL) was used for the analyses.

Results

Table 1 shows patients' baseline characteristics. Although real tDCS group patients were about 13 years younger than sham group patients, the difference was not statistically significant ($P = .06$). Except 1 patient who was stimulated 20 days after the onset of his symptoms, other patients started their stimulation within the first 4 days of their stroke.

None of the patients had received thrombolytic therapy or thrombectomy. The baseline scores of the National Institutes of Health Stroke Scale (NIHSS) were higher in the real DLPFC stimulation group than the sham group; however, the difference was not significant. The 2 most