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Safety of cathodal transcranial direct current stimulation early after ischemic stroke

Introduction

According to the hypothesis of interhemispheric inhibition, the unaffected motor cortex ($M1_{UH}$) may excessively inhibit the motor cortex of the affected hemisphere ($M1_{AH}$) in subjects with stroke leading to exaggeration of the contralateral upper limb paresis. TDCS can be used to either inhibit $M1_{UH}$, excite $M1_{AH}$, or both. Typically, anodal tDCS increases brain excitability and cathodal tDCS (ctDCS) has the opposite effect [1].

Increased excitation of $M1_{AH}$, either directly by ipsilesional anodal tDCS or indirectly by cathodal tDCS of the unaffected hemisphere ($ctDCSM1_{UH}$) might be harmful when applied early after stroke, as suggested by findings of increase in infarct size after anodal tDCS [2] and decrease in cerebral blood flow after ctDCS in rats [3]. Even though no serious adverse events have been reported in humans with stroke, few studies provided detailed information about tolerability and safety of this intervention [4].

We compared safety and tolerability between real and sham stimulation in thirty patients receiving $ctDCSM1_{UH}$ within the first six weeks after stroke.

Methods

Inclusion and exclusion criteria as well as characteristics of the patients are shown in the Supplementary Material.

Patients were randomized to receive either active $ctDCSM1_{UH}$ or sham prior to physical therapy, three times a week, over two weeks. In each session, a sponge anode (7×5 cm) soaked in saline solution was placed over the ipsilesional supraorbital area. The cathode was placed on the contralesional C3/C4 position. The intensity of stimulation was 1mA, ramps up and down lasted for 10 seconds (DC-stimulator plus, Neuroconn, Germany). In the active group, tDCS was applied for 20 minutes and in the sham group, for 30 seconds. Visual inspection of the skin under the electrodes was performed after each session.

The primary outcome was the frequency of adverse events. A blinded investigator asked patients about symptoms with a standard questionnaire adapted from Fertonani et al. [5]. MRI was performed before the first, and after the last session of treatment.

Frequencies of adverse events were compared with chi-square or Fisher's exact tests. Infarct volumes were analyzed with Generalized Estimating Equations (GEE) with factors TIME and GROUP.

Results

The most common adverse events were paresthesias under the anode in both groups (Table 1). Sleepiness was more frequent after active than sham $ctDCSM1_{UH}$ but the between-group difference was not statistically significant.

One patient in the active group (Supplementary Material) spontaneously reported paresthesias in the paretic arm during $ctDCSM1_{UH}$. During the first session of treatment at 11 days post-stroke, the patient reported tingling on the entire palm of the hand and the medial portion of the right forearm. The paresthesias started 5 min after the onset of stimulation and ceased immediately at its end. The patient denied having similar symptoms before. His right arm was not positioned in a way that might favor compression of the ulnar nerve. The neurological examination remained unchanged. The patient refused to undergo another MRI due to claustrophobia. An EEG was normal. He reported no paresthesias in the following sessions of active $ctDCSM1_{UH}$ and completed the study uneventfully. He was assessed three months later and denied any further symptoms.

Infarct volumes were 39.8 ± 46.6 cm^3 before treatment and 35.3 ± 45.9 cm^3 post-treatment for the active group, 25.2 ± 35 cm^3 before treatment and 22.3 ± 32.9 post-treatment for the sham group. GEE revealed a significant main effect of TIME ($p < 0.001$) but no effect of GROUP ($p = 0.418$) or GROUP x TIME interaction ($p = 0.458$). Volumes decreased in both groups after treatment, compared to before treatment ($p < 0.001$). There were no recurrent strokes in either group.

Discussion

The main finding of this study is that active $ctDCSM1_{UH}$ was safe and well tolerated when administered within the first weeks post-ischemic stroke.

In a meta-analysis of adverse events in studies with various types of tDCS montages and intensities in heterogeneous conditions, paresthesias and erythema under the electrodes were significantly more frequent in the active than in sham groups [6]. Three factors likely contribute to the discrepancy between these results and our findings: First, the meta-analysis predominantly included conditions other than stroke (pain, migraine, tinnitus, schizophrenia and depression) and dissimilar tDCS paradigms, stimulation intensities and number of repeated sessions, while our study was concerned only to early stroke patients submitted to 6 sessions of fixed intensity stimulation (1 mA) over the unaffected

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Table 1
Frequency of adverse events in the active and sham groups.

Adverse event	Active (%)	Sham (%)	P-value[a]
Paresthesias under anode			
Tingling	84.6	78.6	>0.999
Itching	69.2	57.1	0.695
Pinching	15.4	21.4	>0.999
Shock	7.7	21.4	0.596
Stinging	0	28.6	0.098
Bite	0	21.4	0.222
Undefined sensation	15.4	21.4	0.999
Sleepiness	61.5	28.6	0.085
Skin redness under anode	15.4	14.3	>0.999
Decreased concentration	7.7	0	0.481
Fatigue	7.1	0	0.481

[a] Chi-square or Fisher's exact tests.

hemisphere. Second, the collection of data in most of the studies included in the meta-analysis was retrospective, while we used standardized questionnaires and performed a systematic inspection of the skin under the anode. Third, it is possible that, because of our relatively small sample size, our statistical analysis was underpowered for showing significant differences between real and sham tDCS groups.

The rate of sleepiness during tDCS was nonsignificantly more than twice greater in the active than in the sham group. Whether tDCS of M1 may promote on-line changes in arousal in subjects with stroke, deserves further examination.

For the first time, we report paresthesias after ctDCSM1$_{UH}$ *ipsilateral* to the symptoms. Paresthesias in the contralateral upper limb were described in healthy subjects during single-pulse or 20Hz transcranial magnetic stimulation (rTMS) of the contralateral postcentral gyrus [7,8]. Also, paresthesias were reported after anodal tDCS of the contralateral M1 in a healthy subject [9]. In this case, the symptom was considered to be part of a migraine aura. Despite the fact that our patient had history of migraine, we consider unlikely that paresthesias could represent a first-ever aura because they were not followed by headache, nausea or vomiting. We hypothesize that disinhibition of the affected hemisphere by ctDCSM1$_{UH}$, at an early stage after stroke when increased excitability of the perilesional tissue is expected, may have led to the symptoms. Because paresthesias are subjective, we cannot completely rule out a functional symptom restricted to the first session of treatment in our patient.

The lack of recurrent strokes or enlargement of lesions post-treatment in either group abates concerns about possible tissue injury caused by ctDCSM1$_{UH}$ delivered early after stroke [3]. Interestingly, a potential neuroprotective role of ctDCSM1$_{UH}$ in humans with stroke has been recently suggested [10].

Conclusions

No serious adverse events occurred during CtDCSM1$_{UH}$ within the first weeks post-ischemic stroke.

Declarations of interest

None.

Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2018.11.009.

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