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Effect of Transcranial direct current stimulation (tDCS) on altered conscious patients after traumatic brain injury & cerebrovascular accident: A randomized clinical control trial

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Abstract

Background & Objective: Traumatic brain injury and cerebrovascular accidents can result in altered levels of consciousness. This study is aimed at finding the effect of transcranial direct current stimulation (tDCS) on the level of consciousness in these patients. *Methods*: A total of 100 patients admitted to the neurological ICU of the hospital were screened and 40 subjects after satisfying inclusion criteria were recruited within the first one to two weeks of injury. They were randomly divided into two groups after written consent from a caretaker, Group A (experimental) (n=20) and Group B (control) (n=20) by computerized randomization. Group A received Anodal tDCS to the motor area (C3/C4 ipsilesional), sensory area (P3/P4 ipsilesional) and left dorsolateral prefrontal cortex (F3) according to the 10/20 EEG montage for two sessions of 20min/day for 7 consecutive days and routine physiotherapy. Group B only received routine physiotherapy similar to Group A. Glasgow coma scale (GCS) and Rancho Los Amigos scale (RLAS) was taken pre and post- intervention to assess the level of consciousness. *Results:* The pretest and post- test GCS and RLAS scores in groups A and B showed statistical significance at $p<0.01$. The differences of mean GCS and RLAS between pretest and posttest in group A showed better improvement than that of group B. The results were statistically significant at $p<0.01$. The effect size was large, calculated by Cohen's d.
Conclusion: The tDCS can be effective in improving GCS and RLAS in altered consciousness patients in the acute period after injury. It is non-invasive, cost-effective with minimal contraindications, and doesnot interfere with other modalities in the intensive care unit.

Keywords: Coma, traumatic brain injury, cerebrovascular accident, tDCS, physiotherapy, altered consciousness

INTRODUCTION

Consciousness is the awareness of self and environment.[1] Vascular insult to the brain can cause altered levels of consciousness. Traumatic brain injury (TBI) and cerebrovascular accident (CVA) can result either in minimally conscious state, coma or vegetative state (VS).[3,4] TBI is a serious public health issue that affects people all over the world.[5] In India and other developing nations, traumatic brain injuries are the primary cause of illness, mortality, disability, and economical losses.[5] An average of 1.5 to 2 million people get admitted to hospitals with head trauma in India every year with a high mortality rate. TBIs are most commonly caused by road traffic accidents followed by falls and violence.[6] About 17% of patients who survive a TBI, experience a period of total unconsciousness or, coma in which they are completely unaware of themselves or their surroundings.[7] cerebrovascular accidents are the second largest cause of death globally, with around 5.5 million deaths each year. Stroke has a high death rate, but it also has a high morbidity rate, resulting in up to 50% of survivors being

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permanently disabled.[8]Stroke prevalence rates in rural areas range from 84-262/100,000, while in urban areas they range from 334-424/100,000.[9]

A disruption in the function of the brainstem reticular activating system (RAS) in the brain stem, or both cerebral hemispheres and thalamus causes coma.[10] Depending on the severity of the brain damage, a coma can last anywhere from hours to days, and some patients can be comatose for months or even years.[11] Several secondary complications develop in comatose patients which can impact the survival rate. From previous studies, it is evident that a long-term unconscious state can negatively impact rehabilitation outcomes.[7,12]

There are various protocols available for attaining post - comatose arousal responses. Various investigators have exemplified that coma arousal therapy is in improving the Glasgow Coma Scale (GCS) of the patient. Currently, available literature emphasizes that sensory stimulation can alleviate the disorder of consciousness. Along with medical management of unconscious patients; multimodal sensory stimulation is used to attain an arousal response.[13] Though these therapies are promising, they take a lot of time for the physician and recovery.

Transcranial direct current stimulation (tDCS) is a non-invasive neurostimulation technique in which a weak polarizing current modulates cortical excitability.[14] It has been used as a non-pharmacological and non-invasive brain stimulation tool to treat neurological ailments and in rehabilitation for over 100 years. It is best known for its capacity to induce neuroplasticity in different brain areas.[15]

This study is aimed at finding the effect of tDCS on altered conscious patients after traumatic brain injury and cerebrovascular accident. The study's objectives are to assess the level of altered consciousness and activity after traumatic brain injury or cerebrovascular accident using GCS and RLAS, and assess the improvement in the GCS and RLAS scores post tDCS application. The level of consciousness is the primary outcome assessed pre- test and post- test by GCS. The level of activity of the subject is the secondary outcome measured by RLAS.

METHODS

Enrollment and recruitment

This study was conducted at the department of neurology and neurosurgery in association with the Physiotherapy department of the university hospital from February 2021 to May 2021. It is a randomized control trial. A total of 100 patients admitted to the neurological intensive care unit were screened and 40 subjects after satisfying inclusion criteria were recruited and randomly divided into two groups, Group A (experimental) (n=20) and Group B (control) (n=20) by computerized randomization. Written informed consent was taken from all the caretakers of the patients before recruitment. All patients having altered levels of consciousness more than 6 hours after TBI or hemorrhagic CVA (bleeding not more than 30 ml) with GCS ≤8, both conservatively and surgically managed patients, have stable cardiac functioning were included in this study. Patients having unconsciousness other than TBI or CVA, ischemic CVA, diffuse axonal injuries, cardiac pacemaker, electric implant in the brain (DBS), scalp dermatitis, infections to CNS, and previous history of epilepsy were excluded from the study. (Figure 1)

This study got ethical clearance from the institutional ethical committee and the trial is registered with Clinical trials of India (CTRI) no: CTRI/2020/07/026553

Intervention

Group A Experimental: After taking the preliminary assessment, anodal transcranial direct current stimulation was given to the motor area (C3/C4 ipsilesional), sensory area (P3/P4 ipsilesional) and left dorsolateral prefrontal cortex (F3) according to the 10/20 electroencephalogram (EEG) montage. The current used in this study was direct continuous in nature having intensity 2.0 mA. The scalp is shaved using a sterile razor. Before the application of electrodes, the scalp was cleaned with an antiseptic solution and dried. Anodes (active electrodes) were placed at the P3/P4, F3, C3/C4 position according to the 10/20 international EEG montage. (Figure 2) Cathode was placed at the opposite shoulder as a reference electrode. The electrodes used were 1.6 cm^2 in area, self–adhesive and conductive. The individual leads connecting the active electrodes were fused into a single channel by a port and connected to the positive terminal of the machine. The indifferent electrode is connected to the negative terminal of the machine. Treatment was given for two sessions of 20 minutes per day for 7 consecutive days. After winding off, any scalp changes were not noted. Routine physiotherapy was also given similar to group B.

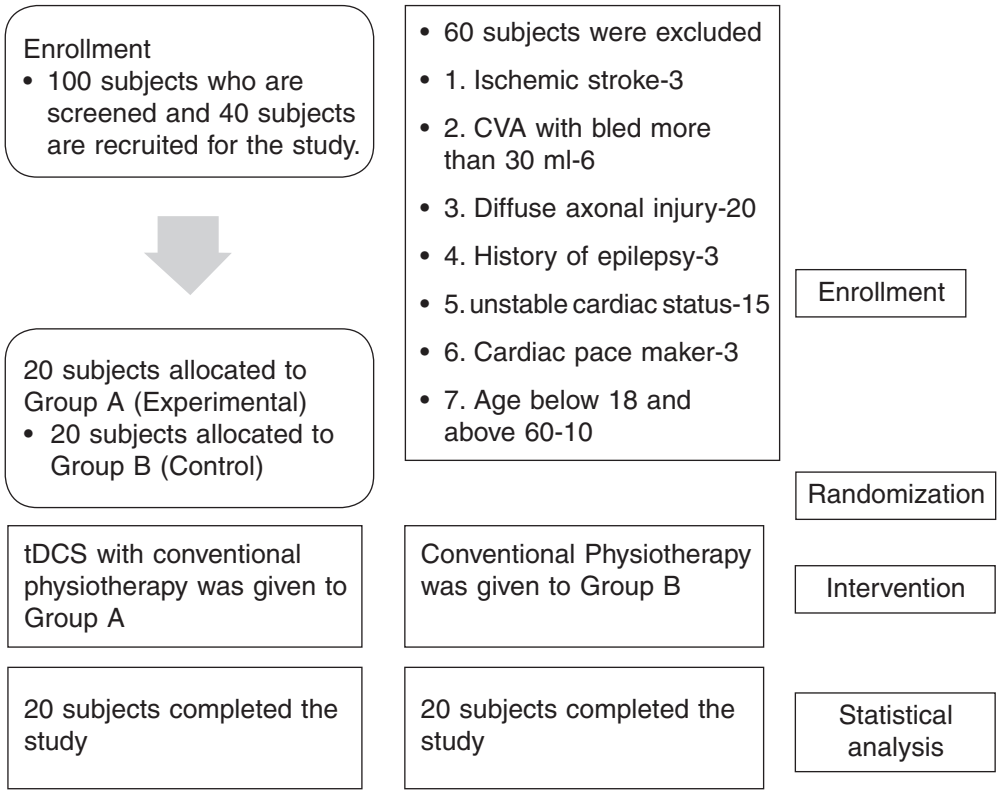

Figure 1. Consort Flow Chart

Group B Control: Routine physical therapy was given for 30 minutes twice daily for 7 consecutive days. The therapy includes the following:1. Passive movements- 10 repetitions of full range of motion exercises of each joint; 2. Bed making and change of positions; 3. Electrical muscle nerve stimulation.

Both Group A and Group B received chest physiotherapy and medical care as per the

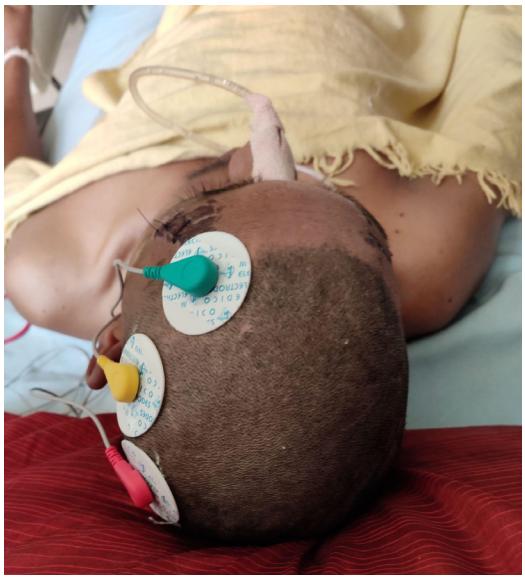

Figure 2. Electrodes placement for tDCS

guidelines of the Neurologist or Neurosurgeon of the University hospital. The subjects in Group A and Group B received interventions under the same environment and handled by the same physiotherapist who has taken the preliminary assessment.

Outcome measures

All the demographic characteristics of the subjects were recorded at the time of enrollment and recruitment of subjects. The altered level of consciousness was assessed using the GCS and RLAS at the time of enrollment (t0), and on days 7 post- intervention (t1). The level of consciousness is the primary outcome assessed pre- test and post- test by GCS. The level of activity of the subject is the secondary outcome measured by RLAS.

GCS is used to objectively describe the level of altered consciousness. The scale evaluates patients' responsiveness in three areas: eye-opening (4), motor (6), and verbal (5) responses. Inter-rater reliability of GCS is good.[16,17] The RLAS describe the cognitive and behavioral pattern found in brain injury patients as they recover from injury. It has eight levels. The maximum score is 8 and minimum is 1. It has good inter-rater reliability and validity.[18]

Statistical analysis

In this study to analyze the role of tDCS on altered consciousness patients, the preliminary baseline data were compared using Mann Whitney U test and assessed for normality. (Table 1). All pretest and posttest scores of GCS and RLAS were expressed as Mean +/- Standard deviation (SD) and were statistically analyzed using paired t test within the groups and unpaired t tests between the groups 95 % level of significance. (Table 2) To explore the practical significance of group differences, the effect size was calculated. The established criteria of the effect size, which reflects the effect of treatment within a population of interest, are small (<0.41), medium (0.41 to 0.7), or large (> 0.70).

RESULTS

A total of 20 subjects in each group completed the study. The data was analyzed for statistical significance. At baseline, there were no significant group differences in the baseline characteristics. The groups passed the normality test. (Table 1).

The pretest and posttest GCS scores in Group A showed statistical significance at $p<0.01$, and in Group B at $p<0.01$. (Table 2).

The differences of mean GCS between pretest and posttest in Group A showed better improvement than that of group B. The results are statistically significant at $p<0.01$. The RLAS scores showed more improvement in Group A

Table 1: Baseline demographic characteristics of Group A and Group B

Characteristics	Group A (Experimental)	Group B (Control)	P Value
Age*	38+/-10.95	43.2+/-12.84	p>0.05
Sex (Male : Female)	13:7	14:6	p>0.05
Side of Injury (Right:Left)	12:8	11:9	p>0.05
Type of management Conservative: Surgical (Craniectomy, VP shunt,etc)	13:7	15:5	p>0.05
TBI :CVA	13:7	11:9	p>0.05
Number of days between incidence of TBI/CVA and recruitment*.	7.2 +/-1.8	7.6+/-1.2	p>0.05
SBP*	129+/-9.49	130.9+/-7.64	p>0.05
DBP*	80.52+/-6.48	84.9+/-6.05	p>0.05
Pulse (BPM) *	75.17+/-6.15	79.35 +/-6.36	p>0.05
Temperature (°F) *	97.69+/-1.29	78.17+/0.97	p>0.05
Respiratory Rate (Cycles per minute) *	19.82+/-2.26	21+/-1.91	p>0.05

** Mean +/-SD , TBI- Traumatic brain Injury, CVA- cerebrovascular accident, SBP-Systolic blood pressure, DBP-Diastolic blood pressure, BPM- Beats per minute.*

Table 2: Comparison of pre-test and post-test GCS and RLAS in Group A and B

Variable	Group A				Difference		Group B				Difference		p Value
	Pre test		Post test				Pre test		Post test		Mean	SD+/-	
	Mean	SD+/-	Mean	SD+/-	Mean	SD+/-	Mean	SD+/-	Mean	SD+/-			
GCS	5.57	1.39	10.42	1.91	4.85	1.42	5.9	1.16	6.9	01.37	0.64	0.64	P<0.05
RLAS	1.23	0.43	4.71	1.14	3.4	0.70	1.3	0.47	1.65	0.75	00.35	0.27	P<0.05

than group B. To explore the practical significance of group differences and the impact of tDCS on GCS and RLAS scores in altered consciousness patients, the effect size was calculated by Cohen's d, the results show that there is a large effect of tDCS on motor recovery. (3.8 & 5.8). At the end of the treatment session, no adverse effects were found on the subjects. The possible adverse effects would be scalp burn due to accumulation of chemicals under the electrode, erythema. All the necessary precautions were taken before the administration of tDCS.

DISCUSSION

In this study to assess the effect of tDCS on altered conscious patients, the results revealed that there was a significant improvement in the GCS and RLAS scores when tDCS was given to patients with altered consciousness. The effect size revealed that tDCS has a large effect and practical significance on GCS and RLAS scores in altered conscious patients.

tDCS is a non-invasive neurostimulation technique in which a weak polarizing current modulates cortical excitability.[14] Anodal stimulation depolarizes the neurons hence increases excitability and cathodal stimulation hyperpolarizes the neuron hence decreases excitability.[19] The tDCS not only changes the electrical neuronal membrane potential but it also changes N-methyl-d-aspartate (NMDA) and gamma-amino-butyric acid (GABA) receptors effectiveness.[20] It shows long- term potentiation (LTP) plasticity and long- term depression (LTD) plasticity. Anodal stimulation decreases GABAergic activity and increases glutamatergic activity hence it shows LTP. Cathodal stimulation increases GABAergic activity and decreases glutamatergic activity hence show LDP.[21] Anodal stimulation depolarizes the neuron membrane and glutamate is released by a presynaptic neuron that binds to NMDA and AMPA receptors. This leads to depolarization and increase of intracellular Ca^{+2} in postsynaptic neurons, which activate protein kinases, like Calcium /calmodulin-dependent kinase (CaMK). Many neural signaling pathways are influenced by a protein kinase, including the transcription, translation, and insertion of new glutamate receptors. CaKM stimulates CREB (transcription factor), which facilitates gene transcription and the creation of new proteins, in a long-term manner.[22] tDCS induces long-lasting effects by changing the excitability of the motor cortex in humans which enhances motor skill learning by increasing synaptic plasticity.[23] When a multi- area stimulation protocol is used, it will enhance the neurosynaptic pathways thus enabling the RAS to respond. The study by Li *et al*. (2019) revealed that tDCS application increases the level of consciousness in the disorder of consciousness.[24] In our study we used the P3/P4 electrode to stimulate the sensory cortex. It is similar to multisensory stimulation which has proven results in attaining arousal response in altered conscious patients.[13] The second electrode is placed on F3, dorsolateral prefrontal cortex which is associated with higher functions and stimulation of it can attain an arousal response.[25] A study done by Thibaut *et al*. (2014) shows that anodal tDCS over the left dorsolateral prefrontal cortex increases the level of consciousness.[25] The third electrode is C3/C4 which is placed on the motor cortex. It stimulates the motor area and aids in motor recovery. The study by Feng *et al*. (2013) found that tDCS application over the motor cortex in post- stroke patients improves the motor functions.[26] The study by Nitsche*et al*. (2005) shows that tDCS interferes with brain excitability through modulation of intracortical and corticospinal neurons hence increases motor function.[27] The findings from our study revealed the same facts exemplified in the above mentioned researches.

The limitations of the study are first, the sample size was small, due to the COVID-19; second, follow-up after 7 days was not assessed due to

the COVID-19 protocols of the hospital.

We conclude based on the results of this study that tDCS can be effective in improving GCS and RLAS in altered consciousness patients in then acute period after injury. It is non-invasive, cost-effective with minimal contraindications and doesn't interfere with other modalities in the intensive care unit. Hence, it can be administered safely under the supervision of a qualified therapist.

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DISCLOSURE

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Conflicts of interests: None

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