



Effect of Transcranial Direct Current Stimulation on Motor Recovery in Altered Conscious Patients after Traumatic Brain Injury and Cerebrovascular Accident: A Randomized Clinical Trial

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Abstract

Background and Purpose Altered levels of consciousness resulting from a vascular insult to the brain can vary from confusion to coma. A disruption in the function of the brain stem reticular activating system in the brain stem or both cerebral hemispheres and thalami causes coma. This study is aimed at finding the effect of transcranial direct current stimulation (tDCS) on motor recovery in altered conscious patients after traumatic brain injury and cerebrovascular accident.

Materials and Methods A total of 100 patients admitted to the neurology and neurosurgery unit of the university hospital were screened and 40 subjects who satisfied 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 caregivers before recruitment. After taking the preliminary assessment, anodal tDCS is 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 montage for two sessions of 20 min/day for 7 consecutive days. Routine physiotherapy was also given the same as group B.

Results At baseline, there were no significant group differences in the baseline characteristics. The groups passed the normality test. The results were tested for statistical significance between the groups by Mann–Whitney *U*-test and by one-way analysis of variance and Tukey Honest Significant Difference for post-hoc comparison; the results were statistically different with *p*-value less than 0.05 with a large effect size.

Conclusion We conclude, based on the results of this study, that tDCS can be effective in motor recovery in altered consciousness patients. It is noninvasive, cost-

Keywords

- ▶ Coma
- ▶ traumatic brain injury
- ▶ cerebrovascular accident
- ▶ tDCS
- ▶ physiotherapy

effective with minimal contraindications, and does not interfere with other modalities in the intensive care unit. Hence, it can be administered safely under the supervision of a qualified therapist.

Introduction

Altered levels of consciousness resulting from a vascular deficit to the brain can vary from confusion to coma.¹ Confusion is a state marked by a loss of ability to think clearly even after repetitions, to notice, respond to, and retain current stimulus along with disorientation.² Clouding of consciousness is the state that exists between regular consciousness and confusion.² Delirium is defined as a state of significantly altered consciousness, motor restlessness, transitory hallucinations, disorientation, and often delusions.³ Stupor is defined as a state in which the patient has little or no spontaneous activity but conscious.⁴ Patients will awaken with a little motor activity and may likely be unable to talk.³ According to the bedside behavioral test, coma and vegetative state are unconscious brain states. Patients with these states are completely unresponsive to external stimuli and are unable to commence goal-oriented behaviours.² According to Plum and Posner, defined coma as a state of unresponsiveness in which the patient lies with eyes closed and even vigorous stimulus cannot make a awaken response.⁵

Major causes of unconsciousness seen in the intensive care unit are unconsciousness after taking the sedative drug with or without alcohol, hypoxic-ischemic insult as a result of cardiac arrest or anesthetic accident, and result of cerebrovascular accidents (CVAs, either hemorrhage or ischemic) and traumatic brain injury (TBI).

TBI is a major public health issue.⁶ In India and other developing countries, TBIs are the major cause of mortality, disability, and financial fatalities.⁷ Every year, an average of 1.5 to 2 million people are injured in India, with a high mortality rate. TBIs are the most commonly caused by road traffic accidents (60%) followed by falls (20-25%) and violence (10%). A history of alcohol intake is present at the time of injury in 15 to 20% of cases of TBIs.⁸ The most severe TBI causes serious mental, and emotional difficulties, and even altered levels of consciousness. About 17% of patients, who survive a TBI, experience a period of total unconsciousness or altered state of consciousness.⁹

In low- and middle-income nations like India, stroke is a main cause of premature mortality and disability.¹⁰ Stroke prevalence rates in rural areas range from 84 to 262/ per 100,000, while in urban areas they range from 334 to 424/100,000.

The state of altered consciousness is mainly due to a disruption in the function of the brain stem reticular activating system, or both cerebral hemispheres and thalamai.³ Depending on the severity of the brain damage, a state of altered consciousness can last anywhere from hours to days, and sometimes months to years.⁵

There are various protocols available for attaining post-comatose motor responses. Various researches have exemplified that coma arousal therapy shall be beneficial in improving the Glasgow coma scale (GCS) of the patient. Currently, available literature emphasizes that sensory stimulation can result in alleviating disorders of consciousness.

Most of the studies revealed the fact that along with medical management of unconscious patients after TBI and CVA, multimodal sensory stimulation is used to produce arousal response. These studies aimed at attaining arousal responses but not motor responses.

Transcranial direct current stimulation (tDCS) is a type of noninvasive neurostimulation technique in which a weak polarizing current is used to adapt cortical excitability.¹¹ It is noninvasive stimulation of brain that is economical and simple to operate. In a study by Estraneo A et al. in craniocerebral injury subjects with motor skills and language impairment, a 1 to 2 mA tDCS has shown that there are no significant adverse effects.¹² A constant weak direct current can pass through the skull and stimulate the cortex behind it. In the brain, it regulates the excitability in the cerebral hemispheres.

This study is aimed at finding the effect of tDCS on motor recovery in altered conscious patients after TBI and CVA. The objectives of the study are to assess the level of motor responses in altered consciousness after TBI or CVA by the GCS and to find out whether there is an improvement in motor responses on the GCS scale and modified Ashworth scale of spasticity (MAS) scales after tDCS application.

Materials and Methods

Enrollment and Recruitment

A total of 100 patients who had altered conscious levels due to TBI and CVA were screened at the department of neurology and neurosurgery in association with the physiotherapy department of the university hospital. 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 single-blinded randomized control trial where the subjects were blinded. Forty subjects ($n=40$) satisfied inclusion criteria and were recruited for the study after informed consent from the caregiver. The subjects were randomly divided into two groups: group A (experimental) ($n=20$) and group B (control; $n=20$) by computerized randomization. Both males and females having altered levels of consciousness for more than 6 hours after TBI or CVA (bleeding not more than 30 mL) with GCS less than or equal to 8, altered consciousness that lasts for more than a week,

stable cardiac functioning, magnetic resonance imaging showing no midline shift, patients with decompressive craniectomy, no structural damage, no thalamic lesions with lesions in each lobe not exceeding 30% of the scope of one side of the brain are included in this study. Patients having unconsciousness other than TBI or CVA, cardiac pacemaker, electric implant in the brain Deep brain stimulation (DBS), scalp dermatitis, infections to central nervous system, and previous history of epilepsy are excluded from the study.

This study got ethical clearance from the institutional ethical committee and the trial is registered with Clinical trials of India.

Intervention

Group A Experimental: After taking the preliminary assessment, anodal transcranial direct current stimulation is applied to the motor area (C3/C4 ipsilesional), sensory area (P3/P4 ipsilesional), and left dorsolateral prefrontal cortex (F3) according to the 10/20 electroencephalogram montage (►Fig. 1). The electrodes used are 1.6 cm² in area, self-adhesive, and conductive. The individual leads connecting the active electrodes are fused into a single channel by a port and connected to the positive terminal of the machine. The current used in this study is direct continuous in nature having intensity 2.0 mA. Cathode is placed at the opposite shoulder as a reference electrode. tDCS was given for two sessions of 20min/day for 7 consecutive days.⁹ Routine physiotherapy was also given similar to that of group B. No seizure activity was observed during or later stage of treatment sessions.

Group B controlled: Routine physical therapy was given for 30 minutes twice daily for 7 consecutive days. The therapy included the following:

1. Passive movements—10 repetitions of full range of motion 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 guidelines of 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.

Outcome Measures

All the demographic characteristics of the subjects were recorded at the time of enrollment and recruitment of subjects. The motor responses were recorded by best motor responses subsection of GCS and MAS at the time of enrollment (t0), and after 7 days post-intervention (t1). Inter-rater reliability of GCS is good.^{8,11}

Statistical Analysis

In this study to analyze the role of tDCS on motor recovery of altered consciousness patients, the preliminary outcome variables were compared using Mann-Whitney U test and assessed for normality (►Table 1). All pre-test and post-test scores of motor responses on GCS and MAS were expressed



Fig. 1 Electrode placement for transcranial direct current stimulation.

Table 1 Baseline demographic characteristics of group A and group B

| Characteristics | Group A (experimental) (n = 20) | Group B (control) (n = 20) | p-Value |
|---|------------------------------------|-------------------------------|---------|
| Age ^a | 38 ± 10.95 | 43.2 ± 12.84 | > 0.05 |
| Sex (male:female) | 13:7 | 14:6 | > 0.05 |
| Side of injury (right:left) | 12:8 | 11:9 | > 0.05 |
| Type of management Conservative: Surgical (craniectomy, VP shunt, etc.) | 13:7 | 15:5 | > 0.05 |
| TBI:CVA | 13:7 | 11:9 | > 0.05 |
| Number of days between incidence of TBI/CVA and recruitment ^a | 7.2 ± 1.8 | 7.6 ± 1.2 | > 0.05 |
| SBP ^a | 129 ± 9.49 | 130.9 ± 7.64 | > 0.05 |
| DBP ^a | 80.52 ± 6.48 | 84.9 ± 6.05 | > 0.05 |
| Pulse (BPM) ^a | 75.17 ± 6.15 | 79.35 ± 6.36 | > 0.05 |
| Temperature (°F) ^a | 97.69 ± 1.29 | 78.17 ± 0.97 | > 0.05 |
| Respiratory rate (cycles per minute) ^a | 19.82 ± 2.26 | 21 ± 1.91 | > 0.05 |

Abbreviations: BPM, beats per minute; CVA, cerebrovascular accident; DBP, diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation; TBI, traumatic brain injury.

^aMean ± SD.

Table 2 Comparison of pre-test and post-test best motor response (GCS and MAS) in group A and B

| Variable | Group A Pretest ^a | Group A Posttest ^a | Group B Pretest ^a | Group B Posttest ^a | U-value | p-Value |
|----------|---------------------------------|----------------------------------|---------------------------------|----------------------------------|---------|---------|
| GCS | 3 | 4 | 1 | 1 | 48 | <0.05 |
| MAS | 4 | 4 | 0 | 0 | 20 | <0.05 |

Abbreviations: GCS, Glasgow coma scale; MAS, modified Ashworth scale of spasticity.

^aMedian.

Table 3 One-way ANOVA with Tukey HSD post-hoc comparison of GCS (best motor response) between group A and B

| Treatments pair | Tukey HSD Q statistic | Tukey HSD p-value | Tukey HSD interference |
|-----------------|-----------------------|-------------------|------------------------|
| A vs. B | 5.0596 | 0.0072128 | p < 0.01 |

Abbreviations: ANOVA, analysis of variance; GCS, Glasgow coma scale; HSD, Honest Significant Difference.

as median and analyzed by Mann–Whitney U test among the groups (► **Table 2**) and one way analysis of variance (ANOVA) with k=2 independent treatments with Tukey Honest Significant Difference (HSD) as post-hoc comparison for between the groups at 5% level of significance (► **Table 3**). To explore the practical significance of group differences, the effect size was calculated. The established criteria of the ES, 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; ► **Table 4**).

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 pre-test best motor response for GCS and MAS median of group A is 3 and 4 and post-test response is 4 and 4, while for group B the pretest and posttest response is 1 and 0 and 1

Table 4 One-way ANOVA with Tukey HSD post-hoc comparison of MAS scores between group A and B

| Treatments pair | Tukey HSD Q statistic | Tukey HSD p-value | Tukey HSD interference |
|-----------------|-----------------------|-------------------|------------------------|
| A vs B | 4.8990 | 0.0085175 | p < 0.01 |

Abbreviations: ANOVA, analysis of variance; HSD, Honest Significant Difference; MAS, modified Ashworth scale of spasticity.

Table 5 Effect size tDCS on motor recovery

| | |
|--|--------------|
| Cohen's $d = (0.4-1.6)/0.54 = 2.222222$ Glass's $\delta = (0.4-1.6)/0.54 = 2.222222$ Hedges' $g = (0.4-1.6)/0.54 = 2.222222$ | Large effect |
|--|--------------|

Abbreviation: tDCS, transcranial direct current stimulation.

and 1, respectively (► **Table 2**). The results were analyzed for statistical difference by Mann–Whitney U -test. The results were statistically significant at p -value less than 0.05 (► **Table 2**).

The results were tested for statistical significance between the groups by one way ANOVA and Tukey HSD for post-hoc comparison; the results were statistically different with p -value less than 0.05 (► **Tables 3 and 4**).

To explore the practical significance of group differences and the impact of tDCS on motor recovery in altered conscious patients, the effect size was calculated by Cohen's d , and the results showed that there is a large effect of tDCS on motor recovery (► **Table 5**).

Discussion

To assess the effect of tDCS on motor responses in altered conscious patients, the results in this study revealed that tDCS when given to altered consciousness subjects, the motor recovery was faster with improved motor responses on GCS scales and MAS scores than that of a control group that was statistically significant at 95% confidence interval ($p < 0.05$). The effect size revealed that tDCS has a large effect and practical significance on motor recovery in altered conscious patients. Even though the sample size was small due to the coronavirus disease 2019 pandemic, the large effect indicates the high significance of tDCS on motor responses and recovery. tDCS is a type of noninvasive neurostimulation technique in which a weak polarizing current is used to adopt cortical excitability.¹³ Anodal stimulation increases cerebral excitability by depolarizing the neuron and cathodal stimulation decreases cerebral excitability by hyperpolarizing the neuron.¹³ tDCS changes the electrical neuronal membrane potential along with a change in N-methyl-d-aspartate (NMDA) and gamma-amino-butyric acid (GABA) receptor's effectiveness.¹⁴ It shows long-term potentiation (LTP) plasticity and long-term depression plasticity. Anodal stimulation decreases GABAergic activity and increases glutamatergic activity, hence showing LTP, while cathodal stimulation increases GABAergic activity and decreases glutamatergic activity, hence showing LDP.¹⁰ Anodal stimulation releases the glutamate at the presynaptic neuron by depolarizing the neuron membrane and glutamate that binds to NMDA and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors. This leads to depolarization and increase in intracellular Ca^{+2} at post-synaptic neurons, which can activate protein kinases, like calcium/calmodulin-dependent kinase. Protein kinase

adopts most of the neuronal signaling pathways leading to the transcription, translation, and insertion of new glutamate receptors. In a long-term mechanism, Calcium/Calmodulin-dependent Kinase (CaMK) activates cAMP-response element binding protein (CREB) (transcription factor), which mediates gene transcription and the formation of new protein.¹⁵ tDCS induces long-lasting effects by changing the excitability of the motor cortex in humans,¹⁴ which enhances motor skill learning by increasing synaptic plasticity.⁹ It works spontaneously on the excitability of the cortex. The excitability is mainly due to constant change in the polarity that causes depolarization and hyperpolarization of the cortex.⁹ The study by Nitsche et al concluded that tDCS interferes with brain excitability through modulation of intracortical and corticospinal neurons, thus increasing motor function.^{7,17} Another study by Feng et al found that tDCS application over the motor cortex in post-stroke patients improves motor functions.¹³ Li et al interpreted that tDCS application increases the level of consciousness in the disorder of consciousness.¹⁸ The study done by Thibaut et al concluded that anodal tDCS over the left dorsolateral prefrontal cortex increases the level of consciousness hence increasing motor functions.⁹

Conclusion

We conclude, based on the results of this study, that tDCS can be effective in motor recovery in altered consciousness patients. It is noninvasive, cost-effective with minimal contraindications, and does not interfere with other modalities in the intensive care unit. Hence, it can be administered safely under the supervision of a qualified therapist.

Funding

None.

Conflict of Interest

None declared.

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