A Randomized Controlled Single-blind Trial of Transcranial Direct Current Stimulation as Early Augmentation in Major Depressive Disorder: Protocol of a Proof-of-Concept Study

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Abstract

Background: Transcranial direct current stimulation (tDCS) used for augmentation improves depressive symptoms in patients who have a partial or poor response to antidepressant medications. However, its role and effectiveness as an early intervention have not been studied much. This study aims to determine the efficacy and safety of add-on tDCS as an early augmentation strategy in drug-naive patients with major depressive disorder.

Methods: A total of 40 patients will be enrolled in the study, randomized into two groups (active and sham), and receive uniform medication Escitalopram 10 mg per day. A total of 10 sessions of tDCS will be given within 2 weeks. Assessments will be done using scales Hamilton Anxiety Rating Scale (HAM-A), Hamilton Depression Rating Scale (HAM-D) and Beck's Depression Inventory (BDI) at baseline, week 2, and week 4 of the study. After each session of tDCS, a side effects checklist will be applied to monitor side effects. The trial has been registered in the Clinical Trials Registry, India (CTRI/2022/01/039123).

Result: After data collection, statistical analysis will be done using a computerized statistical program, Statistical Package for Social Sciences. Mean changes in the rating scale scores will be compared after each assessment and between the groups.

Conclusion: The findings will help to assess the efficacy of tDCS in the early augmentation of depressive disorder

INTRODUCTION

In terms of lifetime prevalence, depression is the second most common psychiatric disorder behind anxiety disorders.1 The lifetime prevalence rate of major depressive episodes ranges from 5-17%.2 According to the National Mental Health Survey (NMHS 2015-16), the lifetime prevalence of depression in India is 5.3%.3,4 It poses a huge disease burden to society. It is associated with poor quality of life and impaired role functioning.

To manage depression and improve the affected individuals’ quality of life, various strategies, including medicines, cognitive and behavioral interventions, and neuromodulation, have been used.5-7 However, the rates of complete
remission range between 22 and 40%. Long-term follow-up studies show that at the end of a three-year follow-up, approximately 12% of patients never achieve remission and 69% of patients reach remission. The rest of the patients either relapse or report recurring depressive symptoms after reaching remission.

The guidelines recommend treatment initiation in the form of pharmacotherapy or psychotherapy as a management strategy for depression. Antidepressants often remain the mainstay of treatment for depression, as it is more convenient to prescribe them in a resource-limited setting. Psychological interventions like cognitive behavior therapy (CBT) have also been found to be effective in managing depression. Various neuromodulation techniques like electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are found to be effective in the management of depression. But these modalities have been opted for only in cases where there is a poor or partial response to treatment. Factors that have been implicated in the refractoriness of depression include – chronicity of illness episodes, non-adherence to treatment, presence of atypical features, and comorbidities.

Evidence suggests various augmentation strategies for the treatment of refractory cases like medications such as antipsychotics and methylphenidate as well as neuromodulation techniques like rTMS or tDCS.

tDCS is a noninvasive brain stimulation technique that modifies cortical activity by simultaneously inhibiting and stimulating cortices involved in a depressive episode. It involves modulation via weak electrical stimulus of about 1 to 2 mA intensity for about 20 to 30 minutes through electrodes placed over the scalp. In depression, neuroimaging findings have shown interhemispheric asymmetry between dorsolateral prefrontal (DLPFC) cortices. There is hypofunction of left DLPFC and hyperfunctioning of right DLPFC. Amongst varying protocols, up to 10 sessions of anodal stimulation over left DLPFC and cathodal inhibition over right DLPFC with a current intensity of 2mA for 20 minutes is the most commonly used protocol. Evidence has shown the efficacy of active tDCS over sham tDCS in the management of refractory depressive symptoms. However, its role as an early augmentation strategy has not been studied much.

Rationale for the Study

Studies have shown the promising effect of tDCS in patients with depression who respond partially to conventional methods of antidepressants. Apart from this, the added benefits include its non-invasiveness, better tolerability and lesser side effects.

Early intervention using tDCS may aid in the early

| Table 1: Selection criteria for the recruitment of participants |
|-----------------|-----------------|-----------------|
| Inclusion criteria | Exclusion criteria | Drop out criteria |
| Drug naive (at least drug free-antidepressant from 1 month) | Depression not responding to adequate dose and duration of SSRIs for the current episode in past | Any patient developing severe intolerable side effects during the course of tDCS therapy |
| Diagnosed with major depressive disorder (DSM-5) | Presence of psychotic symptoms | Withdraws consent during the course of therapy |
| HAM-D score >13 | Patients having active suicidal ideations | Not able to complete 10 sessions over two weeks’ time period |
| Age: 18 years to 60 years | Bipolar depression | Develops any major medical issue during the course of treatment (e.g., COVID-19, accidents, Fracture, etc) |
| Informed consent to participate in the study | Any other psychiatric comorbidity (except tobacco use disorder) | |
| | Medical comorbidities that need immediate attention | |
| | Any contraindication to tDCS | |
resolution of symptoms, leading to early attainment of normal functioning.\textsuperscript{24}

\section*{METHODS}

\subsection*{Aim}
To determine the effectiveness and safety of add-on tDCS as an early augmentation strategy (along with antidepressant medicines) in drug-naive patients with major depressive disorder.

\subsection*{Objective}
To compare the effect and adverse effect of tDCS between groups receiving active tDCS and sham tDCS.

\subsection*{Null Hypothesis}
There will be no significant difference in the improvement of depressive symptoms and any adverse side effects between the two groups.

\subsection*{Study Design}
It is a proof-of-concept study with a single-blind, randomized, interventional, sham-controlled design conducted at a tertiary care psychiatry centre. The institutional ethics committee has approved the protocol and the trial has been registered in the clinical trials registry India on 04/01/2022 (CTRI/2022/01/039123).

\subsection*{Study Setting and Population}
The study will be conducted at the Department of Psychiatry, King George Medical University, Lucknow, India. Patients suffering from major depressive disorder as per the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria will be recruited, if they fulfil the following selection criteria. The patient selection criteria are mentioned in Table 1.

\subsection*{Sampling Technique and Randomization}
Purposive sampling with random allocation of participants by computer-generated random table method using www.random.org was done.\textsuperscript{25} There will be single blinding as the participants will not be aware of the allocation.

\subsection*{Sample Size Calculation}
G\textsuperscript{*}Power version 3.1.9 was used to do a sample size calculation.\textsuperscript{26} Repeated Measure ANOVA (within-between interactions) will be used as statistical tests and accordingly, effect size f of 0.25 is kept with a power of 0.90. There will be 2 groups and the assessment will be done on 3 points. The required sample size was 36 for the entire study (18 in each group). Considering an attrition rate of about 10%, the expected number of participants to be enrolled is 40.

\subsection*{Description of Tools}

\textbf{Hamilton Rating Scale for Depression (HAM-D)}
The Hamilton Rating Scale for Depression is the most widely used scale for assessing the severity of depression. HDRS-17, the original version from 1960, had 17 items in total, but four extra questions were employed to add more clinical data without affecting the final score. The questionnaire's items are scored on a three or five-point scale and a cumulative sum is taken to assess severity.\textsuperscript{27}

\textbf{Beck's Depression Inventory (BDI)}
The Beck's Depression Inventory is 21 items self-rating scale. Each item is are scored from zero to three to reflect their intensity and is summed.\textsuperscript{28}

\textbf{Hamilton Rating Scale for Anxiety (HAM-A)}
The Hamilton Rating Scale for Anxiety is used to measure the severity of anxiety symptoms. There are 14 items, each described by a set of symptoms, measuring both somatic and psychic anxiety ranging from zero (not present) to four (very severe).\textsuperscript{29}

\textbf{tDCS Side Effects Checklist}
The tDCS side effects questionnaire has been adapted from a study done by Eryılmaz et al. (2014) and it contains categorical rating scales in a Likert form (ranging from 0-none, 1- very mildly, 2-mildly, 3- moderate, 4-severe, 5- very severe) for the occurrence of 13 symptoms during or after tDCS.\textsuperscript{30}
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Neurostim by Neurosoft for tDCS
This is a transcranial stimulation device for both unipolar and bipolar stimulation which can produce a stimulus of current up to 5 mA for an adjustable duration of up to 40 minutes. Two electrodes - cathode and anode (of size 25 cm² each) - are placed over the desired cortices. Through the stimulator, inhibitory and facilitatory stimuli are given to the cortices simultaneously. System operation can be done from an external computer via a USB of +5 V or a 9V battery.

Procedure
Patients will be recruited from the adult psychiatry outpatients (APO) and psychiatric emergency services and all the patients with major depressive disorder will be screened. The clinical evaluation will be done to rule out any co-morbid psychiatric illness(es). Selection criteria for inclusion into the study will be applied and the patients willing to give written informed consent will be included.

A semi-structured tool will be used for the assessment of sociodemographic and clinical variables like age, gender, education, marital status, duration of illness and past history. The patients will be allocated into two groups (active and sham tDCS) by computer-generated random table method and will be blinded about the allocation. Both groups will be prescribed escitalopram 10 mg per day. Rescue medications for both groups will be Clonazepam, Etizolam (up to 1 mg/day) or Buspirone (up to 10 mg/day) for anxiety, and Zolpidem (up to 10 mg/day) for sleep disturbances.

On the first day of assessment, baseline HAM-A, HAM-D and BDI will be applied. A total of 10 sessions of tDCS will be delivered over 2 weeks and the tDCS side effect checklist will be applied after each session. HAM-A, HAM-D, and BDI will be applied after the end of 10 sessions of tDCS and then again after 2 weeks since the end of therapy. Two rating scales will be used for measuring depression (BDI & HAM-D) as the HAM-D better evaluates the somatic and behavioral symptom of depression and BDI better estimates the cognitive domains of depression.31

Treatment Protocol
Anode placement (stimulatory) will be done over the left DLPFC while cathode (inhibitory) will be placed over the right DLPFC. Patients receiving active tDCS will receive a current intensity of 2 mA for 20 minutes with a ramp time of 20 seconds. A total of 10 sessions will be delivered in 2 weeks. Right and left DLPFC are being located with the help of Beam F3 application.32,33 Both groups will be prescribed a uniform medication throughout the study period.

In case the patient develops any minor adverse effects due to tDCS, conservative management will be done and the patient will be reassured. If any serious adverse effects develop, the patient will be dropped and appropriate medical care will be provided.

Study Outcomes
The primary outcome will be measured by the change in scores of HAM-A, HAM-D and BDI from baseline to week 2 and week 4 between the two groups. The secondary outcome measure will be the number of patients reporting adverse events in each group following every tDCS session.

Result
After data collection, statistical analysis will be done using a computerized statistical program, Statistical Package for Social Sciences (SPSS). The data will be checked for normality. The mean and standard deviation of various clinical and sociodemographic variables between the two groups will be compared by using the appropriate parametric (student’s t-test)/non-parametric test (Mann Whitney U test).

Figure 1: Analysis plan of the data
Changes in scores of various scales pre- and post-intervention in between and among the groups (active vs sham) will be done using a two-way repeated measure Analysis of One-Way Variance (ANOVA) test. The analysis plan is summarized in Figure 1. The correlational analysis will be done between the outcome (change in depression severity and baseline symptom severity) with sociodemographic (age) and clinical variables (age of onset of illness, duration of illness, duration of current episode, number of episodes).

**Discussion**

Results from various RCTs involving tDCS have shown a substantial improvement in the severity of depressive symptoms with better tolerability. Few meta-analyses have shown Level B evidence of tDCS in the management of depression as an augmentation strategy for patients with refractory depression. There are only a few studies involving tDCS use as an add-on to pharmacotherapy but have shown inconsistent results in reducing depressive symptoms.

Through this proof-of-concept study, we can assess the relevance of tDCS as an early augmenting strategy and its safety during the early phase of managing depressive episodes. This could lead to early mitigation of depressive symptoms, recovery, early attainment of functioning and better quality of life. This could aid in formulating new treatment recommendations for major depressive episodes. Early augmentation may not be a need for all patients with depressive disorder as a majority of them will be responding to conventional treatment protocols. However, patients with poor prognostic factors of treatment response to depression, may be identified through meticulous clinical evaluation and may be considered for early augmentation.

**Conclusion**

The results of this study will help understand the course of illness following the conventional use of antidepressant medication versus the use of tDCS in conjunction at an early phase of intervention. This might help in managing depressive symptoms effectively during the early stage itself leading to less disease burden and better level of functioning.

**References**

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