Transcranial Direct Current Stimulation as an Augmenting Intervention in Depression

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ABSTRCT

Introduction: **Major depressive disorder (MDD) is a disorder of major public health importance, in terms of prevalence, morbidity, mortality, and is a major contributor to the overall global burden of disease. Despite effective pharmacological and psychological therapeutic options available, significant numbers of patients with depression do not respond or fail to achieve or maintain remission. Current study aims at exploring the augmenting effect of transcranial direct current stimulation (tDCS) along with pharmacological treatment for additional benefits in persons with drug resistant depression.**

Methodology: **Interventional study included 35 patients with major depressive disorder, who fulfilled the eligibility criteria, of drug resistant depression with 6 weeks on regular antidepressants. They were screened using Mini International Neuropsychiatric Interview (MINI). All the participants were administered tDCS at 2mA for 20 minutes, twice a day over 2 weeks. They were interviewed pre & post intervention using Montgomery-Åsberg Depression Rating Scale (MADRS) and Trail Making Test (TMT).**

Results: **Mean age of the patients was 37.57 ± 11.8 years, with age of onset of illness was 32.40 ± 9.49 years, and duration of illness was 62.83 ± 61.55 months (range 6 months-22 years). There was a significant reduction in MADRS mean scores from pre-intervention 34.8 to post intervention 21.80 ($p < 0.001$). There was a significant improvement in TMT A score in pre and post intervention (78.43 ± 33.06 to post intervention 66.51 ± 21.32 ($p < 0.001$)).**

Conclusion: **The study reports that add-on tDCS augments the efficacy of antidepressants in drug-resistant depression. Two weeks of tDCS significantly decreased the severity of depressive symptoms and had positive impact in cognitive domain (visual scanning and psychomotor speed).**

KEY WORDS

depression, tDCS, MADRS, cognition, TMT

INTRODUCTION

According to the World Health Organization, depression is responsible for more disability in the world than any other disease conditions (Smith, 2014) with exponential increase by 49.86% in incidence rate over the last 27 years to 25.8 million. There is a need for more research to reduce the burden due to depression (Liu, He, Yang *et al*., 2020).

Depression is associated with hypoactivity in the left dorsolateral prefrontal cortex (DLPFC) as established by PET, fMRI, and resting state EEG activity (Drevets, 1998; Schaffer, Davidson, Saron, 1983). One study found greater incidence of depression in patients affected by stroke with damage to DLPFC (Robinson, Kubos, Starr *et al*.,1984).

The tDCS is a non-invasive neuromodulation technique that delivers low direct current (1-2 mA) over the scalp via electrodes - anode induces depolarization, while cathode induces effective hyperpolarization, that results in cortical neuroplasticity (Filmer, Dux, Mattingley, 2014; Nitsche, Lampe, Antal *et al*., 2006). tDCS is used for treating clinical conditions such as schizophrenia, schizoaffective disorder (Grycuk, Gordon, Gaughran *et al*., 2020), affective disorders (Powell, Boonstra, Martin *et al*., 2014), obsessive-compulsive disorder (Brunelin J, Mondino M, Bation *et al*., 2018) chronic pain (Pinto, Teixeira, Duarte *et al*., 2018) cognitive disorders and other neurological disorders (Mondino , Bennabi, Poulet *et al*., 2014; Cruz, Fong, Brown, 2018).

Various studies have reported that tDCS/rTMS neuromodulation over the left DLPFC helps in increasing the regional activity with improvement in depressive symptoms (Boggio, Rigonatti, Ribeiro *et al*., 2008; Brunoni, Teng, Correa *et al*., 2010; Schutter, van Honk , Laman *et al*., 2010; Loo, Alonzo , Martin *et al*., 2012; Martin, McClintock, Forster *et al*., 2017).

Present study examined the add-on effect of tDCS augmentation to standard ongoing antidepressant therapy in drug resistant depression and its effect on executive functions.

METHODOLOGY

The present study is a single-center interventional study conducted at a tertiary care centre in New Delhi. ICD 10 criteria were used for the diagnosis of depression without psychotic symptoms. Patients of both genders between the age of 18 to 70 years, educated up to primary education and who were on regular antidepressant treatment for at least 6 weeks with inadequate response with two antidepressants in the past were recruited. Exclusion criteria for the study were psychiatric emergencies, pregnancy, frequent headache, chronic skin disease of scalp, co-morbid neurological illness, seizure, metallic implants, and drug abuse (except nicotine). Written informed consent was taken from a willing participant or legally accepted caregiver. Consenting participants and their unaffected relatives were interviewed by using Mini

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Table 1: Difference between pre-treatment and post treatment scores for clinical variables on MADRS (n = 35).

Sr. No	Clinical variable	Pre-Intervention (Mean ± SD)	Post-Intervention (Mean ± SD)	P-value*
1	Apparent Sadness	4.43 ± 0.82	2.69 ± 0.76	< 0.001
2	Reported Sadness	4.46 ± 0.70	2.66 ± 0.73	< 0.001
3	Inner Tension	3.37 ± 0.84	2.26 ± 0.95	< 0.001
4	Reduced Sleep	3.23 ± 1.17	2.34 ± 1.03	< 0.001
5	Reduced Appetite	3.20 ± 1.23	2.14 ± 0.91	< 0.001
6	Concentration Difficulties	3.34 ± 1.0	2.37 ± 1.0	< 0.001
7	Lassitude	3.43 ± 0.98	2.03 ± 9.23	< 0.001
8	Inability to Feel	3.69 ± 0.99	2.26 ± 1.12	< 0.001
9	Pessimistic Thoughts	3.14 ± 1.24	2.03 ± 1.18	< 0.001
10	Suicidal Thoughts	2.51 ± 1.31	1.03 ± 1.07	< 0.001
	Total	34.8 ± 7.53	21.8 ± 6.42	< 0.001

International Neuropsychiatric Interview (MINI) to exclude the co-morbidity, participants were assessed using Montgomery-Asberg Depression Rating Scale (MADRS) and Trail Making Test (TMT). tDCS was administered using advanced equipment (focus v3) with stringent safety measures. The anode was placed over left dorsolateral prefrontal cortex with midpoint of electrode (25 cm2) placed over F3 (10-20 system), and cathode electrode over the right dorsolateral prefrontal cortex at F4 (10-20 system). Current intensity of 2 mA for 20 minutes was used for each session, a total of 20 tDCS sessions were administered, twice daily over a period of 2 weeks (Monday to Friday). The study was undertaken after the Institutional Review board approval.

RESULTS

In the present study, a total number of participants was 35. The mean age of patients was 37.57 ± 11.8 years and the majority of the patients were males (54.3%). Mean age of onset of depressive illness was 32.79 ± 11.1 years in males & 31.56 ± 7.1 years in females and mean duration of illness was 62.83 ± 61.55 months (range 6 months-22 years) respectively.

The clinical items of MADRS scale were analysed as pre and post intervention, there was significant difference in pre and post-treatment scores on all variables in MADRS (Table 1). The mean of a total score of MADRS pre intervention (M = 34.80, SD = 7.526) and post intervention (M = 21.8, SD = 6.42) were compared using paired t-test which suggests a significant reduction after 20 sessions of tDCS intervention ($p < 0.001$).

There was a significant reduction in TMT-A score from pre-intervention (78.43 ± 33.06) to post intervention (66.51 ± 21.32) ($p < 0.001$). However, reduction in TMT B score from pre-intervention (177.77 ± 63.22) to post-intervention (159.97 ± 50.09) was not significant ($p = 0.072$).

DISCUSSION

Depression and tDCS

In the present study, the results suggest improvement in all domains of depression (Table 1) in MADRS scale and cognition with add-on tDCS in drug resistant depression. The results are in accordance with Ferrucci, Bortolomasi, Vergari *et al*., (2009), that reported significant improvement after 10 sessions of tDCS over 5 days (twice daily session, 2mA for 20 minutes, anode over left DLPFT, cathode over right DLPFC) in depressive symptoms in MDD, who were referred for electroconvulsive therapy (ECT) with high suicide risk and the antidepressant effect was sustained after one month, with no improvement in memory and attention unlike in our study. Earlier study by Brunoni, Valiengo, Baccaro *et al*. (2013a) had reported that active 12 sessions of tDCS over 6 weeks, 2 mA, 30 min, anode over left DLPFC and cathode over right DLPFC, improved depressive symptoms in MDD, and documented that combination of tDCS and sertraline had an additive response in participants, which was superior to sham tDCS and sertraline alone, tDCS and placebo. They reported that tDCS was more effective during acute episode (Valiengo, Bensenor, Goulart *et al*., 2013), this effect is because of neuromodulation effect of tDCS on serotonergic system by blocking serotonin reuptake as seen with antidepressant drugs (Brunoni, Kemp, Shiozawa *et al*., 2013b).

However, there are also conflicting results, Bennabi, Nicolier, Monnin *et al*., (2015) in a double-blind sham-controlled study with treatment resistant depression (n-24) reporting no improvement in depression and in cognitive function with 10 sessions of tDCS (2 mA, 30 min, 2 sessions daily for 5 days) (Bennabi *et al*., 2015), this can be explained by suboptimal stimulation of the serotonin system (Brunoni *et al*., 2013a, 2013b). It is reported that tDCS has cortical excitatory effect by modifying N-methyl-D-aspartate (NMDA), serotonin, dopamine, GABA, acetylcholine and adrenaline receptors (Nitsche, *et al*., 2006). Hence, it is vital to select the correct tDCS configuration that delivers current for adequate duration, number of sessions and placement of electrodes that deliver appropriate current density for neuroplasticity to translate into clinical improvement (Nitsche, Lampe, Antal *et al*., 2006; Thair, Holloway, Newport *et al*., 2017).

Suicide and tDCS

Suicide is one of the leading causes of death in depression (Bachmann, 2018). The result of current study showed a significant decrease in suicidal thoughts scores in MADRS scale, as reported by Alonzo, Chan, Martin (2013). The improvement in suicidal thoughts after tDCS was of clinical interest given the mixed findings regarding serotonergic antidepressants increasing suicidal risk (Dudley, Goldney, Hadzi-Pavlovic, 2010). Suicidal variable is associated with morphological alterations of the prefrontal cortex even in normal individuals (Bajaj *et al* 2019), considering that anodal tDCS was applied over the left DLPFC; theoretically this intervention could have improved suicidal thoughts in drug resistant depression (Desmyter, van Heeringen, Audenaert *et al*., 2011) with normalization in brain connection related to emotion and decision making, that resulted in an improvement in cognition and behaviour. (Schmaal, van Harmelen, Chatzi *et al*., 2019).

Cognition and tDCS

tDCS neuromodulation techniques have been explored to improve cognitive performance as it induces anodal cortical excitation (Fregni, Boggio, Nitsche *et al*. 2006). Bashir, Al-Hussain, Hamza *et al*., (2019) report that a single session of tDCS anodal stimulation over left DLPFC (2 mA, 20 min) improves cognitive function in healthy individuals. Similarly, anodal tDCS stimulation to left DLPFC in neurological (Cruz Gonzalez, Fong, Brown, 2018) and psychiatric disorder (Tortella, Casati, Aparicio *et al*, 2015) have shown improvement in cognitive functions too. Present study used the tDCS anodal stimulation over left DLPFC in drug resistant depression and report a significant reduction in TMT A score after 20 sessions, suggesting an improvement in cognitive performance in visual scanning and psychomotor speed. This effect could be possibly because of improvement with depressive symptoms, with facilitation of neuroplasticity (Cavaleiro, Martins, Gonçalves *et al*., 2020). However, Martin, McClintock, Forster *et al*. (2017) reported minimal improvement in cognition with stimulation to DLPFC with rTMS, while Brunoni *et al*., (2013) study did not report improvement with tDCS suggesting cognition could be mood-independent, there is a need to study the effect with more comprehensive neuropsychological test batteries (Loo, Sachdev, Martin *et al*. 2010) and brain imaging to understand the relationship.

Adverse effects and tDCS

It is reported that safety of tDCS is equally safe as sertraline (Brunoni *et al*., 2013). Except for two instances of hypomania, no other significant adverse effects were noted during the study. Mania and hypomania are known adverse effects with tDCS (Brunoni, Amadera, Berbel *et al*., 2011; Loo *at al*. 2012), hence there is a need for caution with tDCS, even more so when administered with antidepressants as reported in this study.

CONCLUSION

Application of novel brain neuromodulation technique for treating major depressive disorder is a rapidly growing field. The present study suggests that augmenting effect of tDCS along with pharmacological treatment has additional benefits to persons with drug resistant depression. The study reports a significant improvement in symptoms of depression in the two weeks study period. The results also showed a significant improvement in cognition after the tDCS sessions, but because of the brief study period, it could not conclude to suggest of having a long-term effect. There is a need for caution while using tDCS with antidepressants as it could induce hypomania or mania.

LIMITATIONS OF THE STUDY

Although adequately powered (as per our calculations), nevertheless sample size was small in the current study, relative to the number of patients who need such novel treatments. This study was conducted at a single centre and findings were not compared with the control group. The efficacy of tDCS was examined only at study end, that is after 2 weeks; thus, present study could not estimate the stability of its medium to long-term antidepressant effects and its cost-effectiveness.

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