PSYCHOLOGICAL MEDICINE

Safety and Tolerability of tDCS: A Review of Three Studies Done in a Tertiary Care Hospital Psychiatry Unit in New Delhi

Gunja Sengupta, Gautam Sharma, Amit Kumar Meena, Linkan Verma, Sabah Aman

ABSTRACT

Background: **Transcranial Direct Current Stimulation (tDCS) is an emerging neuromodulatory technique that has shown promise in a variety of neuropsychiatric disorders ranging from attention deficit hyperactivity disorder (ADHD) to alzheimer's disease along with severe mental disorders like schizophrenia and mood disorders. It is considered a safe and effective technique that acts by modulating cortical function and enhancing neuroplasticity.**

Aims/Objectives: **To evaluate the adverse effects of tDCS in three studies done in a general hospital psychiatric unit (GHPU) setting.**

Methods: **Data from three studies done in a tertiary care general hospital psychiatry unit in New Delhi were analyzed for noting the adverse effects in each study. From each study, sample size, number of sessions and adverse effects were recorded for understanding the safety of TDCS.**

Results: **In these studies, majority of the adverse effects included tingling, itching, burning sensation and headache during the procedure. These side effects disappeared immediately or within a few hours of the procedure. This was not found to be distressful to the patients in the short as well as long term. Two instances of hypomania were reported but are difficult to comment on causality with respect to tDCS.**

Conclusion: **tDCS appears to be a safe procedure with good overall patient tolerability.**

KEY WORDS

transcranial direct current stimulation (tDCS), safety, adverse effect, side effect, hypomania

INTRODUCTION

Over the last decade, non-invasive brain stimulation techniques have emerged as viable, safe and cost-effective methods of treating mental illnesses[1]. One such technique, which was, in fact, introduced in its crudest sense around two centuries ago when Giovani Aldini used electric stimulation to successfully treat a patient with melancholic depression[2]. The technique, forgotten in the era of the emergence of Electro-convulsive therapy has now been modified and standardized and presented in its current form, tDCS (Transcranial Direct Current Stimulation).

tDCS is a neuro-modulatory technique that involves application of weak direct current by electrodes over the scalp region. It is a non-invasive technique that works by modulation of cortical function that induces neuroplasticity. It acts on the functioning of the underlying cortical area as required, as an excitatory by depolarization at anode and inhibitory by hyperpolarization at cathode[3].

The technique, reclaiming its spot in the last decade or so has been used in various studies as a possible treatment for a multitude of neuropsychiatric disorders as follows. *(a) Depression:* Dorsolateral Prefrontal Cortex (DLPFC) stimulation and reinstitution of balance between prefrontal cortices on either side. Other sites used were bifrontal, left frontal and occipital. Most studies noted a significant reduction in depressive symptoms[4], with improvement in cognition[5]. *(b) Schizophrenia:* Left DLPFC and Left temporoparietal junction (TPJ) (cathodal and anodal respectively) improved both negative as well as positive symptoms[6]. *(c) Substance use disorder:* Fronto-temporoparietal region and DLPFC (cathodal and repeated anodal respectively) reduced cravings themselves or increased capability of patients to resist craving[7]. *(d) Alzheimer's Disease:* Temporopolar region (anodal) was seen to improve recognition memory[8]. *(e) ADHD:* Contradictory evidence on Left DLPFC stimulation. Some studies found improvement in executive control[9]. For rehabilitation in a variety of neurological conditions[10] viz. stroke (motor cortex [M1], supplementary motor area [SMA], pre-motor cortex [PMC], primary somatosensory area, cerebellum), *Parkinson Disease* (M1, SMA, DLPFC, cerebellum), *dystonia* (M1), *Multiple sclerosis* (left DLPFC for fatigue), the application of tDCS has shown a positive response.

The usual adverse effects noted in tDCS trials[2,11] were mild lesions on the underlying skin, mild tingling/pain/itching, transient redness, nausea, insomnia and headache. These effects were noted to be transient, safe and tolerable by the subjects. The incidence of the effects was noted to be more during the procedure and only a small minority found it to be distressful[11]. A meta-analysis on tDCS which included more than 30,000 sessions of tDCS did not elicit even a single instance of any serious adverse effect related to the procedure. The usual adverse effects noted were mostly concerned with tolerability rather than safety[12]. One review of data from 6 randomized clinical trials found no significant differences between active and sham tDCS with respect to safety and acceptability[13].

It has been recommended in studies that safe stimulation involves procedures such as a prudent selection of patients, gentle cleaning of the

Received on June 17, 2020 and accepted on October 2, 2020
Department of Psychiatry, Dr. RML Hospital
110001, New Delhi, India
Correspondence to: Gautam Sharma
(e-mail: gautamsharma@dr.com)

Table 1: elaborates on each study and its findings in the domain of the adverse effects (n = 113).

	Major Depressive Disorder	Alcohol Use Disorder	Schizophrenia
Sample Size (Sex)	n = 35 (M = 19/F = 16)	n = 46 (M = 44)	n = 32 (M = 23/F = 9)
Mean Age	37.57 ± 11.8 yrs.	37.22 ± 8.95 yrs.	35.41 ± 9.83 yrs
Duration of illness	5.17 ± 2.43 yrs.	14.96 ± 7.20 yrs.	12.91 ± 8.74 yrs.
Number of sessions (Sessions per day)	20 (2/day)	10 (2/day)	10 (2/day)
Duration of each session	20min	20min	20min
Current/Electrode size	2mA/25 cm2	2mA/25 cm2	2mA/25 cm2
Location of Electrodes	Anode- Left DLPFC, Cathode- Right DLPFC	Anode- Right DLPFC, Cathode- Left DLPFC	Anode-Left DLPFC, Cathode- Temporoperital juction
Adverse Effects			
Headache	4 (11.42%)	11 (23.91%)	3 (9.37%)
Tingling	12 (34.28%)	3 (6.52%)	4 (12.50%)
Itching	9 (25.71%)	28 (60.86%)	1 (3.12%)
Burning	5 (14.28%)	7 (15.21%)	24 (75.00%)
Concentration	No decline	N/A	N/A
Mood change	2 (5.17%) patients developed hypomania	None	None

skin, saline soaking of electrodes, selecting constant current strength to deliver adequate charge density, spacing of sessions, and following the safety measures as suggested by the manufacturer[14].

Presently, there are limited or non-existent safety guidelines for tDCS, hence, it is important to generate data and report adverse events during tDCS which will contribute to development of such guidelines and make tDCS safer.

MATERIALS AND METHODS

Data from three studies done at the Centre of Excellence, Dr. RML Hospital and PGIMER, New Delhi were analyzed and annotated with special emphasis on the adverse effects in each study.

From each study, sample size, number of sessions and adverse effects, if any were noted. Semi-structured pro-formas were used for each study for the collection of socio-demographic and clinical information and a separate pro-forma was used to collect information on adverse effects, which also were entered in the institutional records.

Exclusion criteria for the studies were psychiatric emergencies, pregnancy, frequent headache, chronic skin disease of scalp, co-morbid neurological illness, seizure, metallic implants, and drug abuse (except nicotine and alcohol in study of alcohol dependence syndrome).

All studies were approved in advance by the institutional ethics committee and had no conflicts of interest.

RESULTS

The three studies taken together had a cumulative sample size of 113. The sample size and number of sessions brought together reveals a total of 1480 sessions of tDCS in total, from which we extracted the data on adverse effects. The data is summarized in Table 1.

The studies covered three types of mental illnesses in the form of alcohol use disorder, major depressive disorder and schizophrenia.

DISCUSSION

Previous literature shows that, tDCS is a safe and effective procedure[2,10-12] in the treatment of a variety of disorders. Our study findings corroborate and reiterate the fact that tDCS is a safe procedure. The feared cognitive effects of ECT also do not appear to occur in this technique. Rather it has been seen in studies to improve cognition[15].

In the present three studies done in RML institute, tingling/itching/burning sensation and headache during the procedure was found to be the major adverse effects that disappeared immediately or within a few hours of the procedure. These adverse reactions were found to be well tolerated by the patients and were not too distressing in the short as well as long term.

Hypomanic symptoms were reported in two patients in the study on major depressive disorder (n = 35), after the 20th and 8th sessions of tDCS respectively, which subsequently subsided after stopping the procedure, which has been a possible adverse effect as quoted in studies[16]. There are reported cases of hypomania and mania after transcranial magnetic stimulation to the dorsolateral prefrontal cortex, but it is relatively uncommon with tDCS. Understanding of the pathophysiology of mania, it is plausible that focal brain stimulation to the DLPFC could induce hypomania as mechanism of the antidepressant action of tDCS may lie in enhancing activity of the left prefrontal cortex[17,18]. We theorise that the delivery of a higher and more potent tDCS dose than typically used in studies, combined with antidepressant drug treatment in a patient with MDD, could have induced transitory hypomania. It may be argued that symptoms ranging from mild mood elevation to hypomania may reflect therapeutic response and should not be viewed as adverse effects as these symptoms are time limited, not very troublesome and disappear on discontinuation of tDCS.

In the study with major depressive disorder (n = 35), cognitive functions before and after tDCS using TMT (Trail Making Test) found no decline; in fact, there is improvement in cognitive functioning. There was a significant reduction in TMT-A score from pre intervention (78.43 ± 33.06) to post intervention (66.51 ± 21.32) ($p<0.001$) suggesting improvement in cognitive domain (visual scanning and psychomotor speed). However, reduction in TMT B score from pre intervention (177.77 ± 63.22) to post intervention (159.97 ± 0.09) was not significant ($p = 0.072$). Earlier studies[19-21] too have shown positive effect on cognition in depression. There are studies[22] reporting no improvement, however, no studies have reported decline in cognitive function with tDCS.

It is known that alcohol dependence syndrome (ADS) patients have alcohol withdrawal seizures[22]. In the study with ADS (n = 46), none of the participants had seizure. This could be due to cathodal hyperpolarization supressing the anodal depolarization effect, resulting in antiepileptic effect. There is a report[24] of seizure in a paediatric case post tDCS session, however, it was not conclusive, as there were other confounding factors like change in antiepileptics, antidepressants (escitalopram). There are studies that have treated refractory[25] and focal seizure[26] with tDCS, hence it would be interesting to do EEG and explore tDCS effects pre and post session.

Earlier studies have reported headache[27,28], nausea, fatigue[11], somnolence[5], neck pain/scalp pain, light flashes[29], and skin burn[30], but none of these were reported in our studies except for mild headache that did not last for more than 2-3 hours after session. Except for 2 cases of hypomania switch in major depressive disorder (n = 35), no other adverse effects were reported in the sample. Overall patient tolerability was uneventful.

Minimal side effects were reported in all the three studies as study protocol was followed, participants screened and all precautions were taken. Current within approved levels (2 mA) with optimal duration (20 minutes), broad electrodes (25 cm2), adequately hydrated, firmly fastened with ramping up feature in the device were used (focus v3), hence fewer incidence of flashes and no incidence of burn were reported.

The major inconveniences reported in the patients regarding tDCS, the aberrant sensations during the procedure, got us looking for alternatives. Studies have shown emerging alternatives to saline irrigation of electrodes that have been seen to be reducing this discomfort. McFadden *et al*. in 2011 found decreased discomfort during tDCS by using topical Eutectic Mixture of Local Anaesthetics (EMLA)[31]. Other studies used saline solutions with lower salt concentrations and deionized water to reduce the effects. Among saline solutions best comfort was perceived at a 15 mM to 140 mM concentration of NaCl[32]. In our centre, the use of normal saline diluted with distilled water is showing promise as it seen to be decreasing the discomfort associated with the procedure.

The following were the safety precautions used in our centre which has led to better tolerability of the procedure:

1. Prudent selection of patients using semi-structured pro-forma.
2. The use of bilateral stimulation twice a day with a minimum interval of 3 hour in these studies has been seen to be well tolerable by the patients.
3. Careful soaking of electrodes so as to optimize conduction and minimize the risk of inter-electrode conduction.
4. tDCS instrument with ramping up feature helps reduce the discomfort with stimulation.
5. The use of diluted 0.9% normal saline water has led to a decrease in discomfort in the patients.

CONCLUSION

Despite the stigma and apprehension around tDCS as a newly emerging treatment method, it is a safe and cost-effective procedure with minimal safety concerns when done following standard protocol. There is a need to further explore the long-lasting brain changes and adverse effects.

REFERENCES

1. Fitzgerald P. Brain stimulation techniques for the treatment of depression and other psychiatric disorders. Austral Psych 2008; 16(3): 183-90. doi: 10.1080/10398560701874291.
2. Zhao H, Qiao L, Fan D, Zhang S, Turel O, Li Y, Li J, Xue G, Chen A, He Q. Modulation of brain activity with noninvasive transcranial direct current stimulation (tDCS): clinical applications and safety concerns. Front Psychol 2017; 8: 685. doi: 10.3389/fpsyg.2017.00685.
3. Stagg CJ, Nitsche MA. Physiological basis of transcranial direct current stimulation. Neuroscientist 2011; 17(1): 37-53. doi: 10.1177/1073858410386614.
4. Kalu UG, Sexton CE, Loo CK, Ebmeier KP. Transcranial direct current stimulation in the treatment of major depression: a meta-analysis. Psychol Med 2012; 42(9): 1791-800. doi: 10.1017/S0033291711003059.
5. Brunoni AR, Amadera J, Berbel B, Volz MS, Rizzerio BG, Fregni F. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. Int J Neuropsychopharmacol 2011; 14(8): 1133-45. doi: 10.1017/S1461145710001690.
6. Brunelin J, Mondino M, Gassab L, Haesebaert F, Gaha L, Suaud-Chagny MF, Saoud M, Mechri A, Poulet E. Examining transcranial direct-current stimulation (tDCS) as a treatment for hallucinations in schizophrenia. Am J Psychiatry 2012; 169(7): 719-24. doi: 10.1176/appi.ajp.2012.11071091.
7. Wang Y, Shen Y, Cao X, Shan C, Pan J, He H, Ma Y, Yuan TF. Transcranial direct current stimulation of the frontal-parietal-temporal area attenuates cue-induced craving for heroin. J Psychiatr Res 2016; 79: 1-3. doi: 10.1016/j.jpsychires.2016.04.001.
8. Ferrucci R, Mameli F, Guidi I, Mrakic-Sposta S, Vergari M, Marceglia SE, Cogiamanian F, Barbieri S, Scarpini E, Priori A. Transcranial direct current stimulation improves recognition memory in Alzheimer disease. Neurology 2008; 71(7): 493-8. doi: 10.1212/01.wnl.0000317060.43722.a3.
9. Sotnikova A, Soff C, Tagliazucchi E, Becker K, Siniatchkin M. Transcranial direct current stimulation modulates neuronal networks in attention deficit hyperactivity disorder. Brain Topogr 2017; 30(5): 656-72. doi: 10.1007/s10548-017-0552-4.
10. Morya E, Monte-Silva K, Bikson M, Esmaeilpour Z, Biazoli CE, Fonseca A, Bocci T, Farzan F, Chatterjee R, Hausdorff JM, da Silva Machado DG. Beyond the target area: an integrative view of tDCS-induced motor cortex modulation in patients and athletes. J Neuroeng Rehabil 2019; 16(1): 1-29. doi: 10.1186/s12984-019-0581-1.
11. Poreisz C, Boros K, Antal A, Paulus W. Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. Brain Res Bull 2007; 72(4-6): 208-14. doi: 10.1016/j.brainresbull.2007.01.004.
12. Bikson M, Grossman P, Thomas C, Zannou AL, Jiang J, Adnan T, Mourdoukoutas AP, Kronberg G, Truong D, Boggio P, Brunoni AR. Safety of transcranial direct current stimulation: evidence based update 2016. Brain Stimul 2016; 9(5): 641-61. doi: 10.1016/j.brs.2016.06.004.
13. Moffa AH, Brunoni AR, Fregni F, Palm U, Padberg F, Blumberger DM, Daskalakis ZJ, Bennabi D, Haffen E, Alonzo A, Loo CK. Safety and acceptability of transcranial direct current stimulation for the acute treatment of major depressive episodes: Analysis of individual patient data. J Affect Disord 2017; 221: 1-5. doi: 10.1016/j.jad.2017.06.021.
14. Woods AJ, Antal A, Bikson M, Boggio PS, Brunoni AR, Celnik P, Cohen LG, Fregni F, Herrmann CS, Kappenman ES, Knotkova H. A technical guide to tDCS, and related non-invasive brain stimulation tools. Clin Neurophysiol 2016; 127(2): 1031-48. doi: 10.1016/j.clinph.2015.11.012.
15. Hill AT, Fitzgerald PB, Hoy KE. Effects of anodal transcranial direct current stimulation on working memory: a systematic review and meta-analysis of findings from healthy and neuropsychiatric populations. Brain Stimul 2016; 9(2): 197-208. doi: 10.1016/j.brs.2015.10.006.
16. Brunoni AR, Moffa AH, Sampaio-Júnior B, Galvez V, Loo CK. Treatment-emergent mania/hypomania during antidepressant treatment with transcranial direct current stimulation (tDCS): a systematic review and meta-analysis. Brain Stimul 2017; 10(2): 260-2. doi: 10.1016/j.brs.2016.11.005.
17. Tortella G, Casati R, Aparicio LV, Mantovani A, Senço N, D'Urso G, Brunelin J, Guarienti F, Selingardi PM, Muszkat D, Junior BD. Transcranial direct current stimulation in psychiatric disorders. World J Psychiatry 2015; 5(1): 88. doi:10.5498/wjp.v5.i1.88.
18. Fregni F, Boggio PS, Nitsche MA, Marcolin MA, Rigonatti SP, Pascual-Leone A. Treatment of major depression with transcranial direct current stimulation. Bipolar Disord 2006; 8(2): 203-4. doi: 10.1111/j.1399-5618.2006.00291.x.
19. Wong, H-L, Chan, WC, Wong, Y-L, *et al*. High-definition transcranial direct current stimulation—an open-label pilot intervention in alleviating depressive symptoms and cognitive deficits in late-life depression. CNS Neurosci Ther 2019; 25: 1244-53. doi: 10.1111/cns.13253.
20. Monnart A, Vanderhasselt MA, Schroder E, Campanella S, Fontaine P, Kornreich C. Treatment of resistant depression: a pilot study assessing the efficacy of a tDCS-mindfulness program compared with a tDCS-relaxation program. Front Psychiatry 2019; 10: 730. doi: 10.3389/fpsyt.2019.00730.
21. Dagan M, Herman T, Harrison R, Zhou J, Giladi N, Ruffini G, *et al*. Multitarget transcranial direct current stimulation for freezing of gait in Parkinson's disease. Mov Disord 2018; 33(4): 642-6. doi: 10.1002/mds.27300.
22. Brunoni AR, Tortella G, Benseñor IM, Lotufo PA, Carvalho AF, Fregni F. Cognitive effects of transcranial direct current stimulation in depression: Results from the SELECT-TDCS trial and insights for further clinical trials. J Affect Disord 2016; 202: 46-52. doi:10.1016/j.jad.2016.03.066.
23. Sachdeva A, Choudhary M, Chandra M. Alcohol withdrawal syndrome: benzodiazepines and beyond. J Clin Diagn Res 2015; 9(9): VE01. doi: 10.7860/JCDR/2015/13407.6538
24. Ekici B. Transcranial direct current stimulation-induced seizure: analysis of a case. Clin EEG Neurosci 2015; 46(2): 169. doi: 10.1177/1550059414540647.
25. Fregni F, Thome-Souza S, Nitsche MA, Freedman SD, Valente KD, Pascual-Leone A. A controlled clinical trial of cathodal DC polarization in patients with refractory epilepsy. Epilepsia 2006; 47(2): 335-342. doi: 10.1111/j.1528-1167.2006.00426.x.
26. San-Juan, D., Sarmiento, C. I., González, K. M., & Orenday Barraza, J. M. Successful Treatment of a Drug-Resistant Epilepsy by Long-term Transcranial Direct Current Stimulation: A Case Report. Front Neurol 2018; 9: 65. doi: 10.3389/fneur.2018.00065.
27. Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, Di Iorio R, Di Lazzaro V, Ferreri F, Fitzgerald PB, George MS, Hallett M. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: basic principles and procedures for routine clinical and research application. An updated report from an IFCN Committee. Clin. Neurophysiol 2015; 126(6): 1071-107. doi: 10.1016/j.clinph.2015.02.001.
28. Kumar S, Kumar N, Verma R. Safety and efficacy of adjunctive transcranial direct current stimulation in treatment-resistant obsessive-compulsive disorder: An open-label trial. Indian J Psychiatry 2019; 61(4): 327-34. doi: 10.4103/psychiatry.IndianJPsychiatry_509_18.
29. Antal A, Boros K, Poreisz C, Chaieb L, Terney D, Paulus W. Comparatively weak after-effects of transcranial alternating current stimulation (tACS) on cortical excitability in humans. Brain Stimul 2008; 1(2): 97-105. doi: 10.1016/j.brs.2007.10.001.
30. Oliveira LB, Lopes TS, Soares C, Maluf R, Goes BT, S KN, *et al*. Transcranial direct current stimulation and exercises for treatment of chronic temporomandibular disorders: a blind randomised-controlled trial. J Oral Rehabil 2015; 42(10): 723 2. doi: 10.1111/joor.12300.
31. McFadden JL, Borckardt JJ, George MS, Beam W. Reducing procedural pain and discomfort associated with transcranial direct current stimulation. Brain Stimul 2011; 4(1): 38-42. doi: 10.1016/j.brs.2010.05.002.
32. Dundas JE, Thickbroom GW, Mastaglia FL. Perception of comfort during transcranial DC stimulation: effect of NaCl solution concentration applied to sponge electrodes. Clin Neurophysiol 2007; 118(5): 1166-70. doi: 10.1016/j.clinph.2007.01.010.