EFFECT OF REPETITIVE BIHEMISPHERIC ANODAL TRANSCRANIAL DIRECT CURRENT STIMULATION ON MOTOR FUNCTION OF PATIENTS WITH PARKINSON'S DISEASE.

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INTRODUCTION

Parkinson's disease is the second most common neurodegenerative disease with a prevalence of around 0.5–1% in people aged between 65 and 69 years, increasing to 1–3% among individuals aged over 80 years [1]. It is a leading cause of Disability Adjusted Life Years (DALY) globally with 148% increase from 1960 to 2016 being the most growing neurological disease according to Global Burden of Disease 2016.[2]

It is a chronic, multisystemic, neurodegenerative disorder with various mechanisms underlying its neuropathology[3] including degeneration of substantia nigra pars compacta and dysfunction of striatal pathway with presence of Lewy bodies which are intracytoplasmic inclusion bodies containing protein alpha synuclein.[4] This leads to increased GABAergic signalling from output nuclei of basal ganglia to subcortical structures including thalamus. Clinically, cardinal features of the Parkinson's disease include tremors, rigidity, bradykinesia and postural instability. Other Non-motor features include autonomic dysfunction, sensory and sleep abnormalities, cognitive/neurobehavioral symptoms, freezing of gait and fatigue.[4]

Motor symptoms experienced by the patients are responsible for the increased number of falls and reduction in functional independence [5]. Motor symptoms also act as an independent predictor of mortality in patients with PD[6]. Locomotor function abnormalities in patients with PD include short stepping gait, shuffling, festination, stooping while walking with postural abnormality. These abnormalities are responsible for disability and impaired functional independence.

Although best medical therapy for PD is pharmacotherapy (especially with levodopa), with long term treatment patients develop hallucinations, postural hypotension, motor fluctuation and dyskinesias which can become more debilitating than symptoms of PD[7]. Among the locomotor abnormalities postural instability and gait abnormalities respond poorly with pharmacotherapy with dopaminergic medications.[8]

Surgical interventions, primarily deep brain stimulation (DBS) of various target nuclei, are therapeutic options when conventional therapy fails. Yet DBS is limited to a small well defined patient population and carries the risk of serious surgical complications and significant

neuropsychiatric side effects. Therapeutic alternatives are needed. Thereby, searching for alternative treatment option is essential and non invasive brain stimulation technique like transcranial direct current stimulation is an interesting potential alternative for management in PD.

Transcranial Direct Current Stimulation(tDCS) is a noninvasive brain stimulation technique in which a weak electric current is applied through the scalp to specific areas of brain. It alters the cortical excitability by modulating the neuronal resting membrane potential toward
excitability.[9]

Many previous studies have focused on application of tDCS in patients with PD with few of them showing promising results of motor function improvement following tDCS application. However, there is scarcity of data regarding any specific protocol of tDCS which gives consistent good results. With this background, we hypothesize that with repetitive bihemispheric anodal transcranial Direct Current Stimulation, locomotor function improve in patients with PD.

REVIEW OF LITERATURE

Progression of Parkinson's disease (PD) is characterised by multiple motor as well as non motor deficits. Severity of these symptoms gradually increases with duration and eventually respond less to dopaminergic therapy and thus pose a therapeutic challenge.[10] Neurosurgical procedures involving deep brain stimulation are another option with proven efficacy, but this method presents high cost, surgical risk, and possibility of worsening of verbal fluency and axial motor symptoms [11,12]. Appropriate interventions should present little or no adverse effects, improve functionality and well-being, and delay the progression of the disease. Thus, new therapeutic approaches are necessary to provide a better quality of life and to reduce the financial burden for society and health systems. Non-invasive brain stimulation techniques have shown promising results and may provide a therapeutic alternative which includes tDCS (Transcranial Direct Current Stimulation) and rTMS (Repetitive Transcranial Magnetic Stimulation). tDCS has some advantages over rTMS, including a favourable safety profile, tolerability, easier applicability and cost effectiveness.

Transcranial direct current stimulation (tDCS) is a mode of non-invasive brain stimulation in which a direct current is applied via surface electrodes on the head for a fixed period of time which modulates the cortical excitability and promotes motor learning in healthy individuals. There are multiple studies showing improved motor recovery in chronic stroke patients which has raised interest of tDCS in motor recovery in PD. Because PD is first and foremost a motor disturbance phenomenon, most studies in PD used tDCS to target the primary motor cortex (M1), reporting improvements in motor function and gait, compared with sham stimulation. The previous tDCS studies either stimulated primary motor cortex (M1) and supplementary motor area (SMA) or dorsolateral prefrontal cortex (DLPFC) directing the motor functions or non-motor function respectively. However, both M1 and DLPFC are found to be involved in both motor and non-motor functions and are involved in balance and mobility function. In accordance, a functional MRI study has shown that the anodal tDCS over the primary motor cortex (M1) and DLPFC increases the functional connectivity between the left caudate nucleus and parietal association cortices and modulates the functional connectivity of cortico-striatal and thalamo-cortical circuits resposnsible for motor improvement.[16]

In one of the first studies of tDCS in PD, Fregni et al [13] evaluated the effects of tDCS on both motor function and motor-evoked potentials (MEPs) of the hand in patients with PD. They found that anodal stimulation of primary motor cortex (M1) was associated with a significant improvement of motor function and reaction times. This effect was however not observed for cathodal stimulation of M1 or anodal stimulation of DLPFC, although a small (non statistically significant) improvement in motor function was noted.

Francesca Valentino et al [14] noted that anodal tDCS of primary motor cortex (M1) has a significant improvement of gait, as assessed by the Stand Walk Sit test, with reduction in number and duration of FOG episodes, along with a significant reduction in the Unified Parkinson's Disease Rating Scale score.

In Benninger et al [15] twenty-five PD patients were investigated with randomized, double blind, sham controlled study design with 13 patients receiving anodal tDCS over motor and pre frontal cotices alternatively over 8 sessions and 12 patients received sham stimulation. They noted tDCS improved gait by some measures for a short time and improved bradykinesia in both the on and off states for longer than 3 months.

Rosa maneti et al has also noted that significant motor improvement with improved TUG test score is seen after anodal tDCS of dorsolateral prefrontal cortex of right or left side depending on the particular side of onset of motor symptoms.

LACUNAE IN EXISTING KNOWLEDGE

- Dopaminergic medication and Deep Brain Stimulation (DBS) are current standard interventions for PD. Pharmacotherapy with dopaminergic drugs leads to partial improvement in the motor functions of patients. Invasive therapies like Deep Brain Stimulation have as yet limited availability and accessibility with risk of adverse events as well. Noninvasive therapies like tDCS are currently increasingly being probed for their therapeutic value in view of their safety, portability and convenience of administration.

- Improvement in motor function immediately after a single session of tDCS has been observed. The effect of single stimulation is not sustained beyond a few days. Only a few studies with varied sites of stimulation have evaluated the effect of repetitive tDCS on motor function improvement in patients with PD with conflicting results. There is unmet need to probe the utility of repetitive tDCS on motor function of patients with PD.

RESEARCH QUESTION

Does repetitive bihemispheric anodal transcranial direct current stimulation of dorsolateral prefrontal cortex and M1 cortex lead to improvement in motor function of patients with PD?

RESEARCH HYPOTHESIS

Repetitive bihemispheric anodal tDCS of dorsolateral prefrontal cortex and M1 cortex leads to sustained improvement in motor function of patients with PD (Hoehn and Yahr stage 2 to 4) beyond the immediate period of 4 days after the stimulation

AIMS AND OBJECTIVES

Primary Objective: To determine change in motor function score as assessed by MDS-UPDRS Part – III scale 1 week after the repetitive tDCS

Secondary Objective: To determine the change in Timed Up and Go test score of patients with Parkinson's Disease at 1 week after the repetitive tDCS

MATERIAL AND METHODS

Place of Study: Department of Neurology, ABVIMS & Dr. RML Hospital, New Delhi.

Study design: Randomized, double blind, sham-controlled study.

Sample size:

The study of David H Benninger, et al observed that UPDRS(III) at 1 month post-intervention in tDCS group was 22.7 ± 6.6 and in sham group was 18.6 ± 8.1. Taking these values as reference, the minimum required sample size with 80% power of study and 5% level of significance is 51 patients in each study group. Due to time constraints and non-availability of patients, finite population correction factor is used. Taking population as 30, total sample size calculated is 24. Taking lost to follow up as 15% and to reduce margin of error, total sample size taken is at least 30 (15 patients per group for sample size of 30).

Formula used is:

For comparing mean of two groups

$$N >= 2\frac{(\text{standard deviation})^2 \times (Z_\alpha + Z_\beta)^2}{(\text{mean difference})^2}$$

Where Z_α is value of Z at two sided alpha error of 5% and Z_β is value of Z at power of 80% and mean difference is difference in mean values of two groups.

Pooled standard deviation= $\sqrt{(S_1{}^2 + S_2{}^2)/2}$

Where S_1 is standard deviation of 1 group.

and S_2 is standard deviation of other group.

Finite population correction factor:-

$$SS \geq n/(1 + [\frac{n-1}{Pop}])$$

Where Pop is population

Calculations:

Pooled standard deviation= $\sqrt{(6.6^2 + 8.1^2)/2}$

=7.39

$N >= \frac{2(7.39)^2 \, X(1.96 + 0.84)^2}{(4.1)^2}$

>=50.91=51(approx.)

Total sample size to be taken is 102

Finite population correction factor:-

SS >=102/ (1 + [(102 − 1)/30])>=23.36=24(approx.)

Taking lost to follow up as 155, n>=24/.85>=28.23=29(approx.)

Study population**:** Patients with PD.

Type of Study: - Prospective interventional randomized double blinded comparative study.

Block Randomization

Block Randomization with Sealed envelope system:- In this, one person, who is neither investigator nor personnel applying tDCS, will prepare ten sealed opaque envelopes assigning A and B in 5 envelopes each, where one label represents tDCS group and other label represents sham group. Once a patient will consent to enter a trial an envelope will be opened and the patient will then be offered the allocated group. In this technique, patients will be randomized in a series of blocks of ten. So basically, we are using 3 blocks and in each block, 10 patients will be taken and among those 10 patients, 5 patients will be allocated tDCS group and 5 patients will be allocated sham group. Neither the patient nor the investigator will know which label represents which group making the study double blinded.

The data will be entered in MS EXCEL spreadsheet and analysis will be done using Statistical Package for Social Sciences (SPSS) version 21.0.

INCLUSION CRITERIA

1. Patients fulfilling the Movement Disorder Society (MDS) clinical diagnostic criteria for Parkinson's disease.
2. Patients with Hoehn & Yahr stages 2–4 Parkinson's disease.
3. Patients maintained on stable medical regimen for at least 1 month before entering the study.

EXCLUSION CRITERIA

1. Patients with other confounding neurological and psychiatric disorders.
2. The presence of metal objects or stimulators in the head.
3. Patients with a history of deep brain stimulation.
4. Patients with history of seizures.
5. Patients with skull defect due to surgery e.g. craniectomy
6. Patients with scalp condition likely to obstruct application of electrodes.

PROCEDURAL DETAILS

Patients with PD will be included irrespective of treatment duration, age, gender and duration of illness. The demographic data of all the included patients will be collected and detailed clinical history and examination including neurological assessment will be done in all the patients. The diagnosis of Parkinson's disease will be made by the MDS clinical diagnostic criteria for Parkinson's disease. The severity of motor dysfunction will be assessed according to Movement Disorder Society (MDS)- Unified Parkinson's Disease Rating Scale (UPDRS) revision (MDS-UPDRS) part III. Hoehn and Yahr staging will be done for each subject. Patients will be assessed by Timed up and go (TUG) test.

The study will be double-blind, sham-controlled study wherein whether the patients will recieve sham or real stimulation will be decided by randomization. The patient will be serially given an envelope containing the modality of treatment to be given in coded numbers during sessions. He/she will take the envelope to the personel involved in the stimulation only. The person who will perform tDCS will open the envelope and stimulation will be given as per coded protocol for the sham or the real stimulation. The stimulation record will be stored in the machine or storage device. The patient will be given the appropriate stimulation on next visit based on the type of stimulation given during the previous visit. The envelopes containing the treatment modality will be prepared by another person not connected with the study using randomization software. The patients and the investigators making the pre-stimulation and the post-stimulation assessments will be blinded to the type of stimulation given. The participants will be made to learn the TUG test beforehand to minimize learning effects on the outcome measures from pre to post tDCS.

Transcranial direct current stimulation (tDCS) procedure:

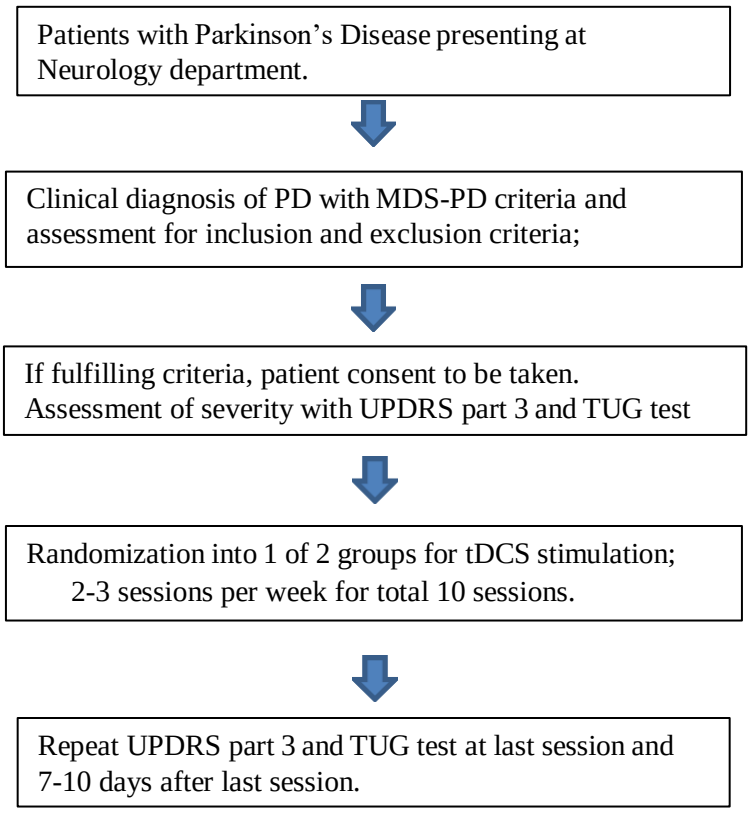
Anodal tDCS will be administered at the beginning of the on period after the participant had taken the levo-dopa dosage (around 1 hour after medication). The stimulation will be delivered by a battery-driven, direct current stimulator (Startism 32, Neuroelectrics, Barcelona S.L., Spain) through an array of electrodes. A direct current of 2 mA will be applied for 20 minutes (with a ramping period of 10 sec at the beginning and end of the stimulation).The current density of ≤ 0.057 mA/cm^2 will be maintained as per the safety guidelines. Thee electrodes will be secured, and an electroconductive gel will be applied under the electrodes before the montage to reduce contact impedance. The international 10–10 system of electrode placement will be used to place the tDCS electrodes. The active anodal electrodes will be placed on left FC1 and right FC2 in order to stimulate the M1 and DLPFC of both the brain hemispheres simultaneously and the one cathode electrodes will be placed over the left or right supra-orbital area. In the sham stimulation, the tDCS montage will be the

same, but the current will be turned off10 s after the stimulation begins and will be turned on for the last 10 s of the stimulation period (the duration of the fade-in and fade-out periods is 10 s), making this condition indistinguishable from the experimental stimulation. The sham or the active stimulation will be done 2-3 times a week for a total of 10 sessions. Assessment with TUG test and MDS-UPDRS part 3 will be done at the end of last session of stimulation and 1 week after the last session.

The Timed Up and Go (TUG) test:

In the TUG test, the patients will be instructed to stand up from the sitting position while seated on a chair on the examiner's signal, and then they will be asked to walk on the floor upto a distance of 3 meters (which will be pre-marked), then they will be asked to turn around and walk back to the chair and sit down. Patients will be instructed to walk at their regular pace.

The TUG test will be measured using a stop watch. The TUG test will be performed before and at the end of 4 weeks and one week after last session of tDCS and recordings will be made by the examiner who is blind to the stimulation condition received by the patient. Video recording of the test will also be done.



REFERENCES

1. Schneider SA, Obeso JA. Clinical and pathological features of Parkinson's disease. Behavioral Neurobiology of Huntington's disease and Parkinson's disease. 2014:205-20.

2. Feigin VL, Vos T. Global, regional, and national burden of neurological disorders during 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. (2019) 18:459–80.

3. Rousseaux MW, Shulman JM, Jankovic J. Progress toward an integrated understanding of Parkinson's disease. F1000Research. 2017;6:1121.

4. Jankovic J. Parkinson's disease: clinical features and diagnosis. Journal of neurology, neurosurgery & psychiatry. 2008 Apr 1;79(4):368-76.

5. Gazibara T, Pekmezovic T, Tepavcevic DK, Tomic A, Stankovic I, Kostic VS, Svetel M. Circumstances of falls and fall-related injuries among patients with Parkinson's disease in an outpatient setting. Geriatric nursing. 2014 Sep 1;35(5):364-9.

6. Forsaa EB, Larsen JP, Wentzel-Larsen T, Alves G. What predicts mortality in Parkinson disease?: a prospective population-based long-term study. Neurology. 2010 Oct 5;75(14):1270-6.

7. Hauser RA. Levodopa: past, present, and future. European neurology. 2009;62(1):1-8.

8. Koller WC, Glatt S, Vetere-Overfield B, Hassanein R. Falls and Parkinson's disease. Clinical neuropharmacology. 1989 Apr 1;12(2):98-105.

9. Brunoni A, Nitsche M, Loo C. Transcranial direct current stimulation in neuropsychiatric disorders. Cham, CH: Springer International Publishing. 2016.

10. Braak H, Del Tredici K, Rüb U, De Vos RA, Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiology of aging. 2003 Mar 1;24(2):197-211.

11. da Costa Capato TT, Domingos JM, de Almeida LR. Versão em Português da Diretriz Europeia de Fisioterapia para a Doença de Parkinson.

12. Munhoz RP, Picillo M, Fox SH, Bruno V, Panisset M, Honey CR, Fasano A. Eligibility criteria for deep brain stimulation in Parkinson's disease, tremor, and dystonia. Canadian Journal of Neurological Sciences. 2016 Jul;43(4):462-71.

13. Fregni F, Boggio PS, Santos MC, Lima M, Vieira AL, Rigonatti SP, Silva MT, Barbosa ER, Nitsche MA, Pascual-Leone A. Noninvasive cortical stimulation with transcranial direct current stimulation in Parkinson's disease. Movement disorders. 2006 Oct;21(10):1693-702.

14. Valentino F, Cosentino G, Brighina F, Pozzi NG, Sandrini G, Fierro B, Savettieri G, D'Amelio M, Pacchetti C. Transcranial direct current stimulation for treatment of freezing of gait: A cross-over study. Movement Disorders. 2014 Jul;29(8):1064-9.

15. Benninger DH, Lomarev M, Lopez G, Wassermann EM, Li X, Considine E, Hallett M. Transcranial direct current stimulation for the treatment of Parkinson's disease. Journal of Neurology, Neurosurgery & Psychiatry. 2010 Oct 1;81(10):1105-11.

16. Costa-Ribeiro A, Maux A, Bosford T, Tenório Y, Marques D, Carneiro M, Nitsche MA, Alberto Filho M, Monte-Silva K. Dopamine-independent effects of combining transcranial direct current stimulation with cued gait training on cortical excitability and functional mobility in Parkinson's disease. J Rehabil Med. 2016 Oct 1;48(9):819-23.

ABBREVIATIONS

PD	Parkinson's Disease
tDCS	transcranial Direct Current Stimulation
M1	primary motor cortex
DLPFC	Dorsolateral Prefrontal Cortex
TUG	Timed Up and GO
FOG	Freezing of Gait
rTMS	repetitive Transcranial Magnetic Stimulation
DBS	Deep Brain Stimulation
H and Y	Hoehn and Yahr