EFFECT OF ANODAL TRANSCRANIAL DIRECT CURRENT STIMULATION (tDCS) OF PRIMARY MOTOR CORTEX ON HEADACHE FREQUENCY IN PATIENTS WITH CHRONIC MIGRAINE

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INTRODUCTION

Migraine is a heterogeneous and complex disorder affecting around 10-15 % of world population and is ranked as the third most prevalent disorder in the world.(1) Pain is the most significant and crucial somatic and autonomic symptom among those that make up the complex clinical illness known as migraine. Five elements have been found to be the most common causes of migraines: stress, fasting, changes in the atmosphere, sleep-related issues, and abnormalities in women's hormones.(2) All patients should receive recommendations for lifestyle modifications and have their triggers addressed during the anamnesis. The attack of migraine lasts for about 4-72 hour and consists of four phases viz – premonitory phase, aura, headache and postdrome. Migraine can be subdivided based on frequency of headache and the presence or absence of aura.

The International Headache Society (IHS) defined chronic migraine (CM) as a subtype of headache that occurs at least 15 days a month and has eight migraine days per month.(3) It is an extremely disabling disorder with a significant physical and emotional burden, as well as substantial direct and indirect expenditures.CM typically evolves from episodic migraine with an annual progression rate of ~ 3% and affects approximately 2% of people with migraines. The diagnosis is mostly dependent on a thorough anamnesis, physical evaluation and testing is usually not necessary. Pharmacological and nonpharmacological therapies form the basis of treatment. The purpose of pharmaceutical interventions is to both treat and prevent headaches. The high prevalence of psychological comorbidities, such as anxiety and depression, and the inability of current pharmaceutical medications to adequately relieve pain are further reasons why CM patients are challenging to treat.

Research has demonstrated that CM is linked not only to an increased frequency of attacks but also to alterations in the neural networks responsible for processing pain, including

hyperalgesia, or the heightened sensitivity to noxious stimuli, and allodynia, a phenomenon that affects as many as 63% of these patients.(4) Furthermore, research on neuroimaging has demonstrated that the pathophysiology of chronic pain and the development and maintenance of migraine problems share a similar brain foundation.(5) For example, these migraine imaging investigations discovered anatomical and functional abnormalities in areas such as the anterior cingulated cortex, primary somatosensory cortex, and the trigeminal somatosensory pathway that are important in processing central pain.(6) These findings imply that central sensitization may arise from recurrent episodes.(5) (7)

Recent studies has brought forward the use of neuromodulation techniques like transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). TMS involves the use of magnetic field to induce an electric current at a particular area of brain whereas tDCS is a cortical stimulation technique, which is carried out with a battery-driven device, and involves application of electrodes to the scalp, with a weak current flowing between the electrodes, through the brain.

With this background, we hypothesize that application of tDCS to prespecified areas in brain would lead to better outcomes in language function, as compared to sham application in patients with chronic migraine.

REVIEW OF LITERATURE

Migraine is typified by attacks of moderate to severe throbbing headache which is mostly unilateral. (Bilateral involvement is seen in around one third of attacks). It is associated with photophobia, phonophobia, nausea/vomiting and is accelerated by physical activity.

Different pharmacological choices are available for prophylaxis, and the drug is often chosen in accordance with the clinical history, physical, and psychological comorbidities of the patient. However, due of their adverse effects, pharmaceutical therapies are occasionally only mildly tolerated, which results in low therapy adherence. Neuromodulation techniques are among the non-pharmacological approaches that have been suggested in recent decades for the treatment of patients with CM. (8)

Neuromodulation techniques are the non-invasive stimulation technique which includes transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). The use of TMS for migraine is predicated on the idea that it may stop the spread of depression, which is thought to be the underlying cause of the aura at the start of the attack, by stimulating cortical neurons.(9) The tDCS has the same potential to cause reversible, restricted, and remote alterations in cortical excitability as rTMS.(10) (11) In migraine patients, the homeostatic plasticity and changes in glutaminergic function is associated with disorders in cortical excitability, thus tDCS can modulate the cortical activity and lessen the discomfort. Whereas tDCS can alter the resting membrane potential of neurons to modify their spontaneous firing rates, rTMS just interrupts or stimulates neuronal activity. Anodal stimulation depolarise the underlying cortical neurons, making them more sensitive to action potentials and therefore known as stimulatory whereas the cathodal stimulation has the opposite effect and lead to hyperpolarisation of underlying neurons, making them less likely to fire and therefore known as inhibitory. (12) (13)

Transcranial direct current stimulation (tDCS) has been effective in modulating refractory pain in patients of fibromyalgia, spinal cord injury ,trigeminal neuralgia and also in other disorders like depression, stroke epilepsy and parkinsonism. (14) (15) (16) The potential of tDCS to modify pain-related neural networks has been deemed the explanation for the good outcomes in small and preliminary investigations, which have been linked to the possibility that CM may be related to central sensitization.

The majority of researches have determined that the primary motor cortex (M1) or the visual cortex should receive the majority of migraine treatment. (4) (17) The processes linked to activation of M1 appear to involve other cortical areas, despite the fact that this region has been identified as the major locus for pain management for certain circumstances. (18) The M1 is involved in a neural network which includes regions like DLPFC (dorsolateral prefrontal cortex), ACC, thalamus and cerebellum. DLPFC is involved in and emotional regulation and exert an inhibitory effect on pain because of its connection with mid brain structures, cingulate cortex and striatal thalamus. (19) (20) (21) Tamura et al. confirmed a large increase in cerebral blood flow of the caudal region of the anterior cingulate cortex (ACC) and a significant drop in the prefrontal cortex's, both of which were connected with a reduction in pain. (22) Though several regions are known for pain control but there is no unanimity on superiority of one region over another. (23)

Andrade et al in their comparative study of tDCS over primary motor cortex vs prefrontal cortex in refractory chronic migraine found a significant reduction in headache impact, pain intensity and quality of life with superior result in DLPFC group as compared to M1 group.

Grazzi et al in their study suggested that tDCS did not affected the frequency of chronic migraine in patients with medication overuse.(24)

In the study of cathodal tDCS of visual cortex in prohylaxis of migraine by Andrea Antal, it was seen that a significant reduction in number of migraine related days, pain intensity, duration of migraine was seen in cathodal tDCS group as compared to sham group, but no such difference was seen in frequency of migraine attacks.(1)

In the study conducted by Auvichayapat for migraine prophylaxis by anodal tDCS , there was a statistically significant reduction in attack frequency, pill use and pain intensity. The current was given at left M1 and it was well tolerated by all patients without any serious adverse effect. (25) Similar result regarding safety of anodal tDCS and their positive effect in pain reduction was demonstrated by Fregni et al.(14)

DaSilva et al showed that tDCS administered across the motor (anodal) and orbitofrontal (cathode) cortices, spaced one month apart, can reduce the patient's clinical impression, the duration of the chronic migraine episodes, and the degree of pain progressively.(4)

Lacunae of Existing Knowledge and the need for the study

There is a paucity of data on the role of Anodal transcranial direct current stimulation (tDCS) of the primary motor cortex on headache frequency in patients with chronic migraine.

Research Question

Does anodal transcranial direct current stimulation of the motor cortex reduce migraine frequency when used in addition to standard medical therapy in patients with chronic migraine?

Research Hypothesis

Anodal transcranial direct current stimulation of the motor cortex reduces migraine frequency when used in addition to standard medical therapy in patients with chronic migraine.

Aims and Objectives

AIM: To evaluate the impact of anodal tDCS of the motor cortex as an add-on therapy in reducing headache frequency in chronic migraine patients in reducing headache frequencies in chronic migraine patients.

OBJECTIVES:

Primary objective:

1. To determine the change in headache frequency at 12 weeks from baseline after nine sessions of anodal tDCS.

Secondary objectives:

1. To determine the change in headache intensity, pill count, and acute medication days at 12 weeks compared to baseline.
2. To determine the effect of anodal tDCS on disability migraine-related disability by measuring the change in Migraine Disability Assessment (MIDAS) Test and Headache Impact Test (HIT6) at 12 weeks compared to baseline.
3. To determine the effect of anodal tDCS on the quality of life by measuring the change in migraine-specific Quality of Life (MSQL) scores at 12 weeks compared to baseline.

Materials and Methods

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

Study Design:- Prospective, randomized, double-blinded study.

Study Population:- Patients with chronic migraine presenting to the Neurology OPD.

Sample size calculation:

The sample size was calculated using the study, 'Anodal transcranial direct current stimulation in chronic migraine and medication overuse headache: A pilot double-blind, randomized sham-controlled trial, by Icco et al. In this study, the number of headache days in the anodal tDCS group was 9.4 ± 7.3 days, while the number of headache days in the sham group was 17.3 ± 7.3 days. Taking these values as a reference, the minimum required sample size with 80% power of study and 5% level of significance is 14 patients in each group.

Considering an attrition of about 10 % , the sample size in each group is 15.4 which is rounded off to 16.

The formula used is:

For comparing the mean of the two groups

$$N \geq \frac{2(\text{pooled standard deviation})^2 X(Z_\alpha + Z_\beta)^2}{(\text{mean difference})^2}$$

Where Zα is the value of Z at a two-sided alpha error of 5%, Zβ is the value of Z at power of 80%, and the mean difference is the difference in mean values of the two groups.

Pooled standard deviation = $\sqrt{(S1^{\,2} + S2^{\,2})/2}$

Where S_1 is the standard deviation of 1 group. and S_2 is the standard deviation of the other group.

RANDOMISATION: -

Randomization will be done using the Stratified block randomization with a sealed envelope system. Stratification will be done according to the presence of MOH (medication overuse headache) and no MOH. In this technique, patients will be randomized in a series of blocks of 4, stratified according to the presence or absence of MOH, using an online randomization generator. Patients will be allocated to either of the groups (group A or group B) in a 1:1 ratio. The randomization list will be generated by the biostatistician and transferred to a sealed opaque envelope, and each envelope will be opened by the primary investigator when the corresponding number of eligible participants is enrolled. This envelope will be handed over to the technician, who will administer the tDCS as per the protocol. Neither the patient nor the investigator assessing the clinical outcomes will know which label represents which group. However, the technician who will be administering anodal tDCS will know about the identity of the groups. Outcomes will be recorded by a blinded accessor.

INCLUSION CRITERIA

1. All patients between 18-60 years of age fulfilling the criteria for chronic migraine as defined by ICHD -3.
2. Patients who are on a minimum of one concomitant preventive medication for not less than three months duration and a dose that is stable for at least one month prior to randomization.
3. Patients willing to give informed consent to participate in the study

EXCLUSION CRITERIA

1. Prior Neurologic diseases like brain tumours, dementia, seizure, encephalitis, meningitis, and stroke.
2. Patients overusing barbiturate-containing analgesics, opioids, or subjects with medical conditions attributable to medication overuse (e.g. peptic ulcer disease from overuse of nonsteroidal anti-inflammatory drugs [NSAIDS]).
3. Patients who do not complete the headache diary for more than six non-consecutive days during the baseline period of 28 days.
4. Illiterate patients whose attendants do not maintain headache diary.
5. Pacemaker in situ, cochlear implant in situ.
6. Pregnancy

METHODOLOGY

All patients presenting with headaches to the Neurology Outpatient Department (OPD) at ABVIMS and Dr RML Hospital will undergo screening. Patients who meet the criteria for chronic migraine as per ICHD-3 and are willing to participate in the study will be included in the study after properly fulfilling the inclusion and exclusion criteria. Before randomization, eligible patients will be required to complete a headache diary over a 4-week screening period to evaluate headache frequency and adherence. All patients will be evaluated using a pre-designed proforma covering all aspects of demography, clinical characteristics, and phenotype of headache and will undergo relevant biochemical and radiological tests. Chronic migraine patients who comply with the headache diary will be randomly assigned to two groups - "Group A" and "Group B" in a 1:1 ratio. Group A will receive conventional medical treatment along with anodal tDCS stimulation, and Group B will receive conventional medical treatment along with sham stimulation.

Randomization will be done using the Stratified block randomization with a sealed envelope system. Stratification will be done according to MOH (medication overuse headache) and no MOH. In this technique, patients will be randomized in a series of blocks of 4, stratified according to the presence or absence of MOH, using an online randomization generator. Patients will be allocated to either of the groups - Group A (Conventional Medical Treatment with anodal tDCS stimulation) or Group B (Conventional medical treatment group with sham stimulation) in a 1:1 ratio. The randomization list will be generated by the biostatistician and transferred to a sealed opaque envelope, and each envelope will be opened by the primary investigator when the corresponding number of eligible participants is enrolled. The technician will do the stimulation as per the allotted group. Outcomes will be assessed by an investigator blinded to the type of stimulation.

Experimental design

The two stages of the current investigation are as follows:

1. A baseline assessment will be conducted four weeks before therapy to record the frequency, severity, and pattern of acute medication use, as well as compliance with completing the headache diary.
2. During the double-blind treatment phase, both groups will receive three sessions of tDCS or sham stimulation each in weeks 1, 5, and 9. The dose of preventive medications will not be altered during the double-blind phase. Patients will be allowed to utilize drugs for acute migraines as necessary.
3. Outcomes will be assessed by a blinded investigator at 5, 9 and 12 weeks.

PROCEDURAL DETAILS of tDCS

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/cm2 will be maintained as per the safety guidelines. The electrodes will be secured, and an electroconductive gel will be applied under the electrodes before the montage to reduce contact impedance. The international 10–20 system of electrode placement will be used to place the tDCS electrodes. The motor cortex is localized to C3/C4 in the 10/20 international system of EEG electrode placement. In patients with hemicranial headache, the hemisphere contralateral to the predominantly painful side will be stimulated. In patients who have holocranial headaches or the same number of attacks on either side, the left motor cortex will be stimulated. The 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 off 10 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. Patients will be questioned about any adverse effects they may have encountered during or following the stimulation. In case of any serious adverse event reported by the patient during the study procedure, tDCS will be stopped, and the patient will be excluded from the study. To assess the effectiveness of blinding, patients will be asked to identify the type of stimulation they received. The patients in both groups will maintain a diary that includes headache frequency, intensity, and pill count for the entire 12 weeks.

STUDY TOOLS

1. Headache Diary to assess the headache frequency, intensity and pill count
2. The severity of the headache will be assessed using a Four Point Score (none, mild, moderate, severe).
3. The change in disability caused by headaches will be assessed using:-MIDAS (Migraine Disability Assessment) Questionnaire,(24) The HIT-6 (Headache Impact Test-6) scale.(25)
4. Quality of life will be assessed using the Migraine Specific Quality of Life Scale (MSQL) scale.
5. Associated comorbid depression will be assessed by a Patient Health Questionnaire (PHQ-9).

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