EFFICACY OF TDCS AND CBT IN MANAGEMENT OF MIGRAINE

ORIGINAL RESEARCH

Efficacy of Trans-Cranial Direct Current Stimulation and Cognitive Behavioral Therapy in Management of Migraine: A Randomized Controlled Trial.

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ABSTRACT

Background: Migraine is a common disabling headache disorder. It has been ranked among the disease causing greatest degree of handicap together with conditions such as quadriplegia, dementia and active psychosis.

Purpose: Objective of present study was to evaluate the efficacy of Trans Cranial Direct Current Stimulation (tDCS) and Cognitive Behavioral therapy (CBT) in Management of Migraine.

Materials and methods: Subjects fulfilling selection criteria were randomly allocated into three groups. Subjects in group one were given tDCS, three sessions per week for six weeks duration. Subjects in group two were given CBT sessions, one session per week, of approximately one hour duration for six weeks along with Sham tDCS. Control group did not receive any treatment. Subjects were asked to record their Headaches in Headache Diary for Baseline and Post Intervention Data.

Results: Results showed a significant decrease in Headache frequency, Pain Intensity and Duration of headache in both tDCS and CBT groups as compared to control group. There was significant difference in headache frequency and pain intensity between tDCS and CBT group.

Conclusion: tDCS and CBT can decrease headache frequency, pain intensity and headache duration in patients of Migraine. tDCS may be more effective in decreasing Headache frequency and in intensity as compared to CBT.

Keywords: Migraine, Headache, Trans cranial Direct Current Stimulation, Cognitive Behavioral Therapy.
Introduction:
Migraine is a common disabling headache disorder. Epidemiological studies have documented its high prevalence and high socio-economic and personal impacts. In the Global Burden of Disease Survey 2010, it was ranked as third most prevalent disorder and seventh-highest specific cause of disability worldwide. Migraine has been ranked among the disease causing greatest degree of handicap together with conditions such as quadriplegia, dementia and active psychosis. Migraine can be triggered by hunger, lack of sleep, excessive sleep, climatic changes, foods particularly cheese, alcohol, menstruation etc. Severity, symptoms and type of migraine varies from individual to individual. A migraine attack can last from four hours to a prolonged duration of 72 hours. Such attacks are usually accompanied by nausea, photophobia and phonophobia. Cortical Spreading Depression (CSD) seems to be one of the basic mechanisms for initiation of migraine attack. CSD triggers the trigemino-vascular system, which in turn releases nitric oxide and calcitonin gene related peptide thus inducing vasodilatation and perivascular nerve activity. CSD has been shown to cause activation and sensitization of trigemino-vascular system initiating a series of neural, vascular and inflammatory events that result in pain. Activation of trigemino-vascular system is thought to initiate a cascade of chemical activity from trigeminal sensory nerve endings. Indirect support for trigemino-vascular activation during migraine attacks comes from observations of a phenomenon called sensitization. Sensitization of primary sensory axons, followed by sensitization of central trigemino-cervical neurons may augment nociceptive inputs during arterial pulsations. Sensitization of central neurons may explain the extra-cranial tenderness and cutaneous allodynia observed in patients with migraine during attack.

Patient with migraine are often refractory to medical management and there are a number of adverse effects of pharmacological management of migraine. Therefore, patients might need other strategies to modulate their pain and other symptoms.
Transcranial Direct Current Stimulation (tDCS) is a noninvasive brain stimulation technique that applies a mild (1-2 mA) direct electric current via scalp to enhance or diminish neural excitability. There is strong evidence that neurons underlying the anode are excited with resting membrane potential shifting towards depolarization and an increased rate of spontaneous neuronal firing while the neurons underlying the cathode are inhibited with resting membrane potential shifting towards hyperpolarization and reduced neuronal firing.\(^8\)

TDCS effects appear to be multifactorial and capable to induce changes in different systems. Thus, the effects underlying tDCS induces physiological changes that result in local and distant plastic changes.\(^9\)

Cognitive Behavioral Therapy (CBT) is an intensive short term problem oriented approach. CBT helps people to look at how they interpret and evaluate what is happening around and effect of these perceptions on their emotional experience.\(^10\) Cognitive approaches are based on the assumption that much of how we feel is determined by what we think. Therefore, a more informal status about the natural course of disease, precipitating factors, and underlying mechanisms may enable patients to develop more effective coping strategies to manage the disease itself.\(^11\)

The aim of present study was to assess the efficacy of tDCS and CBT in Management of Migraine.

**Method and Materials:**

**Ethical approval:** This study was approved by Institution Ethics Committee (IEC) of Department of Physiotherapy, Guru Jambheshwar University of Science and Technology, Hisar in its meeting held on 3/11/15, vide letter no. PTY/2015/800. The IEC of the Department is constituted in accordance with guidelines of the Indian Council of Medical Research.

**Participants:** Participants enrolled in the study were either recruited through referrals from hospitals and outpatient clinic or reported directly to either University Health Centre or O.P.D. of Physiotherapy Department of Guru Jambheshwar University of Science and Technology, Hisar.
Subjects were screened for selection criteria in accordance with the study protocol. Patients were eligible for the study if they fulfilled the criteria of migraine as defined by International classification of Headache Disorder of International headache Society. Patients between 18 to 65 years of age, not taking any prophylactic medication or any herbal hair oil massage were included in the study. Subjects with any co-existent medical and psychiatric disorder as well as any metallic implant in head, skull defect or pacemaker were excluded.

Randomization and Consent-
Participants were randomly allocated to either the experimental groups (Group 1 received tDCS, Group 2 received CBT) or in control group with computer generated random number tables. Written informed consent was collected from all participants.

Study designs and outcome measures-
The design of the trial was randomized controlled. Participants were asked to fill a baseline data of outcome measures. Numbers of headache episodes were recorded by patient on a headache diary for 28 days. Subjects were asked to record Headache Duration (time: to and from), pain intensity (0 as no pain to 10 as worst possible pain) and Frequency (date of each episode) in Headache Diary. Minimum duration for counting the headache episode was > four hours. After six weeks of study protocol, the subjects were again asked to fill the same information in headache diary for four weeks.

Study was divided into three phases.
Phase 1- Baseline evaluation consisting of four weeks period which included registering the frequency of migraine episodes, intensity of pain and duration of headache.
Phase 2 - Six weeks of intervention period.
Phase 3- Post intervention data collection. Patients were asked to fill headache diary again for a period of four weeks registering headache frequency, intensity of pain and duration.

Treatment-Subjects in a group 1 were given tDCS, three sessions per week for six weeks duration. Cathodal tDCS, cathode over Oz and anode over Oz electrode positions according to 10-20 EEG system with a constant current of 2 mA for 20 minutes. Patients in group two
were given CBT sessions, one session per week, of approximately one hour duration for six weeks along with Sham tDCS. For Sham stimulation, electrodes were placed in the same position as the tDCS Group. Stimulation of 2 mA was given for thirty seconds, and after 30 seconds the intensity was ramped off slowly up to zero. Sham tDCS was given for twenty minutes. The control group did not receive any treatment. Only baseline data and post intervention data was collected from the subjects in control group.

**Statistical Analysis:** All Analysis was based on Intention to treat principle. Two subjects dropped out from the study (one in CBT and one in tDCS.) They were followed up and data was obtained from them. Baseline measures were compared among the group. Normality assumption was analyzed using Shapiro-wilk test. Significance level was set up at P<0.25 Group wise comparisons were performed using T test or wilcoxon signed rank test based or normality DATA. Comparisons among groups were performed using one way ANOVA and followed by post HOC analysis by Tukey test. Headache frequency was analyzed using Kruskal Wallis test and Ratio analysis. Significance level was set at P<0.05. Data analysis was performed using Statistical Package for the Social Sciences, 16 version for Windows.

**Results**

**Baseline characteristics:**

There was no significant difference among the baseline data (Table 1). Therefore, it can be suggested that baseline data for all the outcome measures was similar.

**Table 1:** Showing mean values and Standard deviation of all the groups at Baseline levels.

|                      | CBT (Mean±S.D) | tDCS (Mean±S.D) | Control (Mean±S.D) | P Value |
|----------------------|----------------|-----------------|--------------------|---------|
| Headache Frequency   | 4.27±2.00      | 3.81±1.40       | 3.09±1.19          | 0.105   |
| Headache Intensity   | 7.43±995       | 7.89±964        | 7.32±1.05          | 0.135   |
| Headache Duration    | 586±170        | 616±288         | 744±240.81         | 0.75    |
**Headache Frequency:**

Results suggest significant difference in headache frequency among different groups with mean headache frequency rank score of 41.50 for CBT group, 43.45 for tDCS group and 15.55 for Control Group (Table 2). Expressed in the terms of ratio (post/pre), the values of tDCS group (0.481), CBT group (0.525) and control group (1.040) suggest significant decrease in headache frequency in tDCS and CBT Group as compared to control group. Post/Pre ratio of tDCS Group is better than CBT Group.

**Table 2:** Showing data of headache frequency of all the groups expressed in terms of Mean ±Standard Deviation and Rank Frequency Scores

| Group   | Mean Change in Headache Frequency | Pre Intervention Mean Headache Frequency | Post Intervention Mean Headache Frequency | Rank Frequency scores |
|---------|-----------------------------------|----------------------------------------|------------------------------------------|-----------------------|
| CBT     | 2.09±1.37                         | 4.27±2.00                              | 2.18±1.00                               | 41.50                 |
| tDCS    | 2.09±1.06                         | 3.81±1.40                              | 1.72±0.55                               | 43.45                 |
| CONTROL | .09±1.01                          | 3.09±1.01                              | 3.00±1.19                               | 15.55                 |

**Table 3** showing Comparison between pre Intervention and post intervention Mean headache pain Intensity of three groups

| Group   | Baseline (Mean ±S.D) | Post intervention (Mean ±S.D) | P Value |
|---------|----------------------|------------------------------|---------|
| CBT     | 7.43±0.99            | 5.70±1.01                    | 0.0001  |
| tDCS    | 7.89±0.96            | 5.53±0.81                    | 0.0001  |
| Control | 7.31±1.05            | 7.17±1.22                    | 0.256   |

**Pain intensity:** Results of One Way ANOVA suggest a statistically significant difference among the groups. Post HOC analysis suggested significant improvement in mean pain intensity of tDCS group (2.36±0.66) as compared to CBT group (1.73±0.78) and control group (0.14±0.57) (Figure 1). Results suggest a significant decrease in
Figure 1: Showing mean headache pre and post intervention for all groups

Table 4 showing Comparison between Pre Intervention and post intervention Mean headache duration (in minutes) of three groups.

|          | Baseline (Mean ±S.D.) | Post Intervention (Mean ±S.D.) | P value |
|----------|------------------------|-------------------------------|---------|
| CBT      | 586±170.70             | 407±123.67                    | 0.0001  |
| tDCS     | 616±288.34             | 398±163.44                    | 0.0001  |
| Control  | 744±240.81             | 725±258.68                    | 0.310   |

Pain Intensity of CBT Group as compared to Control Group. Pre Intervention and Post Intervention Comparisons suggest a statistically significant decrease in headache intensity in CBT and tDCS group. There was no statistically significant difference between pre and post values of control group (Table 3).

**Headache Duration:**

Results of One way ANOVA suggested that there was significant difference among the groups. Post HOC analysis showed significant decrease in headache duration of CBT (179 min±105.1) and tDCS (218±152.8) group as compared to control (18.31±82.6) group. However, there was no significant difference between tDCS and CBT Group. Pre Intervention and Post Intervention Comparisons suggest a statistically significant decrease in headache duration in CBT and tDCS group. There was no statistically significant difference between pre-intervention and Post Intervention values of control group (Table 4).

**Discussion**

This is a novel randomized controlled trial to compare the efficacy of CBT and tDCS and non-treated controls on headache duration, frequency and intensity in migraines.
The results of our findings suggest that CBT and tDCS can significantly decrease headache frequency, intensity and duration and tDCS may be better in reducing headache related pain and frequency as compared to CBT in migraines. Behavioral treatment and neuromodulatory approaches are being investigated to evaluate their efficacy in management of migraine. Based on the concept of cortical hyper-excitability in migraine, cathodal tDCS in migraineurs is expected to normalize cortical excitability either by prophylactic treatment in the interictal phase or by an acute treatment at the beginning of migraine attack. Manjet C Matharue et al did a PET study on central neuromodulation in chronic migraine patients with sub occipital stimulators on 8 migraineurs. They reported marked response with implantation of bilateral sub occipital stimulators and the beneficial response was maintained for an average follow up period of 1.5 years. A PET study in this group of chronic migraineurs with implanted sub occipital stimulators showed significant changes in regional Cerebral Blood Flow in dorsal rostral pons and cuneus correlated to pain scores and in the anterior cingulate cortex and left pulvinar correlated to stimulation based paresthesia scores. Migraine is a condition of neuronal hyper excitability with a central generator, peripheral pain mechanism and central integration. Decreased neuronal excitability through cathodal tDCS may be a mechanism that influences migraine pathophysiology with application of tDCS. Nicolodi M et al did a study to explore the role of N-methyl D-aspartic acid (NMDA) receptors in migraine. Their study supported the hypothesis that NMDA receptors play an important role in mechanism of migraine. tDCS may have a role in modulation of NMDA receptors activity in migraineurs. Labetanz et al in 2002 suggested that tDCS may be involved in inducing short lasting NMDA receptors modulation. Nitsche MA et al did a study on pharmacological modulation of cortical excitability shifts induced by tDCS in humans. In their study, Dextromethorphan induced NMDA receptor blockade abolished the excitability diminution caused by cathodal tDCS, thus suggesting the role of NMDA receptors in development of tDCS induced after effects. They suggested that long lasting after effects of tDCS may reflect a change of NMDA receptor efficacy. NMDA receptors are involved in neuroplastic changes. This may be implicated as possible mechanisms involved in application of tDCS in migraineurs.

Efficacy of Behavioral treatment in management of migraine is extensively studied and documented. Lifestyle factors such as stress and sleep quality can contribute significantly to onset and course of headaches. Management of these factors including identification of
Environmental triggers is important in the treatment of migraine. Techniques like CBT, Relaxation and Biofeedback allows patient to develop preventive and acute management strategies such as trigger identification, modification of maladaptive interrelated thoughts, feelings and behaviors surrounding headache as well as physiological auto regulation strategies\(^{18}\). CBT includes either avoidance of triggers, implementation of stress management strategies, sleep regulation and optimal level of physical exercises etc\(^{13}\).

Trigger management may be a better method as compared to conservative method of trigger avoidance. The United States headache consortium developed evidence based guidelines for the treatment of migraine based on extensive review of medical literature and compilation of expert consensus and found grade A evidence (multiple well designed, randomized clinical trials) in support of behavioral treatments (thermal biofeedback, EMG biofeedback, CBT and relaxation) for migraine\(^{2}\). Migraine is frequently co morbid with major depressive disorder which confers increased disability and various clinical challenges. Population based studies indicate that migraineurs are 2 to 4 times more likely to suffer from major depressive disorder than those without migraine. Longitudinal and cross sectional studies confirm that relationship between migraine and depression is bidirectional in nature, with each disorder increasing risk of subsequent onset of the other\(^{19}\).This relationship can lead to assumption that migraineurs may have significant improvement in symptoms with CBT as it represents mainstay of psychotherapeutic intervention for depression.

Non-significant changes in control group further corroborate our hypothesis that CBT and tDCS can be effective in reducing headache frequency, duration and intensity. This suggests strong evidence of tDCS and CBT in headache management. Therefore CBT and tDCS can be integrated with medical management of migraine. Adherence to medical pharmacological treatment is usually lower in patient with chronic migraine due to increased side effects, increased cost and psychiatric attributes\(^{12}\).
Therefore management approach which integrates neuro-modulation like tDCS and behavior therapy like CBT combined with medical management can be effective in migraine prophylaxis and management.

**Conclusion**- Results suggest that tDCS and CBT are effective in reducing headache frequency, duration and pain intensity in Migraineurs. tDCS may be more effective in decreasing headache pain intensity and frequency as compared to CBT. Present investigation reestablishes the efficacy of CBT and tDCS in effective management of patients suffering from migraine. Further investigations can be conducted to evaluate any synergistic effect of both interventions. The results of the present study may be a little biased as the sample population could not include patients from diverse ethnic groups, climatic zones etc. Such studies need to be conducted to evaluate the effects on larger population.

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170

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