EFFECT OF DUAL SITE TRANSCRANIAL DIRECT CURRENT STIMULATION ON ANXIETY, WORRY AND SLEEP IN GENERALISED ANXIETY DISORDER - A RANDOMIZED CLINICAL TRIAL

Divya Shanthi Sajja¹, Jeba Chitra²
¹(MPT) student, Department of Neuro Physiotherapy, KLE Institute of Physiotherapy, JNMC campus, Nehru Nagar, Belagavi, Karnataka, India
Email Address: sajjadivyashanthi@gmail.com
ORCID ID: 0000-0002-8827-7121
²Professor, Department of Neuro Physiotherapy, KLE Institute of Physiotherapy, JNMC campus, Nehru Nagar, Belagavi, Karnataka, India
Email Address: jebachitra@klekipt.edu.in

ABSTRACT:

PURPOSE: Studies investigating the effect of tDCS targeting different cortical regions in GAD on Anxiety, Worry and Sleep are limited. So the aim of the current study was to find the effect of Dual Site tDCS on Anxiety, Worry and Sleep in subjects with GAD.

METHODS: 25 subjects with GAD were recruited from various Psychiatry clinics and Tertiary care hospitals in Belagavi, Karnataka. Subjects were randomly allocated into Group-A and Group-B. Group-A subjects received tDCS for two sites (cathode on dlPFC for 15minutes and IPL for another 15minutes with anode on contralateral deltoid) and Group B received tDCS for single site (cathode on right dlPFC and anode on contralateral deltoid for 30 minutes). Total of 10 sessions of tDCS treatment within a period of 3 weeks was given. Pre and post Symptoms were assessed by HARS, PSWQ and SQS in pre and post treatment

RESULTS: The results showed that there was improvement in GAD symptoms for both the groups. But Dual site stimulation targeting right dlPFC and IPL regions was more effective compared to single site stimulation and the difference between the 2 groups has shown to be significant (p<0.05).

CONCLUSION: Dual site stimulation targeting dlPFC and IPL cortical regions was more effective compared to single site stimulation in improving the Anxiety, Worry and Sleep symptoms in GAD. The tDCS is safe and convenient Neuro Stimulation treatment for GAD.

Keywords: GAD, Dual Site tDCS, Worry, Anxiety, Sleep

I. INTRODUCTION

Generalised Anxiety Disorder (GAD) is a most common and wide-ranging Anxiety Disorder. Anxiety, uncontrolled and unfocused-worry are the most common features of GAD. The other characteristic features of GAD are anticipated threat, sleep disturbance, tension, restlessness, difficulty in concentrating, inability to relax, aching pains, headaches, irritability, autonomic symptoms such as palpitations, muscle tension, dried oral cavity, urinary frequency, gastric uneasiness and diarrhoea, feelings of shortness of breath and dizziness. High worries are often associated with negative feeling(1). The lifetime prevalence of GAD was found to be 3.7%(2). In India prevalence rate of GAD is 5.8%, which accounts greater than other Anxiety Disorders(3).GAD is more prevalent in women compared to men.(4)

Worry in these patients is general to any event, which cause excessive and anticipated-threats and distress of future happenings. The effort to avoid anticipated-threat causes more thoughts concerning avoidance of dangers and the conscious processes directed towards attention control to the worrying content. (1) GAD is greatly accompanied
by a symptom of decreased sleep.(5) Individuals with GAD have poor quality of life leading to impairment at work and social functioning.(6)

GAD symptoms can be improved by pharmacological treatment, Cognitive Behavioral Therapy, Anxiety Management Therapy, Relaxation Therapy and Brain Stimulation treatment. Pharmacological treatment can benefit few symptoms and can have negative effect on others. CBT is the moderately effective treatment than anxiety management therapy and is not accessible to everyone, as professional should be trained to give CBT(7,8).

Transcranial Direct Current Stimulation (tDCS) is a type of neuromodulatory treatment method, which modulates spontaneous neuronal activity by delivering low strength or weak electrical stimulus on the skin surface of cranium. It is convenient and well tolerated treatment technique which has proved to treat many psychological disorders such as Depression, Post-Traumatic-Stress-Syndrome(PTSD), Obsessive Compulsive Disorder(OCD) and an emerging treatment in GAD patients.(9) A few studies conducted to study the effectiveness of tDCS on reduction of GAD symptoms targeted DLPFC Cortical region, as emotional-dysregulation with impairment of DLPFC was found in GAD patients through fMRI studies(10–13). And also tDCS delivered to Prefrontal Cortical region functions efficiently by modulating the increased responses to negative stimuli during negative emotional processing(14). Generalised Anxiety Disorder patients also have difficulty in inhibiting and diverting attention from negative stimuli involving alteration of brain activity in multiple regions along with posterior-parietal cortex region is the region which regulates attention- bias(15). An fMRI-study in GAD patients showed an abnormality in intra amygdala network and increased functional connectivity between fronto-parietal regions and amygdala(16). So in this study, DLPFC and Inferior Parietal Lobe(IPL) were targeted for tDCS in GAD patients. In present study, placement of cathode was on targeted Cortical regions and anode was on contralateral deltoid muscle. The purpose by our study was to find the effectiveness of Dual-Site tDCS stimulation on Anxiety, Worrying and Sleep.

II. METHODOLOGY

The current study, was conducted after approval from Institutional Ethical Committee. The study was in accordance with the ethical guidelines of Helsinki Declaration for human experimentation. Objectives and requirements of the study were explained to all the participants and their informed consent was obtained. Twenty Eight subjects with GAD were recruited in the study from Tertiary care hospitals and Psychiatric clinics in Belagavi. The participants in the study were within the age group of 18-60 years, diagnosed as a case of GAD by Diagnostic and Statistical Manual of Mental Disorders(=5M) and with 5 or more score on GAD 7 scale. Patients with other diagnosed psychological illness such as Schizophrenia, Bipolar or other Anxiety Disorders, Substance Use Disorder, Implanted brain metal devices, diagnosed case of Chronic skin problems, Head Injury and Epilepsy had been excluded. Outcome measures such as Hamilton Anxiety Rating Scale (HARS), Penn State Worry Questionnaire (PSWQ) for Worry and Sleep Quality Scale (SQS) were used.(17-19)

A Randomized Clinical Trial where the subjects were randomly assigned to either of the group by using sealed opaque envelopes. Group A received Dual Site tDCS by saline soaked sponge coated rubber electrodes with cathodal placement over the right dlPFC (F4region on 10-20EEG international system), and anode placement extra-cerephalically over the contralateral deltoid with an intensity of 2mA was delivered for 15mins to this site. Another site for stimulation was Inferior Parietal lobe (P4 on 10-20 EEG-system) with Cathode placement over right IPL region and Anode placement over contralateral deltoid muscle with an intensity of 2mA tDCS for 15mins to this site. Group B received single site tDCS by saline soaked sponge coated rubber electrodes with cathodal placement over right dlPFC (F4 region on 10-20EEG-system), and anodal placement extra-cerephalically over the contralateral deltoid with an intensity of 2mA was delivered for 30mins to this site. The intervention was performed for 10 sessions over a duration of 3 weeks. (Figure 1) Outcomes were recorded pre and post 10 sessions of intervention.

III. STATISTICAL ANALYSIS:

Version 23 of Statistical Product and Service Solution was used to verify the results obtained. Normality pretest along posttest scores of different parameters Group A and Group B by Kolmogorov Smirnov test. The homogeneity of the data was checked using the Chi Square Yates's correction Test for gender distribution and Independent t-test used for finding homogeneity of age and GAD 7 score. Dependent t test was used for within group analysis of pre and post intervention scores of HARS, PSWQ and SQS. Independent t-test had been used for comparing two groups post intervention scores of HARS, PSWQ and SQS.
IV. RESULTS

28 individuals with GAD completed study. Homogeneity of the data for gender distribution between the groups showed that there was no difference in the number of males and females in each group. Homogeneity of age and GAD 7 score also has shown that there was no significant difference (Table 1)

Within group analysis results revealed both groups showed greater change for within group analysis of HARS, PSWQ and SQS scores pre-treatment and post treatment with p value of 0.0001 for all outcomes. (Table 2)

Between group analysis has shown that there was significant difference observed for post-treatment HARS scores with p-value of 0.03350 and for the difference of pre and post treatment HARS scores with p-value of 0.0001. The difference was significant for post-treatment PSWQ scores with p-value of 0.0014 and p-value for the difference of pre-post treatment PSWQ scores is 0.0001. For pre-treatment SQS scores, there was significant difference seen between the groups for post treatment SQS scores with p-value of 0.0275 and p-value for the difference of pre-post treatment SQS scores is 0.0010. (Table 3)

V. DISCUSSION

The present Randomized clinical trial, undertaken to investigate the involvement Dual Site tDCS on different symptoms in individuals of GAD and compare same with a single site stimulation. The results of this study illustrated that there was significant decrement in the Anxiety, Worry and Sleep with reference to reduction in scores of HARS, PSWQ and SQS for two groups. Also the difference was significant for between groups suggesting that the subjects included in Group A showed greater reduction of HARS, PSWQ and SQS scores compared to Group B.

The mechanism of anxiolytic-effect of tDCS are based on the cathodal or anodal stimulation on the targeting cortical regions and montage placement. Previous studies showed that TDCS by exciting or inhibiting the targeting regions can alter cortical-activity and modulate the disturbed network in different psychiatry conditions (20–22). Thus, the findings of our study can be explained by an affected network of cortical regions with the amygdala in the following section.

In the present study, there was a significant reduction of HARS scores and PSWQ scores seen both within Group A and within Group B. This might be due to the inhibition of main cortical region i.e. right DLPFC by cathodal tDCS stimulation, which is involved in the GAD that was targeted in both groups. Results of the present study can be supported by the findings of a Literature review, case-report of a middle aged adult female having GAD was given tDCS for Anxiety, Worry and, Depression with the cathodal electrode stimulation to right dLPFC and anodal electrode placement on left Deltoid muscle for a period of 30mins for 15 consecutive sessions, which illustrated that there was an improvement in the Anxiety and Worry symptoms (11). Another study conducted by Fariba et.al also supported our findings, which was undertaken to find the effect of tDCS cathodal stimulation to right DLPFC with anodal placement on contralateral deltoid on Anxiety, Worry and, Depression in GAD also had shown that there was significant improvement of symptoms post alternative day 10 sessions (10). The placement of electrodes in both of the above studies is similar with cathode on right DLPFC and Anode on the contralateral deltoid muscle. The same placement of electrodes was done in this study to avoid the local cortical excitation of anodal placement on cortical region. The other study conducted De Lima et.al. delivered 5 sittings of tDCS for GAD subjects through different electrode placement, Anodal-electrode on left dLPFC and cathodal-electrode on right supraorbital cortex, didn’t show significant improvement in Anxiety, Mood changing symptoms and Depression. These negative findings could be due to lesser number of sessions, although there was significant improvement within the group (12).

HARS and PSWQ scores have shown significant difference between groups with greater reduction in Anxiety scores for Group A compared to Group B. This may be due to the inhibition of both right DLPFC and IPL regions after cathodal tDCS, causing changes in the disturbed Amygdala and frontoparietal network activity, which found in GAD patients. Regulation of activity of the altered function in frontal-parietal network with Amygdala might have been modulation Sylvester et.al. stated in a study that there was an alteration in the activity in frontal-parietal network for Disorders having anxiety as a chief feature with altered processing of emotional stimulus (23). Also there is increase in dynamic amplitude of low-frequency fluctuations seen in different cortical regions including prefrontal and IPL in GAD patients, with correlation of this increased activity to GAD symptoms (24). Y. lin et.al. in their experimental study stated that the 1Hz rTMS dual site stimulation to right DLPFC and right IPL improved
Anxiety and Worry symptoms and reason for the reduction in symptoms was explained by the inhibition of the increased activity in DLPFC and IPL regions by low frequency rTMS, which is commonly used to decrease cortical activity.(26) In Anxiety disorders, there is increased vigilance to threatful stimuli. A study demonstrated that TDCS on DLPFC regions altered that can change the processing of threatening stimuli and has a positive effect on decreasing vigilance of threatful stimuli for both anxiety and depression patients. (14)

Dysfunction of different brain networks such as cingular and opercular, frontal parietal, ventral-attention along with defaulting type networks is found in disorders having anxiety. Worry is the cognitive feature of GAD, it is caused due to altered cognitive processes that is seen in GAD. In the present study, significant difference was seen in between the groups for worry outcome. This improvement in the Dual Site Stimulation Group can be explained by the involvement of the Cortical regions through study conducted by Etkin et.al., where increased amygdalar connectivity to the DLPFC and Posterior parietal cortex along with Amydalofrontoparietal coupling for cognitive control to regulate excessive worry and anxiety was observed in GAD subjects compared to normal individuals(16). Emotion perception processing was shown to involve different networks of brain such as Frontoparietal, Medial Prefrontal regions with dorsal Cingulate, and Subcortical dorsal Insular Cortex along through Amygdala(28). There is Biased attentional processing of emotional information commonly noted in GAD patients as stated by Yiend et.al.(27) Normally, through connection with the Parietal cortex, DLPFC also regulates Executive Functions with Selective Attention and Emotional Reactivity.(28) Cathodal stimulation to this DLPFC and IPL might have helped in altering these Frontoparietal network changes by normalization of altered activity between frontoparietal network activity and amygdala.

In the present study, a SQS had been utilized to evaluate sleep which depicted that change was substantial for between prepost treatment within the group and between the groups as well, with greater decrement in SQS score in Group A, which denotes improvement in sleep quality. A study done by Staner L, indicated that there was an imbalance between the Excitatory (Cholinergic and Glutaminergic) and Inhibitory (GABAergic) Neurotransmitters in Anxiety Disorders. Therefore there is an association between Anxiety and sleep. GAD is mostly associated with Insomnia(5). Since there was improvement found in Anxiety, it might have reflected on sleep. Our findings corroborate a previous study by Lukas Frase et.al, in which comparison of cathodal and anodal tDCS revealed a decrease in total sleep time in Anodal tDCS compared to Cathodal tDCS in normal individuals (29). Another study conducted to find the effectiveness of 10 sessions of 1Hertz frequency rTMS to the right dorsal Parietal Lobe region on Anxiety and Insomnia proved significant improvement on HARS and Pittsburgh Sleep Quality Index scores in GAD patients. These improvement in Anxiety and Insomnia findings were positively correlated to each other. (30)

The limitations of study are outcomes measure the alteration in brain activity was not considered, long term effects of Dual Site tDCS on Anxiety, Worry and Sleep in GAD was not comprehended, sham tDCS group was not present in the study for comparison and due to Covid-19 pandemic, there was difficulty in recruiting subjects.

VI. CONCLUSION
Dual site stimulation targeting Right DLPFC and IPL cortical regions was more effective compared to single site stimulation in improving the Anxiety, Worry and Sleep symptoms in GAD. The tDCS is safe and convenient Neuro Stimulation treatment for GAD.

FUNDING: This research didn’t receive any specific grant from funding agencies in the public, commercial or profit and non-profit sectors

CONFLICT OF INTEREST: None

Ethical Approval was obtained from Research and Ethics Committee KAHER Institute of Physiotherapy and the approval number is 789

ACKNOWLEDGEMENT: The authors thanks all the participants of the study for their co-operation
REFERENCES


### Table 1: Homogeneity Analysis with respect to demographic data of the group

<table>
<thead>
<tr>
<th>Groups</th>
<th>Group A</th>
<th>Group B</th>
<th>Statistic</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1(7.14%)</td>
<td>2(14.29%)</td>
<td>$\chi^2$=0.6699</td>
<td>0.4130</td>
</tr>
<tr>
<td>Female</td>
<td>13(92.86%)</td>
<td>12(85.71%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>33.07±10.43</td>
<td>35.64±10.28</td>
<td>t=-0.6570</td>
<td>0.5170</td>
</tr>
<tr>
<td>GAD 7 scale score</td>
<td>15.36± 2.44</td>
<td>15.21±2.26</td>
<td>t=0.1608</td>
<td>0.8735</td>
</tr>
</tbody>
</table>

### Table 2: Comparison of within Group analysis of Group A and Group B for pretest and posttest HARS, PSWQ and SQS scores

<table>
<thead>
<tr>
<th>Outcome Measures</th>
<th>Groups</th>
<th>Treatment times</th>
<th>Mean±SD</th>
<th>%of change</th>
<th>t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A</td>
<td>Pretest</td>
<td>36.57±8.49</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Posttest</td>
<td>21.64±7.31</td>
<td>40.82</td>
<td>18.1647</td>
<td>0.0001*</td>
</tr>
<tr>
<td></td>
<td>Group B</td>
<td>Pretest</td>
<td>37.29±9.45</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Posttest</td>
<td>28.21±8.60</td>
<td>24.32</td>
<td>13.7751</td>
<td>0.0001*</td>
</tr>
<tr>
<td></td>
<td>Group A</td>
<td>Pretest</td>
<td>51.64±10.53</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Posttest</td>
<td>31.57±7.56</td>
<td>38.86</td>
<td>12.5580</td>
<td>0.0001*</td>
</tr>
<tr>
<td></td>
<td>Group B</td>
<td>Pretest</td>
<td>54.14±7.64</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Posttest</td>
<td>41.9±7.77</td>
<td>22.55</td>
<td>19.9302</td>
<td>0.0001*</td>
</tr>
<tr>
<td></td>
<td>Group A</td>
<td>Pretest</td>
<td>51.14±13.29</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Posttest</td>
<td>33.21±10.89</td>
<td>35.05</td>
<td>12.0495</td>
<td>0.0001*</td>
</tr>
<tr>
<td></td>
<td>Group B</td>
<td>Pretest</td>
<td>54.36±10.94</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Posttest</td>
<td>42.86±10.97</td>
<td>21.15</td>
<td>12.8618</td>
<td>0.0001*</td>
</tr>
</tbody>
</table>

*p<0.05

### Table 3: Comparison of between Group analysis of Group A and Group B for pretest and posttest HARS, PSWQ and SQS scores

<table>
<thead>
<tr>
<th>Outcome measures</th>
<th>Treatment times</th>
<th>Group A Mean±SD</th>
<th>Group B Mean±SD</th>
<th>t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pretest</td>
<td>36.57±8.49</td>
<td>37.29±9.45</td>
<td>-0.2104</td>
<td>0.8350</td>
</tr>
<tr>
<td></td>
<td>Posttest</td>
<td>21.64±7.31</td>
<td>28.21±8.60</td>
<td>-2.1775</td>
<td>0.0387*</td>
</tr>
<tr>
<td></td>
<td>Difference</td>
<td>14.93±3.08</td>
<td>9.07±2.46</td>
<td>5.5616</td>
<td>0.0001*</td>
</tr>
<tr>
<td></td>
<td>Pretest</td>
<td>51.64±10.53</td>
<td>54.14±7.64</td>
<td>-0.7189</td>
<td>0.4786</td>
</tr>
<tr>
<td></td>
<td>Posttest</td>
<td>31.57±7.56</td>
<td>41.93±7.77</td>
<td>-3.5741</td>
<td>0.0014*</td>
</tr>
<tr>
<td></td>
<td>Difference</td>
<td>20.07±5.98</td>
<td>12.21±2.29</td>
<td>4.5901</td>
<td>0.0001*</td>
</tr>
<tr>
<td></td>
<td>Pretest</td>
<td>51.14±13.29</td>
<td>54.36±10.94</td>
<td>-0.6986</td>
<td>0.4910</td>
</tr>
<tr>
<td></td>
<td>Posttest</td>
<td>33.21±10.89</td>
<td>42.86±10.97</td>
<td>-2.3349</td>
<td>0.0275*</td>
</tr>
<tr>
<td></td>
<td>Difference</td>
<td>17.93±5.57</td>
<td>11.50±3.35</td>
<td>3.7033</td>
<td>0.0010*</td>
</tr>
</tbody>
</table>

*p<0.05
Figure 1: Consort Chart

Enrollment

Assessed for eligibility (n=37)

Excluded (n=9)
- Not meeting inclusion criteria (n=6)
- Declined to participate (n=1)
- Other reasons (n=2)

Randomized (n=28)

Group A
Dual Site tDCS Group (n=14)
- Received allocated intervention (n=14)
- Did not receive allocated intervention

Group B
Single site tDCS Group (n=14)
- Received allocated intervention (n=14)
- Did not receive allocated intervention

Allocation

Treatment (3 weeks)

Post treatment Assessment (n=14)
- Discontinued intervention (n=0)

Analysis

Analysed (n=14)
- Excluded from analysis (n=0)