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Effect of Transcranial Direct Current Stimulation of Motor Cortex versus Insula Cortex on Chronic Post-Mastectomy Pain: Randomized Sham-Controlled Trial

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Abstract

Background: Transcranial direct current stimulation (tDCS) across cortical brain areas appears to improve various forms of pain, yet evidence of tDCS efficiency and ideal stimulation target is lacking. This study aimed to compare the add-on analgesic efficacy of concentric electrode transcranial direct current stimulation (CE-tDCS) stimulation over the primary motor cortex versus the insular cortex on the management of chronic postmastectomy pain. **Method:** Prospective randomized double-blind sham-controlled study enrolled eighty patients with chronic postmastectomy pain that were randomly assigned to four groups: active motor (AM), sham motor (SM), active insula (AI) and sham insula (SI) group, each received 5 sessions for 20-minute duration with 2 mA tDCS over the targeted area of the contralateral side of pain. Our primary outcome was VAS score, the secondary outcomes were VDS score, LANSS score and depression symptoms by HAM-D scores, assessment was done at 4 time points (prestimulation, after 5th session, 15th day and one month after the last session). **Results:** Both active tDCS groups (motor and insula) showed reduction of VAS ($P < 0.001$), VDS ($P < 0.001$), LANSS ($P < 0.001$) and HAM-D score ($P < 0.001$) than sham groups. **Conclusion:** Active tDCS stimulation either targeting the primary motor cortex or the insula cortex has add-on analgesic effect for controlling neuropathic chronic post mastectomy pain and the maximum effect was at 15 days after the last session.

Keywords

Transcranial Direct Current Stimulation, tDCS, Postmastectomy Pain, Motor

Cortex, Insular Cortex

1. Introduction

Breast cancer is the most common cancer in Egyptian women, making up 38.8% of cancer cases in this age range [1]. Post-mastectomy pain syndrome (PMPS) represents chronic pain persisting for at least 3 months after surgery [2]. It affects the upper arm, shoulder, and chest, worsened by movement, and is described as dull, aching, or burning with intermittent stabbing [3]. The prevalence is approximately 25% - 60% and it frequently affects quality of life and physical ability.

There are no gold-standard therapy recommendations for PMPS, its treatment options include conventional medicine and surgery. Although management of pain had advanced significantly, they may still fail to reduce pain in cancer patients or develop adverse side effects. Despite its effectiveness in treating pain, opioids can cause unpleasant side effects [4].

Given their capacity to alter brain activity in the area of neural stimulation and interconnected regions, various neurostimulation approaches have been successfully tested as therapeutic tools for chronic pain disorders. Indeed, due to their non-invasive nature and their capacity to alter the excitability of cortical neuronal circuits, 2 of these techniques—transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS)—have gained increasing interest. Due to its portability, simplicity of use, and affordability, tDCS may also have some additional benefits. [5]

High-definition tDCS (HD-tDCS), a new type of montage that surrounds the active electrode with many return electrodes, was recently proposed. HD-tDCS is particularly encouraging since it may provide more concentrated stimulation and prevent current from spreading to unwanted regions [6]. Bortoletto and colleagues investigated the focality and efficacy of a different HD-tDCS configuration that employs two concentric electrodes (CE-tDCS). They revealed that CE-tDCS may allow for more precise regulation of current distribution [7].

The primary motor cortex (M1) is the most often planned target for tDCS. Several investigations revealed the benefits of tDCS over M1 in terms of pain, mood, functional impact, and quality of life [8]. Recently, the significance of investigating potential novel stimulation targets has been stressed, one of them is the insular cortex (IC) which is an area involved in the cerebral recognition of pain [9].

We aimed to compare the add-on analgesic efficacy of CE-tDCS stimulation over the **M1** versus **IC** on the management of chronic postmastectomy pain.

2. Materials and Methods

This randomized, double blinded, sham-controlled study was approved by the

Research Ethics Committee of the South Egypt Cancer Institute, Assiut University, Assiut, Egypt, after obtaining participant's written informed consent. Our protocol was registered in Clinical trials.gov (Identifier: NCT05544604) and complying with CONSORT checklist.

We enrolled patients aged 18 to 65 with post-mastectomy neuropathic pain who had not responded to medical treatment, for at least two months, with tramadol hydrochloride 100 mg twice daily, pregabalin 75 mg twice daily, and amitriptyline 25 mg once daily. We excluded patients who refused to participate, those with pacemakers or intracranial metallic devices, and those with extensive myocardial ischemia or known to have epilepsy.

Based on a computer-generated randomization table, 80 patients were randomly assigned to one of four groups of 20 patients each, and underwent one of the following interventions:

- **Active motor (AM) Group**: active tDCS (2 mA) for 20 minutes on the primary motor cortex of the contralateral side of pain for five sessions in five days (one session per day),
- **Sham motor (SM) Group**: sham tDCS over the primary motor cortex with the identical stimulation parameters was employed, but the device was switched off after 30 seconds without the patient's awareness.
- **Active insula (AI) Group**: active tDCS (2mA) targeting the insula on the contralateral side of the pain for 20 minutes for five sessions over five days (one session each day),
- **SI (sham insula) Group** The identical stimulation parameters were utilised for the group with sham tDCS over the insula, but the device was turned off after 30 seconds without the patient's awareness.

Participants were situated in a comfortable seat in a quiet room and advised to remain calm for the stimulation session. A battery-powered DC stimulator (Neuroconn GmbH, Ilmenau, Germany) was used to give tDCS at a current strength of 2 mA for 20 minutes (10 s ramp up/ramp down). The current was ramped up and down at the start and end of the sham-tDCS session. Current was delivered via two concentric electrodes (target electrode: central round electrode, radius = 1.0 cm, area = 3.14 cm^2; return electrode: outer ring electrode, inner radius = 3.5 cm, outer radius = 4.0 cm, area = 11.78 cm^2). To avoid electrode migration, we first flooded the electrode cage with an electroconductive gel (Elektrogel, Italy), then situated the electrodes, with the target electrode over the FDI hotspot, and finally fastened the electrodes with a cylindrical net-shaped elastic bandage in mesh tissue. This approach intended to reduce contact impedance between the electrodes and the scalp, hence minimising unequal current distribution [10]. According to the study group, we placed the central electrode (anode) at C3 or C4 (for primary motor cortex stimulation), and the stimulating electrode will be mounted on the scalp at T7 or T8 for insular cortex stimulation using the 10 - 20 electroencephalography (EEG) system.

Patients were followed up at zero (pre-stimulation), 5^{th} session, 15^{th} days and one month after the last session, using the following measurements: visual ana-

logue scale (VAS), verbal descriptor scale (VDS), Leeds Assessment of neuropathic Symptoms and Signs (LANSS) scale and Hamilton rating scale for depression (HAM-D) score. Also, the presence of side effects that related to tDCS as scalp redness or irritation, tingling, headache or discomfort had been recorded. The measurements had been done by a blind assessor who didn't know the type of stimulation applied.

Our primary goal was pain reduction on the VAS score after the fifth session, 15 days and one month later, and our secondary outcomes were VDS, LANSS, and depression symptoms by HAM-D after the fifth session, 15 days and one month afterwards.

The sample size was computed using G power software version 3.1.3 (12). ANOVA test (Fixed effects, omnibus, one-way) for comparing the differences in VAS scores between four groups, hypothesised effect size 0.4, alpha error prob 0.05, power (1- beta error prob) 0.80. The minimum required sample size was 76 patients (19 patients in each group), which was raised to 20 patients in each group [11].

Statistical Analysis

The Statistical Package for Social Science (SPSS), version 26.0 for Windows, was used to analyse the data. According to the Shapiro-Wilk test, qualitative data was displayed as frequency and percentage, while quantitative data were represented as mean SD. To compare proportions between groups, the Chi square test was performed. At each time point, the mean VAS, VDS, LANSS, and HAM-D in the four groups were compared using One-Way ANOVA, followed by one-way repeated measures ANOVA test was performed to determine the influence of time in measurement in each group independently. Two-way repeated measures ANOVA was utilised to find time interaction in the study's groups. The percentage of reduction/improvement in each scale (VAS, VDS, LANSS, and HAM-D) were calculated by subtracting each point from pre-stimulation point and multiply by 100 and divided by pre-stimulation ((pre-stimulation score − post-stimulation score) × 100)/pre-stimulation score). The level of significance was considered at P value < 0.05.

3. Results

Eighty-eight patients with post mastectomy neuropathic pain were assessed for eligibility. Six patients were excluded, then, eighty-two patients were randomly assigned to one of four groups, although two patients were withdrawn from the trial because they did not finish the tDCS sessions. Follow up parameters in the form of VAS, VDS, LANSS and HAM-D scores were obtained from 80 patients who completed the study (**Figure 1**). In terms of demographic data, there was no statistically significant difference between the four groups (**Table 1**). Different rating scores showed no statistically significant difference at the pre-stimulation time.

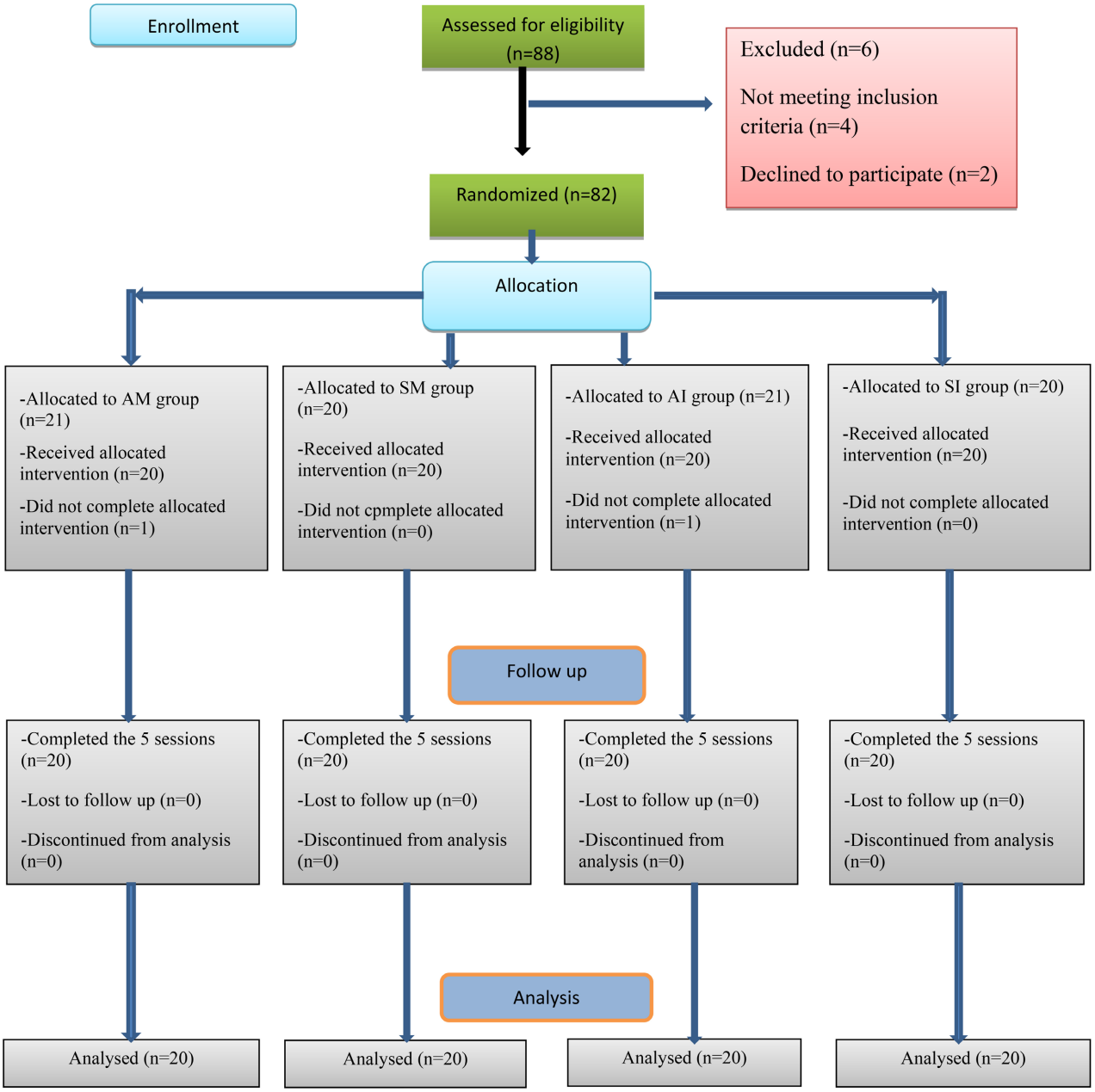

Figure 1. CONCORT flow chart.

Scores on all rating scales altered over time, with the AM and AI groups experiencing the most changes. For the primary outcome, there was a statistically significant change in the mean VAS score of AM and AI groups separately over time from pre-stimulation to one month after stimulation. The effect of Time × groups is statistically significant over time, P value < 0.001 (**Table 2**). While, no statistically significant change was in mean VAS score of SM and SI groups separately over time from pre-stimulation to one month after stimulation.

In comparison to the pre-stimulation point, there was a statistically significant change in the mean percentage of reduction in VAS score of group AM and AI separately over time, while no statistically significant changes in group SM and

Table 1. Characteristics of the patients in the study groups.

Variables	AM Group (n = 20)	SM Group (n = 20)	AI Group (n = 20)	SI Group (n = 20)	P-value
Age (years)					
▪ Mean ± SD	55.65 ± 4.84	55.75 ± 4.81	54.80 ± 6.62	58.25 ± 5.55	0.233*
Duration of pain (month)					
▪ Mean ± SD	9.70 ± 4.43	10.80 ± 5.23	10.10 ± 4.33	10.60 ± 5.59	0.894*
Adjuvant therapy					
▪ Radiotherapy	9 (45.0%)	8 (40.0%)	11 (55.0%)	9 (45.0%)	0.812**
▪ Chemotherapy	11 (55.0%)	12 (60.0%)	9 (45.0%)	11 (55.0%)	
Diagnosis					
▪ Rt MRM	10 (50.0%)	10 (50.0%)	10 (50.0%)	9 (45.0%)	0.985**
▪ Lt MRM	10 (50.0%)	10 (50.0%)	10 (50.0%)	11 (55.0%)	

Data were expressed as mean ± SD, or frequency (%); *One Way ANOVA test was used to compare mean difference between groups; **Chi square test was used to compare the proportion difference between groups.

Table 2. Comparison of VAS among studied groups and percentage of reduction in VAS in each group at each point in comparison to pre-stimulation point.

VAS	AM Group (n = 20)	SM Group (n = 20)	AI Group (n = 20)	SI Group (n = 20)	P-value*
Pre-stimulation	5.35 ± 1.08	5.00 ± 1.02	5.40 ± 1.23	4.95 ± 0.88	0.419
5th day of stim.	4.30 ± 1.21	4.60 ± 1.18	4.15 ± 1.08	4.75 ± 1.07	0.335
15 days after stim.	4.15 ± 1.26	4.80 ± 1.15	3.80 ± 0.95	4.75 ± 0.96	**0.012**
1 month after stim.	4.80 ± 1.32	4.80 ± 1.00	4.75 ± 1.11	4.65 ± 1.04	0.971
P-value**	**<0.001**	0.056	**<0.001**	0.241	
P-value (Time × groups)***			**<0.001**		
VAS (percentage of reduction)	**AM Group (n = 20)**	**SM Group (n = 20)**	**AI Group (n = 20)**	**SI Group (n = 20)**	**P-value***
5th day-pre	20.27%	8.38%	21.88%	4.50%	**<0.001**
15 days-pre	22.95%	3.63%	27.98%	3.54%	**<0.001**
1 month-pre	10.72%	3.46%	10.70%	5.83%	0.454
P-value**	**<0.001**	0.152	**<0.001**	0.798	
P-value (Time × groups)***			**0.001**		

Data were expressed as **mean ± SD for VAS;** Data were expressed as **mean% for percentage of reduction in VAS;** ***One Way ANOVA** test was used to compare mean difference between groups; ****One Way repeated measures ANOVA** compare mean difference within each group overtime; *****Two-way repeated measures ANOVA** compare effect of time × groups.

SI separately over time. Also, in comparison between groups, there was a significant percentage reduction in the scales after the 5th session and 15th day after the

end of stimulation and no significance after one month (Table 2).

There was statistically significant change in mean VDS score over time from pre-stimulation to one month after stimulation In AM and AI groups separately, the effect of Time × groups is statistically significant over time, P value < 0.001, while no statistically significant change was detected in SM and SI groups separately over time (Table 3).

There was no statistically significant difference in the mean percentage of reduction of VDS score between the four groups at the 5th day or after one month of stimulation in comparison to the pre-stimulation time. However, there was statistically significant difference in mean percentage of reduction of VDS score between the four groups at the 15 days of stimulation- the pre-stimulation time, mean percentage of reduction in VDS score was 13.75%, 4.58%, 21.25% and 4.16% in group AM, SM, AI and SI respectively, P-value < 0.001 (Table 3).

Mean LANSS score of AM and AI groups separately showed statistically significant change over time from pre-stimulation to one month after stimulation, The effect of Time × groups is statistically significant over time, P value < 0.001, while no statistically significant change was observed in group SM and SI separately over time from pre-stimulation to one month after stimulation. (Table 4)

There was statistically significant difference in mean percentage of reduction of LANSS score between the four groups at the 5th day, 15th day, and one month

Table 3. Comparison of VDS among studied groups and percentage of reduction in VDS in each group at each point in comparison to pre-stimulation point.

VDS	AM Group (n = 20)	SM Group (n = 20)	AI Group (n = 20)	SI Group (n = 20)	P-value*
Pre-stimulation	3.20 ± 0.41	3.10 ± 0.30	3.20 ± 0.52	3.10 ± 0.30	0.738
5th day of stim.	2.80 ± 0.52	2.95 ± 0.39	2.75 ± 0.55	3.00 ± 0.45	0.430
15 days after stim.	2.75 ± 0.55	2.95 ± 0.39	2.50 ± 0.51	2.95 ± 0.39	**0.009**
1 month after stim.	2.95 ± 0.51	3.01 ± 0.31	2.90 ± 0.44	2.95 ± 0.39	0.474
P-value**	**<0.001**	0.076	**<0.001**	0.433	
P-value (Time × groups)***			**0.010**		
VDS (percentage of reduction)	**AM Group (n = 20)**	**SM Group (n = 20)**	**AI Group (n = 20)**	**SI Group (n = 20)**	**P-value***
5th day-pre	12.08%	4.58%	10.83%	3.33%	0.080
15 days-pre	13.75%	4.58%	21.25%	4.16%	**0.001**
1 month-pre	7.50%	0.41%	8.33%	4.16%	0.090
P-value**	0.074	0.105	**0.009**	0.939	
P-value (Time × groups)***			0.098		

Data were expressed as **mean ± SD in VDS;** Data were expressed as **mean% for percentage of reduction in VDS;** ***One Way ANOVA** test was used to compare mean difference between groups; ****One Way repeated measures ANOVA** compare mean difference within each group overtime; *****Two-way repeated measures ANOVA** compare effect of time × groups.

Table 4. Comparison of LANSS among studied groups and percentage of reduction in LANSS in each group at each point in comparison to pre-stimulation point.

LANSS	AM Group (n = 20)	SM Group (n = 20)	AI Group (n = 20)	SI Group (n = 20)	P-value*
Pre-stimulation	15.55 ± 2.21	14.90 ± 2.33	15.35 ± 1.98	15.35 ± 2.88	0.849
5th day of stim.	13.85 ± 1.46	14.70 ± 2.55	13.15 ± 1.46	14.90 ± 2.98	0.056
15 days after stim.	13.90 ± 1.33	14.50 ± 2.35	13.40 ± 1.60	14.80 ± 2.87	0.170
1 month after stim.	13.75 ± 1.61	14.50 ± 2.46	13.45 ± 1.90	14.95 ± 3.00	0.160
P-value**	**<0.001**	0.130	**<0.001**	0.057	
P-value (Time × groups)***			**<0.001**		
LANSS (percentage of reduction)	**AM Group (n = 20)**	**SM Group (n = 20)**	**AI Group (n = 20)**	**SI Group (n = 20)**	**P-value***
5th day-pre	10.23%	1.47%	13.96%	3.03%	**<0.001**
15 days-pre	9.89%	2.53%	12.37%	3.50%	**<0.001**
1 month-pre	10.89%	2.72%	12.08%	2.56%	**<0.001**
P-value**	0.720	0.563	0.448	0.743	
P-value (Time × groups)***			0.625		

Data were expressed as **mean ± SD for LANSS;** Data were expressed as **mean% for percentage of reduction in LANSS;** ***One Way ANOVA** test was used to compare mean difference between groups; ****One Way repeated measures ANOVA** compare mean difference within each group overtime; *****Two-way repeated measures ANOVA** compare effect of time × groups.

after stimulation in comparison to the pre-stimulation time, P value < 0.001 (Table 4).

There was statistically significant change in mean HAM-D of group AM and AI separately over time from pre-stimulation to one month after stimulation, while no statistically significant change in mean HAM-D of group SM and SI separately over time. The effect of Time × groups is statistically significant over time, P value < 0.001 (Table 5)

Mean percentage of reduction of HAM-D score showed statistically significant differences between the four groups at the 5th day, 15th day and after one month of stimulation in comparison to the pre-stimulation time (Table 5).

There were no serious side effects from tDCS sessions detected between the four studied groups except in the form of irritation, tingling, headache, and discomfort which was of no statistically significant difference (Table 6).

4. Discussion

TDCS is a non-intrusive neuromodulatory procedure that lessens bidirectional polarity-dependent changes in underlying cortical areas. The International Society for Neuropsychopharmacology's tDCS guidelines indicated that using tDCS to stimulate the left M1 region was highly effective in improving neuropathic pain (NP) and was thus a level B recommendation [12]. The International

Table 5. Comparison of HAM-D among studied groups and percentage of reduction in HAM-D in each group at each point in comparison to pre-stimulation point.

HAMD	AM Group (n = 20)	SM Group (n = 20)	AI Group (n = 20)	SI Group (n = 20)	P-value*
Pre-stimulation	13.00 ± 2.24	12.50 ± 4.11	12.70 ± 4.43	12.70 ± 4.02	0.981
5th day of stim.	11.30 ± 2.38	12.45 ± 4.31	11.65 ± 4.15	12.75 ± 3.90	0.589
15 days after stim.	10.90 ± 2.53	12.40 ± 4.29	11.25 ± 4.02	12.50 ± 4.12	0.446
1 month after stim.	10.80 ± 2.50	12.35 ± 4.06	11.45 ± 3.84	12.40 ± 4.03	0.456
P-value**	**<0.001**	0.833	**0.004**	0.436	
P-value (Time × groups)***			**<0.001**		
HAM-D (percentage of reduction)	**AM Group (n = 20)**	**SM Group (n = 20)**	**AI Group (n = 20)**	**SI Group (n = 20)**	**P-value***
5th day-pre	13.16%	0.75%	8.41%	0.89%	**<0.001**
15 days-pre	16.22%	0.94%	11.44%	1.60%	**<0.001**
1 month-pre	16.81%	0.88%	8.37%	2.04%	**<0.001**
P-value**	0.253	0.993	0.411	0.447	
P-value (Time × groups)***			0.783		

Data were expressed as **mean ± SD for HAM-D;** Data were expressed as **mean% for percentage of reduction in HAM-D;** ***One Way ANOVA** test was used to compare mean difference between groups; ****One Way repeated measures ANOVA** compare mean difference within each group overtime; *****Two-way repeated measures ANOVA** compare effect of time × groups.

Table 6. Comparison of side effects in the study groups.

Variables	AM Group (n = 20)	SM Group (n = 20)	AI Group (n = 20)	SI Group (n = 20)	P-value*
Irritation	2 (10.0%)	1 (5.0%)	3 (15.0%)	3 (15.0%)	0.711
Tingling	3 (15.0%)	1 (5.0%)	2 (10.0%)	1 (5.0%)	0.632
Headache	0 (0.0%)	1 (5.0%)	0 (0.0%)	1 (5.0%)	0.562
Discomfort	3 (15.0%)	3 (15.0%)	3 (15.0%)	2 (10.0%)	0.957

*Chi square test was used to compare the proportion difference between groups.

Federation of Clinical Neurophysiology (IFCN) guidelines said that tDCS in M1 (contralateral to pain side) in chronic lower limb NP following SCI was a level C recommendation [13]. Although present evidence suggests that tDCS was less efficient than rTMS in alleviating pain when the M1 area was stimulated, the most interesting finding was that tDCS appeared to be more beneficial for NP following SCI in the lower extremities [14].

In this study, we discovered that active M1 tDCS improved clinical pain more than sham stimulation. Also, the percentage of reduction in VAS and VDS scores was greater in active M1 after the 5th day and 15 days after stimulation but not after one month.

There are different studies that looked at the therapeutic efficacy of tDCS in treating chronic pain from different sources, including back pain, fibromyalgia, brachial plexus injury (BPI), SCI, and stroke patients. In 2009, Boggio *et al.* [15] looked at whether tDCS and transcutaneous electrical nerve stimulation (TENS) together were more effective than tDCS alone or sham stimulation for relieving localized NP of the arm. The findings demonstrated that TENS and tDCS together had a greater impact than tDCS alone, and that both techniques reduced pain in comparison to sham stimulation. Similar to this, Antal *et al.* showed that five daily treatments of tDCS over the hand region of M1 (1 mA, 20 min) resulted in significant pain alleviation in 21 patients with chronic NP [16]. These findings were supported by a case study by Portilla *et al.* from 2013, which showed that tDCS reduced overall cortical excitability in individuals with chronic NP after burn injury [17].

When de Assis and his colleagues compared the efficiency of rTMS and anodal tDCS techniques placed across the motor cortex in patients with neuropathic pain due to brachial plexus injury, they discovered that both active rTMS and tDCS were superior to sham in reducing continuous and paroxysmal pain with no differences between the two active techniques [18].

In 2017, Chwistek used tDCS in patients with neuropathic cancer pain and concluded that M1-tDCS stimulation on the side opposite the pain are useful for treating a variety of neuropathic pain disorders [19]. Hu *et al.* [20] used M1-tDCS as a supplemental neuronal mechanism-driven analgesia management for patients with head and neck cancer for the second time. Furthermore, tDCS can shield patients from escalating opioid misuse and the harmful consequences that come with it [21]. Garcia-Larrea *et al.* [22] recently showed that 6 out of 12 NP patients with varied illnesses (such CPSP, SCI, or BPI) were able to adjust their pain intensity in a suitable manner. This study proved that 20 tDCS sessions over the M1 (2 mA, 20 min) were secure and effectively reduced pain.

Furthermore, Hanna *et al.* investigated the effect of 5 sessions of bilateral anodal tDCS of M1 for 20 minutes on each side versus sham group on pain, depression, and shoulder movement range in post-mastectomy pain syndrome and concluded that the use of tDCS reduces the intensity of pain and improves shoulder range of movement in breast cancer patients after total mastectomy operation [23].

In contrast to prior trials, the analgesic effect of tDCS was questioned by certain studies, Lewis *et al.* [24] conducted a study at 2018 included 30 patients with upper limb NP of diverse causes including BPI or CRPS and concluded that active tDCS over M1 didn't have any positive effect in pain relief. Another study conducted by O'Neil *et al.* [25] on 21 patients with unilateral NP of varied sources (e.g., CPSP, SCI, TGN, or phantom pain) received tDCS over the contralateral M1 found that there was no discernible change seen between anodal, cathodal, or sham tDCS treatment.

The insula was the second target activated in the current study. Elevated glutamine and glutamate levels in the posterior insula have been linked to pain

processing in FM patients, as have reduced GABA levels in the anterior insula. [26]. Anodal M1 stimulation alleviated FM symptoms and raised GABA levels in the anterior insula in prior research [27], the results of our study found improvement in the clinical pain after active insula tDCS than after sham stimulation with marked improvement after 2 weeks follow up.

In previous study on healthy volunteers with capsaicin-induced pain and hyperalgesia, using (HD-tDCS) stimulation, they discovered a significant decrease in areas of primary and secondary hyperalgesia as well as VAS score after motor or insular cortex stimulation. Volunteers in the stimulation groups also reported much quicker pain score reductions [28]. Another study that used active rTMS over the operculo-insular cortex (OIC) in individuals with persistent neuropathic pain found that it increased thermal pain thresholds more than sham stimulation [29].

In contrast to our study, Samartin-Veiga *et al.* delivered 15 sessions of tDCS over the M1, OIC and dorsolateral prefrontal cortex (DLPFC) in fibromyalgia patients, the results did not demonstrate that the actual tDCS had a more potent analgesic effect than the sham control group [30].

PMPS and breast cancer survivors have more psychological distress and depressive symptoms [31]. Several researches have demonstrated that tDCS stimulation decreases pain intensity and alleviates patients' depressive symptoms [32] [33]. Our study found that active tDCS groups showed improvement in depressive symptoms measured by HAM-D score than sham groups. In accordance to Nguyen *et al.*, who described a case study of metastatic cancer bladder that was uncontrolled by strong opioid and pregabalin; they used 5 daily sessions of tDCS on the motor cortex, (20-min sessions, intensity of 1 mA), by the second day of treatment, the pain had started to subside. On the fifth day, the amount of medication was reduced since the patient's depression subsided quickly [34].

Consequently, because there were no variations in the presence of adverse effects between the active and sham groups, we concluded that tDCS is a secure and easily tolerated treatment.

Study Limitation and Future Studies

Our study has some limitations, such as the low number of tDCS sessions, which may affect the duration and effectiveness of pain relief, the lack of objective measurement parameters and the fact that all measurement parameters were subjective and dependent on patient response. Therefore, in future studies, we advise using more than five tDCS sessions and adding objective parameters to assess the effectiveness of tDCS in controlling pain, such as measuring the endogenous endorphin levels. Also, small sample size of our study can be considered as a limitation so we recommend increasing the sample size in future studies

5. Conclusion

We concluded that active tDCS stimulation either activating the primary motor

cortex or the insula has nearly the same analgesic effect for controlling neuropathic chronic post mastectomy pain when compared with sham stimulation, and the maximum effect was at 15 days after the last session.

Conflicts of Interest

The authors declare that there is no conflict of interest.

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