Transcranial Direct Current Stimulation (tDCS) on Post Mastectomy Pain Syndrome

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ABSTRACT

Breast cancer is to be considered one of the most prevalent types of cancer in Egypt. Post Mastectomy Pain Syndrome (PMPS) is a common complication after surgical intervention for breast cancer. PMPS very badly affects patient's quality of life in aspects of losing shoulder full range of motion, pain, and depression. Transcranial Direct Current Stimulation (tDCS) was used as it is one of the non-invasive brain stimulation techniques and has been proven to have a positive feedback on reducing pain in cancer patients.**Aim:** To investigate the effect of bilateral anodal tDCS of motor cortex (M1) on pain, depression, and shoulder range of motion (ROM) in Post-mastectomy pain syndrome.**Study design:** Randomized controlled trial.**Methods:** A total of 30 female patients with post mastectomy neuropathic pain were randomized into two groups; intervention group which received bilateral tDCS on motor cortex (M1) and control group that received sham bilateral tDCS on M1. As pain affects shoulder range of motion (ROM) so shoulder ROM was measured by electronic goniometer pre and post tDCS application. In addition the levels of pain and depression have been measured pre and post treatment. **Results:** A significant difference was noted in group A regarding pain, depression and shoulder ROM (p= 0.001, p= 0.003, and p= 0.003 respectively). Between group comparison revealed a significant difference of VAS scores and shoulder flexion ROM between groups, the study group and the control group (p=0.041 and 0.048 respectively). **Conclusions:** The Application of tDCS decreases the severity of complications suffered by breast cancer patients after mastectomy and improves their quality of life.

Key words: Transcranial Direct Current Stimulation, mastectomy, neuropathic pain

INTRODUCTION

As per the National Cancer Registry Program (NCRP) report of 2014 and with an incidence of 15.4 % of all cancer patients and 13.5% of all female population in Egypt, breast cancer is to be considered one of the most prevalent types of cancer in Egypt. And with the fact that pain is one of the greatest complications of cancer treatment, it constitutes an increasing challenge especially with the increasing rate of cancer survivors nowadays **(Ibrahim, et.al. 2014)**.

Breast cancer has multitude of treatment approaches with surgical intervention as one of the main treatment approaches. Post Mastectomy Pain Syndrome (PMPS) is a common complication after surgical intervention for breast cancer **(Khan, et.al. 2019)**.

Although PMPS is defined by Stevens in 1995 as "paroxysms of sharp pain in a background of burning, aching and constriction", that are worsened by movement and are neither improved nor relieved by narcotics, and being considered as pain and sensory abnormalities that are neuropathic in nature due to damage of intercostobrachial neve (ICBN), its causes are not yet clearly understood. In 2016, Waltho defined PMPS as neuropathic pain with moderate severity occurs after any breast surgery, and is located in the ipsilateral side of breast, chest wall, axilla, and /or arm; also it lasts at least for 6 months **(Chwistek, 2017; Waltho, et.al. 2016; Fabro, et. al. 2012).**

The pain of PMPS very badly affects patient's quality of life, in terms of disturbance of mood, sleep pattern and quality, body image and cognition, which leads to depression and anxiety. The disappointment encontered in the treatment of PMPS has brought up the actual need for further research to reveal better and effective treatment approach **(Tait, et. al 2018; Ahles, et. al 2017).**

With the increasing rates of cancer survivors, pain treatment has become more challenging, considering that invasive techniques like chronic opioid therapy has many side effects. This had paved the way for the research to be directed towards non-invasive brain stimulation (NIBS) techniques in the treatment of various diseases and symptoms, especially knowing that it shows better outcomes and prognosis and less adverse effects as compared to traditional invasive methods **(Palm, et. al 2017; Wiethoff, et. al 2014).**

Transcranial Direct Current Stimulation (tDCS), one of those NIBS techniques, has been proven to be more useful, easily used by therapists and well tolerated by patients. So, therapists has started paying more attention towards tDCS in fields; neuropsychiatric, neurocognitive, chronic pain syndromes as well as cancer patients **(Thair, et. al 2017; Giordano, et. al 2017; Turski, et. al 2017; Nguyen, et. al 2016; Ibrahim, et. al 2017).**

Transcranial direct current stimulation is used in treating various types of pains in different diseases, such as; neuropathic and visceral pain in cancer patients, neuropathic pain in diabetic patient and chronic pain syndromes. It has been also proven to be effective in many neurological problems as stroke patients, multiple sclerosis patients and trigeminal pain, in addition to some neuropsychiatric disorders as depression, anxiety, fibromyalgia, neurocognitive impairment and behavior modification **(Palm, et. al 2017; Turski, et. al 2017; Knotkova, et. al 2014).**

Post mastectomy patients are one of the cancer survivors who suffers a lot of chronic pain in the form of PMPS, which lacks enough research to find out the effect of tDCS on PMPS **(Chwistek, 2017; Zibelli, 2018; Ngernyam, et. al 2013; Tait, et. al 2018).**

Key words: Transcranial Direct Current Stimulation, mastectomy, neuropathic pain.

Material and Methods

Study design

Randomized control trial (RCT). The protocol of the trial was registered in Pan African Clinical Trials Registry (registration No. PACTR202011764107216). The study received ethical approval from Cairo University Faculty of Physical therapy Research Ethical Committee (approval No.: P.T.REC/012/002945). A G power analysis was conducted and yielded a requirement of 30 female participants.

Participants

Women who were receiving treatment in "IPC" physical therapy clinic in Misr Al Gededa, Cairo, Egypt, were invited to participate. Before being recruited in the study, all patients signed a consent form for their approval of participation, which deliberately explained the purpose of the study, procedures, expected outcomes, and further use of the results.

Key inclusion criteria were female patients, with PMPS aged 35 to 45 years, who were assessed for the presence of neuropathic pain post mastectomy surgery by DN4 questionnaire and their pain lasts at least for 6 months (**Waltho, et.al. 2016)**.

And key exclusion criteria were; epilepsy or a history of epilepsy or Epileptic drugs, medical diagnoses of psychological or neurological disorders, history of migraines, scalp or skin condition (e.g., psoriasis or eczema), metallic implants (e.g., intracranial electrodes, surgical clips, shrapnel or a pacemaker), head injury resulting in a loss of consciousness that has required further investigation (e.g., a brain scan), seizure, chance of pregnancy, and patients on contraceptive pills, moderate or severe lymphedema **(Thair, et. al 2017).**

Measurement procedures

A full medical history has been taken from each patient by physiotherapist to exclude patients according the exclusion criteria or to confirm patient inclusion as per inclusion criteria. All participants were assessed for the presence of neuropathic pain by using DN4 score. The female patients who scored 4 or more out of 10 in DN4 were included in the trial **(Bouhassira, et. al. 2005).** Then participants were randomized into two equal groups; group A (intervention group) and group B (control group). All participants were assessed pre- and post-treatment for pain, depression questionnaire, and shoulder range of motion(ROM) for flexion and extension by using VAS, Beck-Depression-Inventory-BDI, and electronic goniometer, respectively **(Mordillo-Mateos, et. al 2017; Ibrahim, et.al 2017; Villamar, et. al 2013; Sankarasubramanian, et. al 2017; Wiethoff, et. al 2014; Nguyen, et. al 2016; Ngernyam, et. al 2013).**

Evaluation Procedure

All Participants before receiving treatment were assessed for pain, depression level, and shoulder range of motion (flexion and extension) by using VAS, Beck-Depression-Inventory-BDI, electronic goniometer and VAS, respectively.

ROM was measured using a digital goniometer. For measuring active shoulder flexion range, Patient is supine with knees flexed. Palm facing medially and thumb is up. To start the test arm is to be by the patient's side. Goniometer Placement: the axis was on middle of humeral head laterally, the stationary arm was parallel with the trunk and the movement arm was in line with the mid line of the humerus (lateral epicondyle). Then patient was asked to flex her shoulder. For measuring active shoulder extension range, Patient is prone, with the face turned away from the shoulder being tested. Palm facing medially and thumb is down. To start the test arm is to be by the patient's side. Goniometer Placement: the axis was over the lateral aspect of the greater tubercle, the stationary arm was parallel with the trunk and the movement arm was in line with the mid line of the humerus (lateral epicondyle). Then patient was asked to extend her shoulder **(Norkin, et. al. 2016).** Three ROM measurements were conducted and averaged for analysis **(Hilde, et. al. 2020).**

Beck-Depression-Inventory-BDI questionnaire distributed to the patient, it is a 21 items self-report rating inventory, that rate the attitude of a person and their depression symptoms. After that the patient was asked to answer the BDI questionnaire by choosing only one statement appealing to her in each item **(West, 1985).**

Visual Analog scale (VAS) was distributed to the patient and the patient was asked to determine her pain severity on scale from 0 to 10, where 0 means no pain at all and 10

indicates the highest severity of pain.

Treatment procedures:

Participants allocated to the intervention group received bilateral/ bicephalic tDCS **(Cioato, et. 2015)** for 20 minutes on each side of hemisphere. On the other hand, participants allocated to the control group received sham bilateral tDCS on M1.

All Participants of both groups underwent tDCS stimulation session for 5 alternating days. Each session lasted for 40 minutes; 20 minutes on right hemisphere and 20 minutes on left hemisphere. The patient was in sitting position. Electrodes were placed on the motor cortex (M1) using the Caputron universal strap. Electrodes were sized 2" x 2"**(Villamar, et. al 2013; Sankarasubramanian, et. al 2017; Ngernyam, et. al 2013; Nguyen, et. al 2016).**

Intervention group received anodal M1- tDCS with current intensity 2mA. On the other hand, control group received sham tDCS, where current applied for 30 seconds only **(Villamar, et.al. 2013).** Administration of sham tDCS involves three steps. First step named ‘'ramping up” in which the stimulator reaches the maximum current 2mA. Ramping up is then followed by a short stimulatory period, in which the participant receives stimulation for 30 seconds. Finally, “ramping down” involves the current gradually being switched off **(Thair 2017).**

Data analysis

Unpaired t-test was used to compare between subjects demographic data of the two groups. MANOVA was performed to compare within and between groups’ effects for all measured variables. Statistical package for the social sciences computer program (version 20 for Windows; SPSS Inc., Chicago, Illinois, USA) was used for data analysis. P less than or equal to 0.05 was considered significant.

Results

The main aim of this study was to determine the effect of bilateral anodal tDCS of motor cortex (M1) on pain, depression and shoulder range of motion in Post-mastectomy pain syndrome. Data were expressed as mean± SD.

Normality test:

Data were screened for normality assumption, homogeneity of variance, and presence of extreme scores. Shapiro-Wilk and Kolmogrov-smirnov tests for normality showed that all measured variables are normally distributed.

Demographic data of patients:

A total of 30 patients participated in this study; they were assigned into 2 equal groups at random, as shown in table (1); the mean age of groups A and B was (40.5±2.8) and (40.2±3.1) years respectively. There was no

significant difference between both groups of mean age (p= 0.808).

Table (1): Age of subjects in both groups

	Group A	Group B	t-value	p-value
Age (years)	40.5±2.8	40.2±3.1	0.245	0.808

Data represented as mean ±SD

As shown in table 2 and 3, Within group difference, all measured items in group A showed significant difference between pre and post treatment. Between group differences, there were no significant differences in depression index.

Table (2): Comparison between pre- and post-treatment mean values of depression and pain between and within groups

Variables	Pre-treatment Mean ±SD	Post-treatment Mean ±SD	% of change	P value
Depression index				
Group A	26.7 + 9	25.7 + 9.3	3.7%	0.003*
Group B	27.8 ± 8.1	27.4 ± 8.8	1.4%	0.172
(P-value)	0.721	0.604		
VAS				
Group A	6.9 ± 1.9	4.7 ± 2.1	32%	0.001*
Group B	6.5 ± 2.4	6.3 ± 2.2	3%	0.567
(P-value)	0.681	0.041*		

SD: standard deviation p-value: probability value *: significant

Table (3): Comparison between pre- and post-treatment mean values of shoulder ROM between and within groups

Shoulder ROM (degrees)	Pre-treatment Mean ±SD	Post-treatment Mean ±SD	% of change	P value
Flexion				
Group A	136.3 ± 19.2	143.7 ± 19.3	4.8%	0.001*
Group B	131.6 ± 13.6	131.5 ± 12.3	-0.07%	0.866
(P-value)	0.452	0.048*		
Extension				
Group A	48.9 + 8.6	51.6 + 8.6	5.5%	0.002*
Group B	47.5 ± 7.3	47.8 ± 7.1	0.6%	0.726
(P-value)	0.632	0.195		

SD: standard deviation p-value: probability value *: significant

Discussion

The findings of this trial indicated that the application of tDCS decreases the severity of complications suffered by breast cancer patients after mastectomy compared with the control condition. Moreover, tDCS was effective in improving quality of life of women with mastectomy. The goal of the trial was to decrease the intensity of neuropathic pain suffered by breast cancer patients who received mastectomy. The trial showed significant change between group difference in VAS and shoulder flexion range of motion, also showed no significant change in group difference in Beck-Depression-Inventory-BDI and shoulder extension range. These results highlight the effect of tDCS application on pain and shoulder range of motion in post mastectomy female patients.

Post Mastectomy neuropathic pain has been proven to be persistent pain and didn't respond well to opioids treatment, so it turns to be chronic condition **(Waltho, et.al. 2016)**. The presence of chronic neuropathic pain leads to further complications. First patient avoids using his painful shoulder in its full range of motion so the range decreases. Second, a high percent of women with mastectomy suffers from depression for several reasons; some suffer from it as a side effect to the administrated medications, others due to the persistent chronic pain and other due to the distorted body self-image after breast removal. And here comes the role of tDCS, which is a non-invasive brain stimulation technique that plays role in PMPS **(Chang, et.al. 2021).**

There was significant reduction in pain (VAS) measurement; this could be explained as tDCS was proven to be effective in reducing pain with neuropathic nature **(Palm, et. 2017; Cioato, et. 2015)**.Then a significant improvement have been seen in shoulder range of motion, this could be secondary to the pain reduction. Finally a minimal improvement has been shown in level of depression that could be a result of pain reduction.

Pain is a multi-dimensional personal, sensory and emotional experience which is difficult to quantify. Pain has two aspects; psychological and biological aspects **(Talbot, et.al. 2019).** Psychological responses could be anxiety, fear, distress, and those are normal responses which must be understood and managed as they can moderate the pain state. Biological perspective, either nociceptive (local injury/ mechanical stress/ inflammation) or neuropathic pain (mechanical irritation of nerve tissue, inflammation of nerve structures). Pain is processed in central nervous system (CNS). CNS can become sensitized in some conditions e.g.: neuropathic pain and sever pain.

Transcranial electrical stimulation approaches pass electrical current directly to the brain via electrodes on the head **(Paulus et al. 2013)**. tDCS is the only class of neuro-modulation technique that delivers a sustained direct current (DC). Thus, the use of a sustained direct current is a characteristic feature of tDCS, and one that should be kept in mind when considering any unique neurophysiologic, cognitive, or behavioral outcomes as direct current stimulation (DCS) changes neuronal excitability and plasticity. Majority of studies investigated the underlying physiological effect of tDCS on primary motor cortex. M1-tDCS stimulation affects membrane polarization leading to alteration of cortical excitability. Anodal M1-tDCS produces motor evoked potentials (MEPs) and stimulates motor cortex excitability **(Nitsche, et.al. 2000; Nitsche, et.al. 2001).**

Many authors supported that tDCS has positive effect in decreasing different types of pain in different types of patients**.** Bicephalic tDCS is effective to promote anti-nociceptive behavior in neuropathic pain, which can be reflected by a spinal neuroimmuno-modulation linked to pro- and anti-inflammatory cytokine levels observed in the long term. Plus, their is a role of the central immune system in the neuropathic process, which can be implicated in maladaptive neuroplastic changes. Considering those alterations, to achieve a lasting benefit with a non-pharmacological and noninvasive treatment, this intervention should be able to modulate the entire signaling pathway **(Cioato, et.al. 2015). Chwistek in 2017** used tDCS in neuropathic cancer pain patients and concluded that repetitive anodal M1-tDCS sessions on contralateral to the pain side is effective for various neuropathic pain syndromes. **Ibrahim in 2017**, used tDCS on primary motor area in Hepatocellular carcinoma (HCC) patients and it relieved visceral pain. Again, **(hu, et.al.2016)** applied M1-tDCS as an adjuvant neuro mechanism-driven analgesic therapy for head and neck cancer patients, in addition to that tDCS can protect paients from escalating opioids over use and its associating side effects **(Schaller, et.al. 2015)**. Although, tDCS have been applied on different cancer patients but never on neuropathic pain associated with post mastectomy patents then further clinical trials with large sample size not only case studies were needed **(ngernyam, et.al, 2013; Zibelli, 2018;Lefaucheur, 2009).**

Some trials didn't support the analgesic effect of tDCS. **(luedtke2015)** concluded that tDCS do not influence pain or disability in patients with non-specific chronic low back pain.

Depression is the common cold of the Era. According to the **(world health organization [WHO], 2019)** depression is considered an illness that Causes sadness and inability to do the

normal daily activities for not less than 2 week. Depression is highly distributed in the population worldwide. It affects more than 300 million people of all ages worldwide. Patients who suffer from depression tend to function poorly at work. Breast cancer survivors and PMPS suffer from depression and have higher psychological distress **(Pyszel, et.al. 2006).**

Although Beck-Depression-Inventory-BDI index score, within group difference, in group A showed significant difference between pre and post treatment but between group differences, there were no significant differences. This can be explained as tDCS placement for depression improvement is on dorsolateral prefrontal cortex (DLPFC) and not on motor cortex **(mu, et.al. 2017; knotkova, et. al.2014)** as pain that is why no direct effect occurred, no significant difference between group differences, on the other hand the improvement that occurred within group difference between pre and post treatment could be secondary to the pain improvement but not a tDCS direct effect **(Fabro,et. al. 2012).**

PMPS leads to substantial functional impairment in shoulder, limited range of motion of the affected arm and reduction in swinging phase during walking. This could be out of pain the patient avoids using her shoulder leading to loss in ROM **(zibelli, 2018; Balzarini, et. al.2006). O**ur study showed a significant improvement in shoulder ROM in flexion post tDCS application, this results need further research to understand the underlying mechanism.

Others used repetitive transcranial magnatic reasonance (rTMS) in stead of tDCS **(mu, et.al. 2017).** On comparing rTMS and tDCS we can notice that the mechanism of action of tDCS sdiffer from that of rTMS. In fact, tDCS is a purely neuromodulation technique, whereas rTMS exerts both neurostimulatory and neuromodulatory effects. Also tDCS has some advantages, it is small, can be portable, cheap, easily application even in home and at same time gives analgesic effect as rTMS **(Lefaucheur, 2009)**.

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