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ORIGINAL RESEARCH ARTICLE

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Efficacy of transcranial direct current stimulation (tDCS) on pain and shoulder range of motion in post-mastectomy pain syndrome patients: a randomized-control trial

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Abstract

Background Post-mastectomy pain syndrome (PMPS) is a highly prevalent complication after surgical treatment for breast cancer, and it affects the patient's quality of life in aspects of losing shoulder full range of motion, pain, and depression. Transcranial direct current stimulation (tDCS) is non-invasive brain stimulation technique that was used in numerous clinical applications and in pain reduction in cancer patients. However, the effectiveness of tDCS on PMPS has never been evaluated in an experimental study.

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; the intervention group which received bilateral tDCS on motor cortex (M1) and the control group that received sham bilateral tDCS on M1. As pain affects shoulder range of motion (ROM), 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. Pain has been measured with visual analogue scale (VAS) and depression with Beck-Depression-Inventory-BDI questionnaire (BDI).

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). Pain decreased by 32% and Shoulder flexion increased by 4.8% post-treatment while there were no significant difference in group B (p=0.567 and p=0.866, respectively).

Conclusions The application of tDCS decreases the severity of pain and improves shoulder range of motion suffered by breast cancer patients after total mastectomy surgery.

Keywords Transcranial direct current stimulation, Mastectomy, Neuropathic pain

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Introduction

As per the National Cancer Registry Program 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 [1].

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 [2]. The prevalence of incidence of PMPS in postoperative breast cancer patients is 36.2% [3]. Simply, it is a chronic neuropathic pain condition [4].

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 nerve damage, e.g., the damage of intercostobrachial nerve (ICBN) and other smaller nerves, leading to neuroma formation, yet PMPS causes are not clearly understood. In 2016, Waltho defined PMPS as pain with the following characteristics: neuropathic pain such as numbness, needle, and burning, and pain with moderate severity occurs after any breast surgery and is located in the ipsilateral side of the breast, chest wall, axilla, and/or arm; also, it lasts at least for 6 months [3, 5–9].

The pain of PMPS very badly affects patient's quality of life because patients have variability in response to pain and psychological distress in terms of catastrophizing, poor-coping strategies, disturbance of mood, sleep pattern, body image, and cognition, which leads to depression and anxiety. Women frequently report that PMPS interfered on a daily basis with occupational or domestic work and activities [10–13].

In the past, PMPS was largely unrecognized or ignored leaving patients feeling alone and helpless. But recently, many options were introduced to treat PMPS but not all of them were effective and many had strong adverse effect. Some of those options were conservative as pharmacologic and tropical medications, and others were non-conservative, e.g., surgical. The use of anti-epileptics as "levetiracetam" was not worthy in reducing pain in patients with chronic neuropathic pain condition. Tricyclic antidepressants "amitriptyline and venlafaxine" effective in many neuropathic pain conditions, but their adverse effects could be serious as serotonin syndrome, which may include symptoms such as confusion, hallucination, seizure, extreme changes in blood pressure, increased heart rate, fever, excessive sweating, shivering or shaking, blurred vision, muscle spasm or stiffness, tremor, incoordination, stomach cramp, nausea, vomiting, and diarrhea. Opioid analgesics and tramadol are used and provided pain relief, but the sustained use is hazardous in renal and hepatic dysfunction patients and can lead to misuse or addiction. Topical treatment had statistically significant effect but the burning sensation was a frequent adverse effect. Surgical treatment by fat injection reduces pain in burn scars and improves neuropathic pain, yet it is an invasive approach. Regional anesthesia, e.g., Pectoral blocks safe to be used [4, 11].

Prevention techniques were thought to be effective in reducing the risk of PMPS incidence, but several studies found no difference in PMPS occurrence following lumpectomy verses mastectomy unfortunately. However, axillary lymph node dissection is associated with PMPS development so the performance of lesser surgery with a sentinel lymph node dissection alone could result in less chronic pain, but there is conflicting evidence whether preserving sentinel lymph node is effective or not [11, 13].

So we conclude that the treatment of PMPS is quite challenging as treatment options are not highly effective and expensive, and some have serious side effects and some are invasive techniques plus no assured results achieved regarding prevention techniques. The disappointment encountered in the treatment of PMPS has brought up the actual need for further research to reveal better and effective treatment approach [13].

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 [14, 15].

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, and chronic pain syndromes as well as cancer patients [16–20].

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. Plus it helps in decreasing postsurgical opioid consumption [14, 20–22].

The underlying mechanism of action of tDCS on pain is thought to be altering and modulating activity in the brain areas that is responsible for pain processing [23]. The emerging application of tDCS for pain appears promising. Pain scores can be significantly reduced even when patients use less opioids [24]. In summary, the field of non-invasive brain stimulation for pain is expanding rapidly. tDCS appears to have the potential to serve as an adjunct to pain management strategies, and it is promising in decreasing the burden of neuropathic pain suffered by patients [25]. So if PMPS patients suffer from serious neuropathic pain problem, and tDCS is effective in treating this type of pain why not to try applying tDCS in PMPS on large scale and check the results.

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, whether tDCS will have effect on pain, shoulder range of motion, and depression in PMPS or will not? [6, 13, 25, 26].

Ngernyam recommended the need for further larger higher evidence base clinical trials, e.g., RCTs to fill many research gaps as many of the trials were case studies. However, a randomized control trial was carried on in 2017 on hepatocellular carcinoma and the results were promising [17]. Now this trial is RCT, this is a high clinical evidence base trial. It covers research gap regarding many points; the effective treatment dose of tDCS (frequency and number of treatment sessions) and shows the efficacy of using tDCS with new population the post-mastectomy females and the use of tDCS in managing PMPS [25].

Material and methods

Study design

Randomized control trial (RCT): randomized sample using lottery into two groups equal in number

- Group A: patients in this group will receive bilateral tDCS on M1
- Group B: patients in this group will receive sham bilateral tDCS on M1.

The protocol of the trial was registered in Pan African Clinical Trials Registry (registration No. PACTR202011764107216), Registered on 5 November 2020, https://pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=9564. The study received ethical approval from Cairo University Faculty of Physical Therapy Research Ethical Committee (approval No.: P.T.REC/012/002945).

The sample size calculation was done using pain by VAS, as reported in [27], with 95% power at $\alpha = 0.05$ level, number of measurements 2, for 2 groups and effect size = 0.41756 using F test MANOVA within and between interaction effects. The minimum proper sample size was 30 subjects, 15 participants in each group. The sample size was calculated using the G*Power software (version 3.0.10) [17]. is the sample size reference article.

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. Patients were randomly assigned into two groups (Fig. 1).

Inclusion criteria of the subjects

1- Thirty female subjects with age range of 35–45 years were assigned into two groups, Group (A) and Group (B).
2- Females with unilateral/single mastectomy, total mastectomy (with sentinel lymph node dissection), modified radical mastectomy (with axillary lymph node dissection), nipple-sparing mastectomy (with either sentinel or axillary lymph node dissection), and skin-sparing mastectomy.
3- No or mild lymphedema.
4- Female patients with PMPS.
5- The subjects were assessed for the presence of neuropathic pain post mastectomy surgery by DN4 questionnaire.
6- Patients with neuropathic pain that lasted for 6 months at least or more [7, 9, 13, 28–30].

Exclusion criteria of the subjects

All subjects assigned in this study had none of the following conditions:

1- Epilepsy or a history of epilepsy or epileptic drugs intake
2- Medical diagnoses of psychological or neurological disorders
3- History of migraines
4- Scalp or skin condition (e.g., psoriasis or eczema)

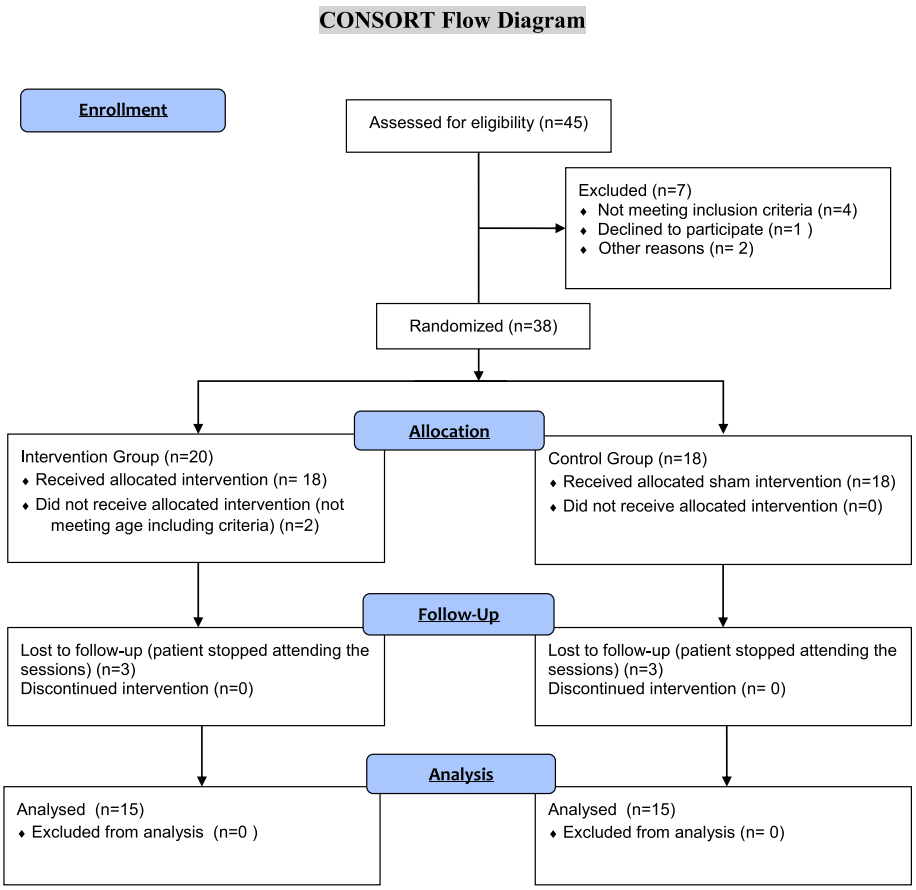

Fig. 1 Flow chart of study procedure

5- Metalic implants, including intracranial electrodes, surgical clips, shrapnel or a pacemaker, or any metallic accessories or cloth
6- Head injury resulting in a loss of consciousness that has required further investigation (e.g., a brain scan)
7- Seizure
8- Chance of pregnancy and patients on contraceptive pills
9- Moderate or severe lymphedema [19]

Measurement procedures

A full-medical history has been taken from each patient to exclude patients according to exclusion criteria or to confirm patient inclusion as per inclusion criteria. Also, patient's personal details and history was taken and recorded in a recording data sheet (Additional file 1: Appendix V). All participants were assessed for the presence of neuropathic pain by using the Arabic version of DN4 score. The female patients who scored 4 or more out of 10 in DN4 were included in the current study [31]. Then, the participants were randomized into two equal groups; group A (intervention group) and group B (control group). All participants were assessed before the first M1-tDCS session and after the last M1-tDCS session for pain, depression, and shoulder range of motion (ROM) in flexion and extension by using VAS, Beck-Depression-Inventory-BDI, and electronic goniometer, respectively [15, 17, 18, 25, 32–34].

Evaluation procedure

All participants before receiving the first M1-tDCS session 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, the 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, the patient was asked to flex her shoulder. For measuring active shoulder extension range, the patient is in prone position, with the face turned away from the shoulder being tested. The palm is facing medially and the 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, the patient was asked to extend her shoulder [35]. Three ROM measurements were conducted and averaged for analysis [36].

An Arabic version of Beck-Depression-Inventory-BDI questionnaire distributed to the patient, it is a 21-item self-report rating inventory that rates the attitude of a person and their depression symptoms [37]. The patient was asked to answer the BDI questionnaire by choosing only one statement appealing to her in each item. After completing the questionnaire and collecting the questionnaire, the scoring starts. Add up the score for each of the twenty-one questions by counting the number to the right of each question marked. The highest possible total for the whole test would be sixty-three. This would mean you circled number three on all twenty-one questions. Since the lowest possible score for each question is zero, the lowest possible score for the test would be zero. This would mean you circles zero on each question. You can evaluate depression resulted score according to Table 1 [38, 39].

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 [40] for 20 min on each side of cerebral hemisphere (Fig. 2). On the other hand, the participants allocated to the control group received sham bilateral tDCS on motor cortex (M1). All participants of both groups underwent 5 tDCS stimulation session in 5 days. Each session lasted for 40 min: 20 min on the right hemisphere and 20 min on the left hemisphere. The patient was in sitting position. Electrodes were placed on the motor cortex (M1) using the Caputron universal strap (Fig. 2). Electrodes were sized 2 in. by 2 in [18, 25, 33, 34]. .The intervention group received anodal M1-tDCS with a current intensity of 2mA. On the other hand, the control group received sham tDCS, where the current applied for 30 s only [34]. The 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 s. Finally, "ramping down" involves the current gradually being switched off [19]. All the participants after receiving the last M1-tDCS session were assessed for pain, depression level, and shoulder range of motion (flexion and extension). The study duration was about 1 year.

Table 1 Depression result score

Total score	Levels of depression
1–10	These ups and downs are considered normal
11–16	Mild mood disturbance
17–20	Borderline clinical depression
21–30	Moderate depression
31–40	Severe depression
Over 40	Extreme depression

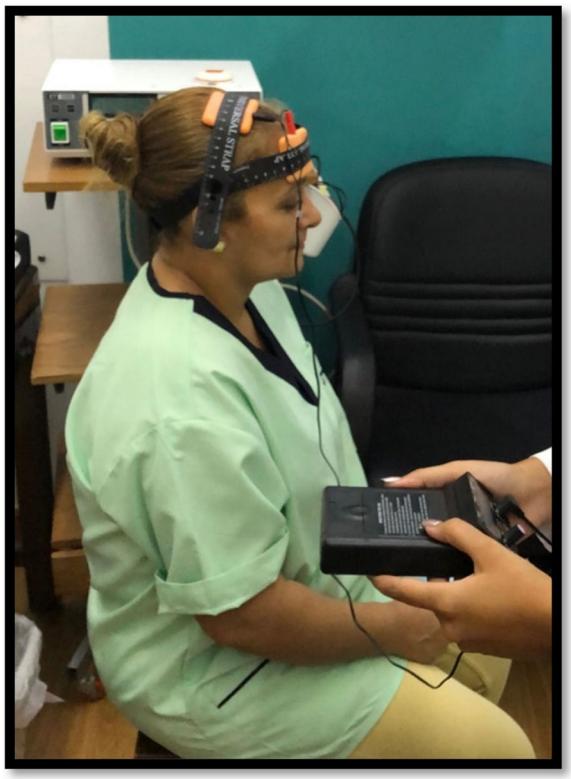

Fig. 2 Illustrates the tDCS application

Table 2 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

Table 3 Comparison between pre- and post-treatment mean values of measured variables 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*		
Shoulder 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*		
Shoulder 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

Data analysis

Unpaired *t* test was used to compare between subject 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, so MANOVA was performed to compare within and between groups' effects for all measured variables.

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 Tables 2 and 3; the mean age of groups A and B were

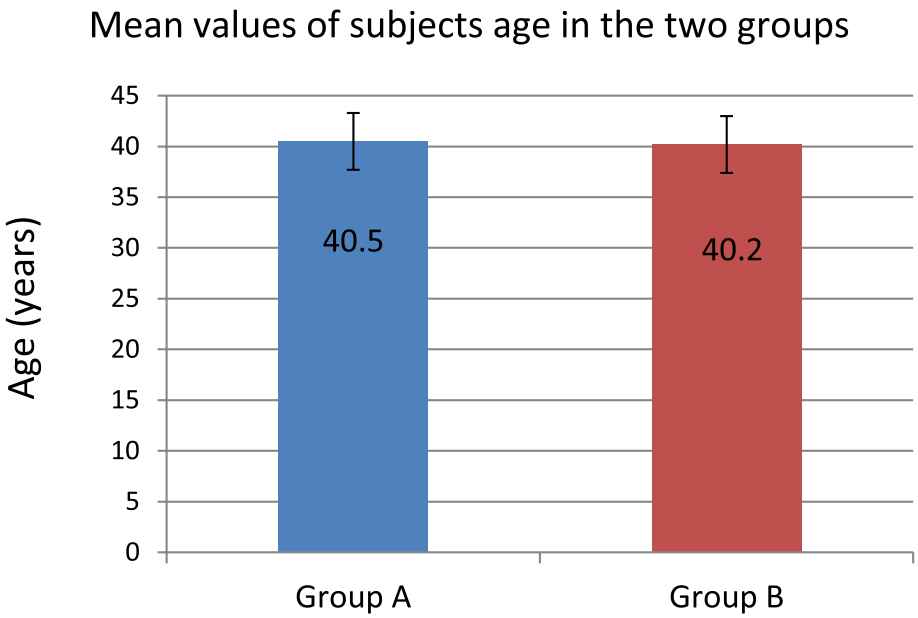

Fig. 3 Mean values of subjects' age in the two groups

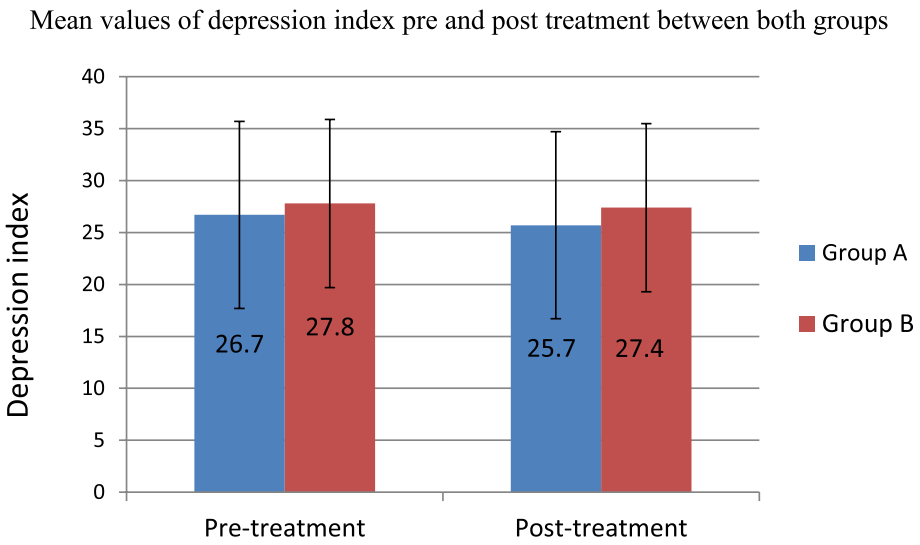

Fig. 4 The mean values of depression index pre- and post-treatment between both groups

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) (Fig. 3).

Effect of treatment on depression

Pre-treatment between groups As demonstrated in Fig. 4, shown in Table 3, the mean ± SD of depression index for subjects in groups A and B pre-treatment were 26.7 ± 9 and 27.8 ± 8.1, respectively. There was no statistical significant difference in pre-treatment mean values of depression index between the two groups (P=0.721).

Post-study between groups The mean ± SD of depression index for subjects in groups A and B post-treatment were 25.7 ± 9.3 and 27.4 ± 8.8, respectively. There was no statistical significant difference in post-treatment mean values of depression index among the two groups (P=0.604).

Pre- and post-treatment within groups (Fig. 5) There was a statistical significant difference between pre- and post-treatment mean values of depression index in group A (p= 0.003), depression decreased by 3.7% post-treatment, while there was no significant difference in group B (p=0.172).

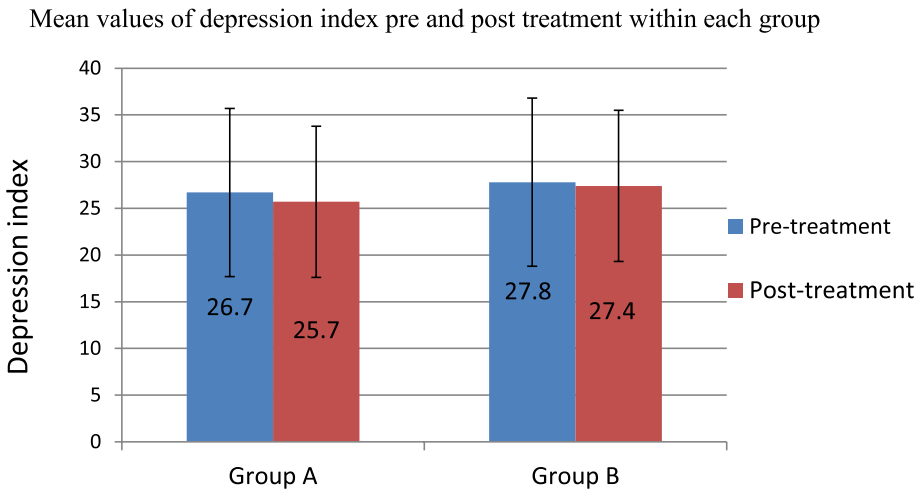

Fig. 5 Mean values of depression index pre- and post-treatment within each group

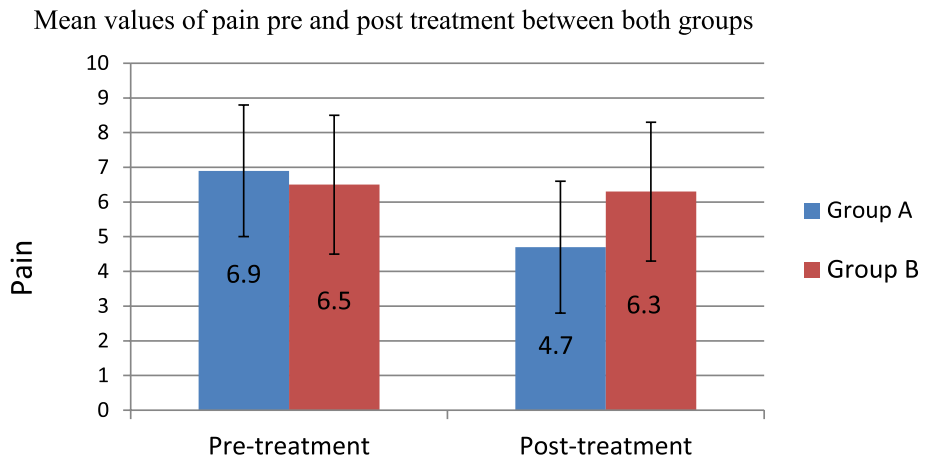

Fig. 6 Mean values of pain pre- and post-treatment between both groups

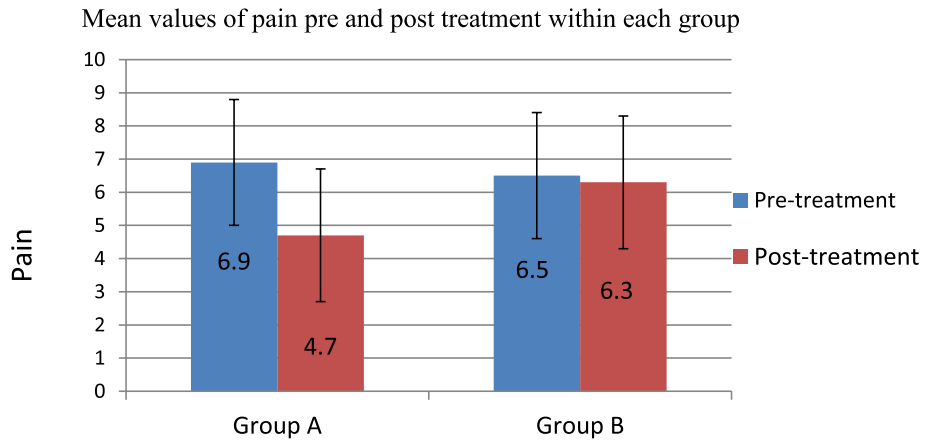

Fig. 7 Mean values of pain pre- and post-treatment within each group

Effect of treatment on pain

Pre-treatment between groups As demonstrated in Fig. 6, shown in Table 3, the mean ± SD of pain for subjects in groups A and B pre-treatment were 6.9 ± 1.9 and 6.5 ± 2.4, respectively. There was no statistical significant difference in pre-treatment mean values of pain between the two groups (P=0.681).

Post-study between groups The mean ± SD of pain for subjects in groups A and B post-treatment were 4.7 ± 2.1 and 6.3 ± 2.2, respectively. There was a statistical significant difference in post-treatment mean values of pain among the two groups (*P*=0.041) in favor of group A.

Pre- and post-treatment within groups (Fig. 7) There was a statistical significant difference between pre- and post-treatment mean values of pain in group A (p= 0.001), pain decreased by 32% post-treatment, while there was no significant difference in group B (p=0.567).

Effect of treatment on shoulder ROM

Flexion Pre-treatment between groups

As demonstrated in Fig. 8, shown in Table 3, the mean ± SD of shoulder flexion for subjects in groups A and B pre-treatment were 136.3 ± 19.2 and 131.6 ± 13.6°,

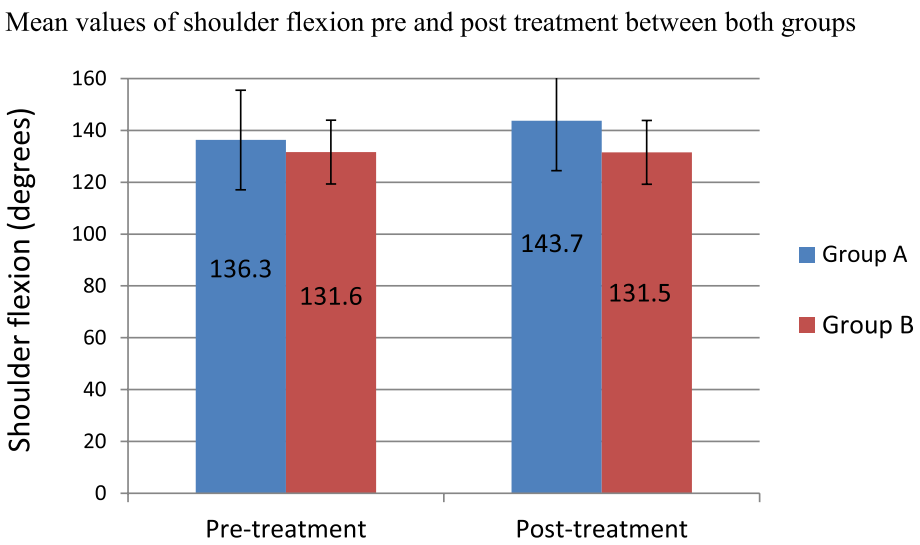

Fig. 8 Mean values of shoulder flexion pre- and post-treatment between both groups

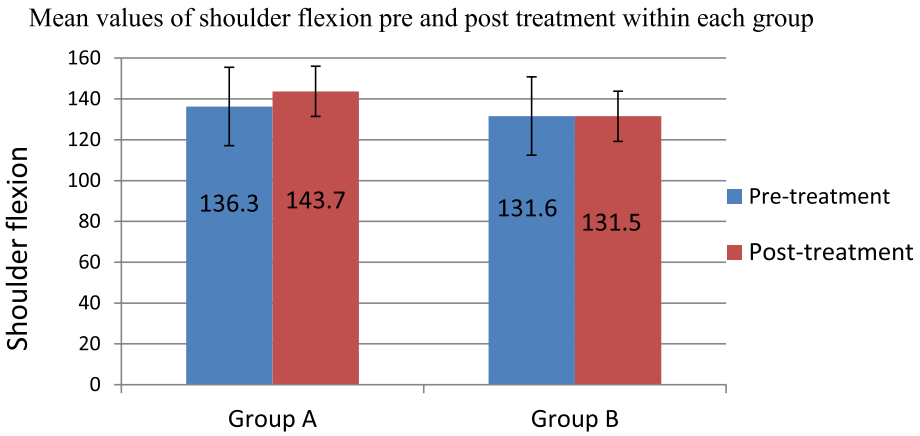

Fig. 9 Mean values of shoulder flexion pre- and post-treatment within each group

respectively. There was no statistical significant difference in pre-treatment mean values of shoulder flexion between the two groups (P=0.452).

Post-study between groups

The mean ± SD of shoulder flexion for subjects in groups A and B post-treatment were 143.7 ± 19.3 and 131.5 ± 12.3°, respectively. There was a statistical significant difference in post-treatment mean values of shoulder flexion among the two groups (p=0.048) in favor of group A.

Pre- and post-treatment within groups (Fig. 9)

There was a statistical significant difference between pre- and post-treatment mean values of shoulder flexion in group A (p= 0.001), and shoulder flexion increased by 4.8% post-treatment, while there was no statistical significant difference in group B (p=0.866).

Extension Pre-treatment between groups

As demonstrated in Fig. 10, shown in Table 3, the mean ± SD of shoulder extension for subjects in groups A and B pre-treatment were 48.9 ± 8.6 and 47.5 ± 7.3°, respectively. There was no statistical significant difference in pre-treatment mean values of shoulder extension between the two groups (p=0.632).

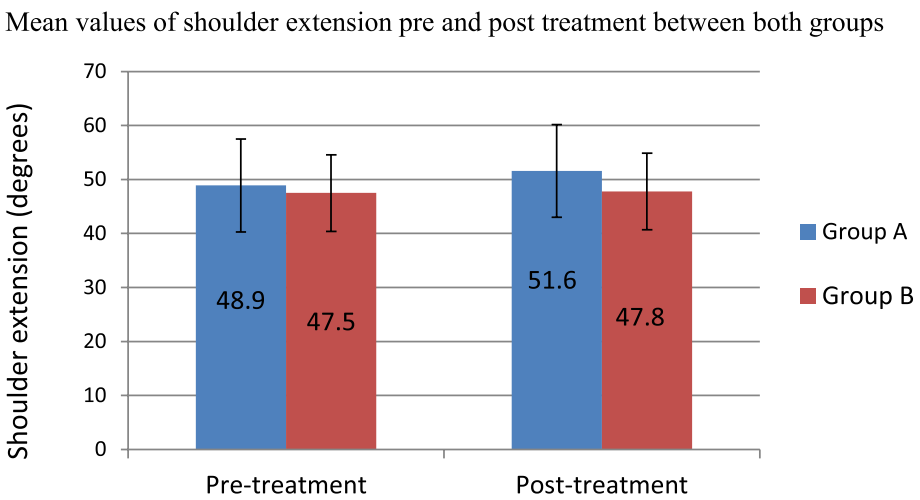

Fig. 10 Mean values of shoulder extension pre- and post-treatment between both groups

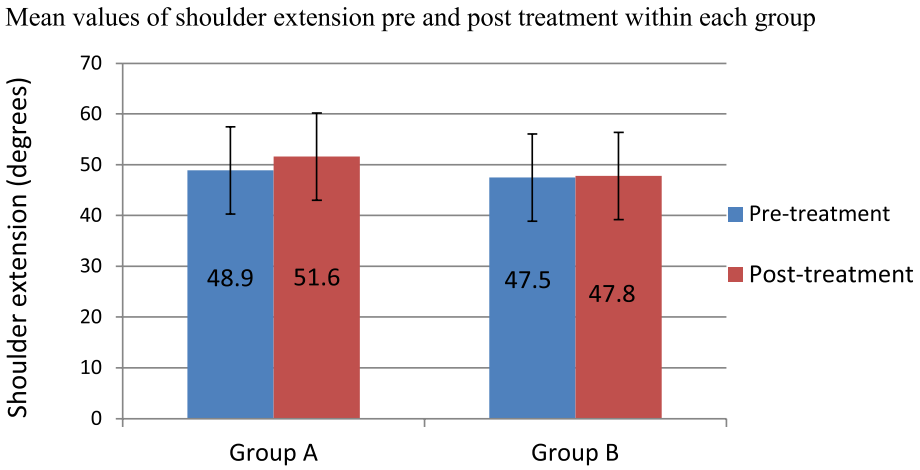

Fig. 11 Mean values of shoulder abduction pre- and post-treatment within each group

B- Post-study between groups

The mean ± SD of shoulder extension for subjects in groups A and B post-treatment were 51.6 ± 8.6 and 47.8 ± 7.1°, respectively. There was no statistical significant difference in post-treatment mean values of shoulder extension among the two groups (p=0.195).

Pre- and post-treatment within groups (Fig. 11)

There was a statistical significant difference between pre- and post-treatment mean values of shoulder extension in group A (p= 0.002), and shoulder extension increased by 5.5% post-treatment, while there was no statistical significant difference in group B (p=0.726).

As shown in Table 3, within and between group differences, 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.

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 the 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 did not respond well to opioid treatment, so it turns to be chronic condition [9]. 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 [5].

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 [14, 40]. Then, a significant improvement has been seen in shoulder range of motion, and 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 [41]. Psychological responses could be anxiety, fear, and 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 [42]. 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 [43, 44].

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, there 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 [40]. 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, [24] applied M1-tDCS as an adjuvant neuro mechanism-driven analgesic therapy for head and neck cancer patients, in addition to that tDCS can protect patients from escalating opioids over use and its associating side effects [45]. Although tDCS have been applied on different cancer patients but never on neuropathic pain associated with post-mastectomy patients, then further clinical trials with a large sample size not only case studies were needed [25, 26, 46].

Some trials did not support the analgesic effect of tDCS [47]. 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 [8], depression is considered an illness that causes sadness and inability to do the normal daily activities for not less than 2 weeks. 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 [48].

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 [22, 49] 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 [7].

Theoretically, a psychosocial intervention such as cognitive behavioral therapy prior and during breast cancer treatment to help decrease anxiety, improve coping, manage stress, and depression would have a benefit on the effects of chronic pain [11].

PMPS leads to substantial functional impairment in shoulder, a 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 [26, 50]. Our study showed a significant improvement in shoulder ROM in flexion post-tDCS application. These results need further research to understand the underlying mechanism.

Others used repetitive transcranial magnetic reasonance (rTMS) instead of tDCS [49]. On comparing rTMS and tDCS, we can notice that the mechanism of action of tDCS differ 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, and it is small, can be portable, cheap, and easy to apply even at home and at the same time gives an analgesic effect as rTMS [46].

PMPS patients after sentinel lymph node biopsy suffers from complications that affect physical function in the form of shoulder and arm morbidity (e.g., loss of range of motion [ROM]) and strength and pain due to axillary web syndrome and cording (in addition to lymphedema) is highly prevalent. Also, handgrip strength is decreased and aerobic capacity and upper extremity strength are generally lowered. In a review that was republished in 2010, shoulder flexion thought to be one of the most affected ranges of motion in post-mastectomy patients [51]. So patients require episodic physical therapy and yoga to decrease impairments and improve functional limitations, regain the diminished arm function and improve quality of life [52–56].

In study by Lancaster in 2016, nerve block by local injections was introduced to be successful in alleviating pain and suggesting that it could be the best choice to decrease pain in PMPS patents [11]. The most favorable option for nerve block is the pectoral nerve block (PECs II block) where injection is done to block the pectoral nerves and upper intercostal nerves which supply the chest and axilla, injection done with the patient in the supine position, under ultrasound guidance, with a recommended local anesthetic dose of 0.4 ml.kg–1 0.25% levobupivacaine. However, a recent systematic review on PECs II block technique revealed several limitations in the literature where the studies size were small, the follow-up window was short (up to 24 h), the inter-study difference could indicate that the extent of the therapeutic benefit differs considerably between practitioners as it depends on practitioner skill. So larger-scale studies is recommended to assess the effect of regional anesthesia and the cost-effectiveness. On the other hand, tDCS is highly evidence-based technique, cheap, safe, easy to apply as patient can apply it even for himself home-use as Remote Supervised tDCS, and its effect is independent from the practitioner skill and can be applied several times with nearly null side effects [5, 57, 58].

Conclusion

This is the first randomized controlled trial to examine the efficacy of the tDCS application on pain and shoulder range of motion in PMPS patients. The intervention of tDCS demonstrated clear beneficial effects informs of reducing pain by 32% and improves shoulder flexion range of motion by 4.8% compared with control.

How might this paper impact on clinical practice in the near future?

> ➢ It is useful to implement tDCS treatment sessions as part of PMPS pain management strategies.
> ➢ It is favorable to use tDCS in PMPS patients who suffer from decrease in shoulder range of motion.

In the future, further studies are needed to assess how long the treatment benefit is maintained.

Limitations

The current study includes few limitations. It is the loss of patient's follow-up after receiving the treatment sessions because patients' response to phone calls for receiving the follow-up feedback was weak.

Abbreviations

tDCS	Transcranial direct current stimulation
PMPS	Post-mastectomy pain syndrome
M1	Motor cortex
ROM	Range of motion
VAS	Visual analogue scale
BDI	Beck-Depression-Inventory-BDI questionnaire
ICBN	Intercostobrachial nerve
rTMS	Repetitive transcranial magnetic reasonance
DLPFC	Dorsolateral prefrontal cortex
PECs II block	Pectoral nerve block

Supplementary Information

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Additional file 1.

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Authors' contributions
Mira Hany Zaky Hanna realized the idea, designed the study, recruited and executed the practical part of the study, collected the data, interpretated the results and write the manuscript. Soheir Shehata Rezk-allah helped in the idea formulation, supervised the carryon of the study, and revised the results and data interpretation. Amr Sadeldeen Shalaby supervised the manuscript writing and the practical application of the device. Mounir Zaky Hanna revised the part of study that is related to oncology and supervised the recruiting process. The authors read and approved the final manuscript.

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Availability of data and materials
Data and materials are available upon request.

Declarations

Ethics approval and consent to participate
The study received ethical approval from Cairo University, Faculty of Physical Therapy Research Ethical Committee (approval No.: P.T.REC/012/002945).

Consent for publication
Additional file 1: Appendix 1

Competing interests
The authors declare that they have no competing interests.

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