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Photo-Biomodulation Therapy for Chemotherapy Induced Peripheral Neuropathy in Breast Cancer Patients

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Abstract:

Background: Breast cancer (BC) is the second most prevalent kind of cancer globally and the most common type of cancer among women.

Objective: To evaluate the therapeutic efficacy of photo bio-modulation therapy for treatment of neuropathic pain, inflammation and sensation defect in chemotherapy induced peripheral neuropathy in breast cancer patients.

Patients and methods: Sixty female patients who had breast cancer and suffered from peripheral neuropathy at least after one cycle of chemotherapy at the National Cancer Institute –Cairo University were included in this study. Both groups of patients were equally divided using a randomization procedure. (thirty patients for each group). Group (A) "Study group": Thirty patients who were given photo bio-modulation therapy (pulsed diode laser) and the routine medical care, Group (B) "control group": Thirty patients who were given the routine medical care only, both before and six weeks following treatment, the participants underwent evaluations using Chemotherapy Induced Peripheral Neuropathy Assessment Tool (CIPNAT) and Visual Analogue Scale (VAS).

Results: There was a substantial reduction in CIPNAT as well as VAS of group A contrasted with group B following treatment ($p = 0.001$) while the percentage of improvement pre and post values of group A in VAS was about 42% and in CIPNAT was about 35% and in Group B was 16% and 19% respectively.

Conclusion: There was a detectable improvement in the Chemotherapy-Induced Peripheral Neuropathy Assessment Tool (CIPNAT) of about 22% and VAS about 21% difference in patients treated with photo-biomodulation (PBM) therapy compared to routine medical care. PBM treatment may provide significant symptom benefits in patients with established Chemotherapy induced peripheral neuropathy (CIPN).

Keywords: Breast cancer, Chemotherapy Induced Peripheral Neuropathy Assessment Tool (CIPNAT) Photo Bio-Modulation therapy (PBM), Pulsed Diode Laser (PD), Visual Analogue Scale (VAS)

1. Introduction

Breast cancer (B.C) is a significant global public health issue. Breast cancer is the predominant form of cancer among women, particularly in poor nations. (Parkin et al., 2005). The incidence rates of BC exhibit significant variation across different parts of the world, with rates varying from 27 per 100,000 in Middle Africa as well as Eastern Asia to 96 in Western Europe. (Ferlay et al., 2015). The prevalence of BC in Egypt is 29.9 cases per 100,000 individuals in the age group of 34 and below. (Ibrahim et al., 2014). The cancer-related side effects frequently exert a significant impact on the overall quality of life of patients, as they might disrupt their ability to perform daily activities. (Palesh et al., 2014). Treatments for cancer, including chemotherapy, radiation, hormone therapy, as well as surgery, add to the overall impact of side effects that patients endure. (Kesler et al., 2017).

Chemotherapy Induced Peripheral Neuropathy (CIPN) is a frequent adverse effect of neurotoxic chemotherapy agents, including taxanes, vinca alkaloids, platinum compounds, bortezomib, as well as thalidomide. CIPN mostly affects the sensory peripheral nerves, although certain patients may also develop motor symptoms including weakness along with autonomic neuropathy. (Seretny et al., 2014). CIPN typically affects 30-40% of patients, however its occurrence can range from 0 to 70%. The most often observed symptoms of CIPN are sensory neuropathies, which include abnormal sensations (parasthesias) as well as pain. The symptoms typically begin in the fingers and toes and then extend towards the center of the body in a pattern resembling a glove and stocking. (Windebank et al., 2008).

CIPN present in several manifestations. The most prevalent manifestation is sensory disruptions, encompassing both the negative symptom of numbness as well as the positive sensations of pain and parasthesias. The sensory complaints typically initiate in the peripheral extremities, following a pattern known as 'glove-and-stocking' distribution. In addition, motor symptoms may arise, typically appearing as weakness in the extremities, such as a condition known as foot drop. (Dougherty et al ., 2007).

Sensory peripheral neuropathy commonly manifests in a pattern like a stocking and glove, resulting in symptoms such as pain, allodynia, sensory loss, paresthesia, numbness, tingling, as well as difficulty walking. CIPN can result in substantial impairment of functional capabilities and have a detrimental impact on the overall quality of life. This, in turn, may necessitate dosage adjustments, termination of treatment, as well as eventually influence the overall chances of survival. (Vanden et al ., 2017).

The current approach to treating CIPN focuses on managing symptoms. This often involves using medications that target neuropathic pain, such as opioids, tricyclic antidepressants, anticonvulsants, serotonin-norepinephrine reuptake inhibitors, as well as non-steroidal anti-inflammatory drugs. Additionally, nutritional supplements may also be recommended. (Dougherty et al., 2015).

Although these agents have not been proven to effectively treat CIPN, they have been shown to work for other types of neuropathic pain. Given the limited treatment options, it is acceptable to consider these agents alongside duloxetine or as an alternative if duloxetine is not effective or well-tolerated. Patients should be provided with accurate information regarding the lack of

scientific data and receive guidance on the potential risks and advantages. (Hershman et al., 2014).

Photobiomodulation treatment (PBM) involves using laser diodes or light-emitting diodes to apply visible and/or (near)-infrared light to encourage tissue regeneration, decrease inflammation, and alleviate neuropathic pain. In the past two decades, low level laser therapy has emerged as a novel treatment approach in the field of supportive cancer care. (Zecha et al., 2016).

Photobiomodulation utilizes non-ionizing, low-power laser light therapy and has demonstrated efficacy in enhancing brain function, as evidenced by pre-clinical and small-scale trials. Animal studies have shown that PBM can relieve mechanical and cold sensitivity caused by oxaliplatin, as well as promote nerve regeneration and enhance motor recovery following nerve crush injury. (Wang et al., 2014).

As far as we know, there is barely any of research about the efficacy of photo-biomodulation therapy in treatment and controlling of chemotherapy induced peripheral neuropathy in cancer patients. So, the aim of this study was to evaluate the therapeutic efficacy of photo bio-modulation therapy for treatment of neuropathic pain, inflammation and sensation defect in CIPN among BC patients.

Patients and methods

This study was applied to sixty female patients who had breast cancer and suffered from peripheral neuropathy grade I (neuropraxia) at least after one cycle of chemotherapy, they were between the ages of 35 and 55. Researchers at Cairo University's National Cancer Institute recruited the subjects. Each of the two groups of patients would consist of 30 individuals selected at random for this research. Group (A) "Study group" Thirty patients received photo-bio modulation therapy (pulsed diode laser) and the routine medical care in form of pain killers medication (NSADs) and food supplements e.g. (Vitamin E, B complex and calcium).Group (B) "Control group" Thirty patients who had received the routine medical care in form of pain killers medication (NSADs) and food supplements e.g. (Vitamin E,B complex and calcium) only. Inclusive criteria: - All patients were female patients. Their ages ranged from 35 to 55 years old. All patients received chemotherapy at least one cycle. All patients suffered from chemotherapy induced peripheral neuropathic pain and sensory defect (grade I). All patients were assessed carefully by the same physician prior to the commencement of the study protocols. All patients were conscious. All patients received the same necessary or required drugs and diet regime. Exclusive criteria: Patients who had other pathological conditions or histories of neuropathy e.g. (liver diseases, alcoholism and diabetes mellitus). Patients with evidence of local recurrence or distant metastasis, patients who takes other medications that may affects the results, patients who was not cooperative during assessment and treatment and patients who suffer from post mastectomy lymphedema.

Outcome measures
Assessment procedures

The (CIPNAT) and (VAS) were recorded 2 times: (pre and after 6 weeks post treatment). All measurements were conducted by a different physiotherapy assessor who was unaware of the subject group allocation.

Visual Analogue Scale (VAS):

The Intra Class Correlation (ICC) indicates that the VAS is highly reliable for measuring acute pain. 90% of pain assessments had a high level of reproducibility within a margin of nine millimeters. These data suggest that the VAS is a reliable instrument that can be utilized to assess acute pain with a good level of precision. (Bijur et al.,2001).

Pain levels were evaluated for all groups before and during the treatment period using the VAS, which measures pain on a 10 cm line ranging from 0 (no pain) to 10 (worst pain). The patients were instructed to indicate their current level of pain by marking a point on a line ranging from 0 to 10. (McCaffery and Beebe 1999).

Chemotherapy-Induced Peripheral Neuropathy Assessment Tool (CIPNAT):

The development was founded on the idea of unpleasant symptoms, which asserts that a comprehensive evaluation of unpleasant symptoms should encompass the assessment of symptom incidence, severity, distress, frequency, as well as interference with routine activities. The CIPNAT consists of two evaluation scales. The initial component is the symptom experience scale, which consists of nine neuropathy symptoms along with their respective attributes such as occurrence, severity, distress, as well as frequency. Each symptom is assessed by a series of yes/no questions, while the severity, distress, and frequency of the symptoms are rated on a scale of 0-10. The maximum score that may be obtained for each symptom is 31. The cumulative sum of all things is 279.

The interference with life scale consists of 14 items, which encompass activities such as walking, picking objects, holding objects, driving, working, engaging in hobbies or leisure activities, exercising, sexual activity, sleeping, maintaining relationships, writing, performing typical home duties, and experiencing enjoyment in life. The scoring system assigns a numerical value between 0 and 10 to each item, resulting in a maximum potential score of 140. (Tofthagen et al., 2011).

The Arabic version of CIPNAT scale was used with patient during evaluation process (Abdullah O. et al., 2020).

Therapeutic procedures:

Before to commencing the initial evaluation, a comprehensive explanation of the experimental protocol was provided to each patient, and a written consent form was obtained from each patient before to the trial. Patients were directed to promptly notify of any negative effects that may arise during the course of the treatment sessions.

Laser therapy (PBM):

The laser unit, known as the ASTRA scanning mood, complies with the current regulations set by the United States Food and Drug Administration. It is produced by Laser Technology Pty Ltd in Australia. The system provides two options for laser therapy: continuous as well as pulsed.

Protective eye glasses

Protective eyewear was utilized to prevent irreversible eye injury caused by direct exposure to the laser beam during its administration. (Gama, 2008).

A therapy room with an activated laser was available. Prior to and during treatment, patients were required to wear opaque, laser-protective eyewear for safety reasons and to ensure proper

blinding. Each patient received treatment three times weekly for a total of eighteen sessions. Treatments were intended to be administered every other day; however, deviations from this schedule to accommodate patients' schedules were not deemed protocol violations. Regardless of the level of impairment, a standardized treatment plan of 30 minutes per visit was adopted to minimize the possibility of artifact caused by different treatment durations. Using a handheld wand, treatments were applied to specific areas of the skin at a distance of 1 cm for 1-12 minutes. The entire treatment took 30 minutes. (Hsieh et al.2015).

Statistical analysis

To compare the ages of the groups, descriptive statistics and an unpaired t-test were used. To compare CIPNAT as well as VAS between groups, an unpaired t-test was used.

A paired t-test was performed to compare CIPNAT as well as VAS prior to and following treatment in each group. The significance limit for all statistical tests was established at $p < 0.05$.

The statistical analyses were conducted using the SPSS software, specifically version 25 for Windows. IBM SPSS is located in Chicago, IL, USA.

Results

Ages of 48.87 ± 4.78 years for group A and 47.30 ± 5.21 years for group B were the mean ± SD, respectively. The mean ages of the groups did not differ significantly from one another ($p = 0.23$). (Table 1)

Table (1): Comparison of age between group A and B.

Age (years)	Group A	Group B
$\bar{x}$± SD	48.87 ± 4.78	47.30 ± 5.21
Maximum	55	55
Minimum	38	38
MD	1.57	
t-value	1.21	
p-value	0.23	
Significance	NS	

$\bar{x}$: MeanSD: Standard deviationMD: Mean differencet value: Unpaired t-valuep-value: Probability valueNS: Non-significant

The mean values of CIPNAT for group A prior to and following treatment: The mean ± SD of CIPNAT prior to treatment in group A was 310.53 ± 8.15, whereas following treatment it was 202.03 ± 9.73. The mean difference among the prior to and following treatment measurements was 108.5, and the percentage of change was 34.94%. There was a substantial reduction in CIPNAT in group A following treatment contrasted with prior to treatment ($p = 0.001$). While prior to and following treatment mean values of VAS of group A: The mean ± SD VAS prior to treatment of group A was 8.30 ± 0.66and that following treatment was 4.80 ± 0.71. The mean difference prior to and following treatment was 3.5 and the percentage of change was 42.17%. There was a substantial reduction in VAS in group A following treatment contrasted with prior to treatment ($p = 0.001$). Prior to and following treatment mean values of CIPNAT of group B: The

mean ± SD CIPNAT prior to treatment of group B was 311.40 ± 6.09then that following treatment was 260.20 ± 10.62. The mean difference between prior to and following treatment was 51.2and the percentage of change was 16.44%. There was a substantial reduction in CIPNAT in group B following treatment contrasted with prior to treatment (p = 0.001). Whereas prior to and following treatment mean values of VAS of group B: The mean ± SD VAS prior to treatment of group B was 8.43 ± 0.56and that following treatment was 6.77 ± 0.68. The mean difference between prior to and following treatment was 1.66and the percentage of change was 19.69%. There was a substantial reduction in VAS in group B following treatment contrasted with prior to treatment (p = 0.001) (table 2).

Table (2): Comparison between Pre and post treatment mean values of CIPNAT and VAS of both group A and B

	Group A				**Group B**			
	CIPNAT		**VAS**		**CIPNAT**		**VAS**	
	pre	**Post**	**pre**	**post**	**pre**	**post**	**Pre**	**post**
x̄±SD	310.53 ±8.15	202.03 ± 9.73	8.30 ±0.66	4.80 ± 0.71	311.40 ± 6.09	260.20 ± 10.2	8.43 ±056	6.77 ±0.68
MD	-0.87		-0.13		-0.87.		-0.13	
%	34.94		42.17		16.44		19.69	
t-value	39.44		23.73		26.87		10.81	
p-value	0.64	0.001	0.40	0.001	0.64	0.001	0.40	0.001
Sign	NS	S	NS	S	NS	S	NS	S

x̄: Mean SD: Standard deviation MD: Mean difference
t- value: Paired t-value p-value: Probability value S: Significant

The mean ± SD CIPNAT following treatment of group A was 202.03 ± 9.73 and that of group B was 260.20 ± 10.62. The mean difference among the groups was -58.17. There was a substantial reduction in CIPNAT of group A contrasted with group B following treatment (p = 0.001). While following treatment mean values of VAS of both groups (A and B): The mean ± SD VAS following treatment of group A was 4.80 ± 0.71and that of group B was 6.77 ± 0.68. The mean difference among the groups was -1.97. There was a substantial reduction in VAS of group A contrasted with group B following treatment (p = 0.001) (table 3).

Table (3): Comparison of Post treatment means values of CIPNAT and VAS of both groups (A and B):

	Post treatment			
	CIPNAT		**VAS**	
	Group A	**Group B**	**Group A**	**Group B**
% of change	34.94	16.44	42.17	19.69
t-value	39.44	26.87	23.73	10.81
p-value	0.001	0.001	0.001	0.001
Sig.	S	S	S	S

$\bar{x}$: Mean SD: Standard deviation MD: Mean difference
t- value: Paired t-value p-value: Probability value S: Significant

Discussion

Common symptoms associated with breast cancer, such as fatigue, insomnia, as well as cognitive impairment, have consequences that are physical as well as psychological. Recent research has found that pharmaceutical, psychological, in addition exercise interventions have been effective in treating these side effects. The majority of existing medicinal therapies typically provide temporary relief for symptoms without addressing the root issues. (Palesh et al., 2014).

Complications associated with cancer are common among those diagnosed with BC. Pharmacological therapies can offer temporary relief, but their main effectiveness lies in short-term symptom control rather than long-term resolution. Most importantly, pharmaceutical treatments don't deal with the root of the problem when it comes to managing symptoms. (Siegel et al., 2016).

Chemotherapy-Induced Peripheral Neuropathy (CIPN) is a common side effect of antineoplastic drugs, occurring in a significant proportion of patients, with prevalence ranging from 19% to over 85%. Clinically, CIPN is primarily a sensory neuropathy that may also include motor and autonomic abnormalities of variable severity and duration. (Walker et al., 2007).

As of yet, CIPN treatment has not improved patient outcomes much. Despite various attempts, no pharmaceutical medication has demonstrated efficacy. Consequently, a significant number of patients are compelled to decrease the dosage or stop taking neurotoxic medications that have the ability to cure their condition. There are two primary approaches to treatment: preventive and symptomatic. (Xiao et al., 2008).

Symptomatic treatments focus on alleviating the symptoms of CIPN among patients who have already developed it following the administration of neurotoxic medications. This issue affects all patients with PN, regardless of the underlying cause. Consequently, the majority of experiments have been conducted on the most commonly observed symptomatic neuropathies, particularly those associated with diabetes mellitus. The majority of substances tested have been anticonvulsants or antidepressants. (Pachman et al., 2015).

Regrettably, neither group of medications has been effective in alleviating the symptoms of CIPN when these findings are extrapolated to CIPN. This may be attributable to the distinct pathophysiology along with qualities of toxic CIPN in comparison to other etiologies. (Rosenstock et al., 2004).

Multiple trials that have concentrated on the management of CIPN symptoms, particularly pain, have been unsatisfactory. In 2009, the National Comprehensive Cancer Network Task Force was unable to suggest any directed therapy. (Lavoie et al., 2013).

The main findings of this study were as follow: There was a substantial reduction in CIPNAT in group A following treatment contrasted with prior to treatment ($p = 0.001$)in addition the percentage of change was 34.94% also there was a substantial reduction in VAS in group A following treatment contrasted with prior to treatment ($p = 0.001$) and the percentage of change was 42.17% contrasted with group B and that reduction in both CIPNAT as well as VAS There was a detectable improvement in the CIPNAT about 22% & VAS about 21% difference in patients treated with Photo-Biomodulation (PBM) therapy compared to routine medical care. PBM treatment may provide significant symptom benefits among patients with established CIPN.

This improvement can be due to the therapeutic effect of PBM therapy in management of CIPN inflammation, pain as well as neural circulation.

These findings are in line with those studies reported by (Peter et al., 2016; Joy et al., 2022; Teng et al., 2023; (Dworkin et al., 2009; Anders et al., 2014) Peter et al., 2016 suggested that PBM therapy is a highly successful and low-toxicity treatment for CIPN. Approximately 90% of patients observe substantial enhancement in mTNS scores, which commences within a few weeks of commencing treatment and endures for a minimum of 10 weeks following the completion of therapy. The advantages seem to accumulate in a comparable manner for individuals with different durations and intensities of neuropathy symptoms, as well as for patients with varying levels of exposure to chemotherapy.

Joy et al., (2022) who discovered that patients' pain levels were assessed using a numeric rating scale that ranged from 0 (no pain) to 10 (the most severe pain conceivable). A borderline substantial difference was observed at follow-up among the control group (n=16) as well as the PBM group (n=16).

Additionally, the findings of this study align with those of Teng et al., (2023), who reported that the response rates for CIPN were -48% and 53% at 6 weeks, and 45% and 33% at 12 weeks, for the laser as well as control groups, respectively. The null hypothesis, stating that the actual response rate in the laser arm is 5%, was rejected at both the 6-week and 12-week intervals

($p<0.001$ for both). Following the intervention, both the laser group as well as the control group showed improvement in patient-reported CIPN contrasted to the baseline.

Dworkin et al., 2009, proposed that PBM could potentially alleviate neuropathy symptoms via many possible means, including as preventing neural cell death and promoting the development of neural cells. Studies at the molecular level indicate that low-level laser energy is absorbed by proteins on the mitochondrial trans-membrane. This absorption leads to enhanced cellular respiration along with increased activation of oxidation-sensitive pathways, such as nuclear factor–KB as well as activator protein 1. These pathways provide protection against signals that promote apoptosis, such as tumor-necrosis factor-α as well as lysosomal pathways.

Anders et al., 2014 found that 111 genes showed different levels of expression when human fibroblasts were exposed to PBM. More than half of these genes were related to either cellular proliferation or the suppression of apoptosis. Another study conducted on human neural progenitor cells in a laboratory setting indicated that laser light promotes the growth of neural cells. Additionally, whole animal studies on mice showed that similar PBM strategies resulted in substantial enhancement in functional recovery following nerve crush injury as well as platinum exposure.

This study was limited to some factors. An essential one is that patients' psychological status may impact the outcomes depending on their state of mind throughout the procedure. In addition, small sample size may affect the results. Finally, possible errors in measuring and patients' evaluation.

Additional research with extended duration is required to examine the impact of PBM therapy on CIPN among BC patients. Future investigations should employ meticulously designed randomized controlled trials or extensive comparative observational studies. These studies should include a representative sample of patients with similar age, gender, as well as disease severity. Moreover, the sample size of future studies should be sufficiently large to yield meaningful conclusions and to account for any factors that may distort the results.

Conclusions

It can be concluded that Photo Bio-modulation (PBM) therapy is an effective modality in management of chemotherapy-induced peripheral neuropathy pain, inflammation as well as sensory defects among breast cancer patients.

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