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RESEARCH ARTICLE

REDUCTION OF TAXOL-INDUCED NEUROPATHY WITH CRYOTHERAPY: A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is the most common neurological complication of cancer treatment. The prevention and management of chemotherapy-induced peripheral neuropathy (CIPN) remains a challenge. The purpose of this study was to investigate the effect of prophylactic cryotherapy on taxol- induced neuropathy. **Methodology:** Forty patients with breast cancer were assigned into two equal groups (group I & group II): Group (I) received cryotherapy (the cooled mitts and slippers) and group (II) received the un cooled mitts and slippers along the 12 taxol cycles for 15minutes before the dose ,60 minutes during the dose, 15 minutes after the dose, the total cooling time was 90 minutes on both sides. Modified Total Neuropathy Score (mTNS) was used to assessseverity of taxol-induced neuropathy. The sural nerve action potential amplitude (SNAPA) was measured pre and post treatment using the Russian electrophysiolgical equipment. **Results :** There was a statistically significant reduction in the mean value of sural SNAPA in both groups post treatment with more significant reduction in the control group compared with the study group. while,there was a statistically significant increase in the median value of mTNS in both groups post treatment with more significant increase in the control group compared with the study group. **Conclusion:** The cryotherapy reduces the incidence and severity of taxol -induced neuropathy, so cryotherapy is non invasive, inexpensive, safe and effective strategy for reduction of taxol- induced neuropathy in cancer patients receiving taxol treatment.

INTRODUCTION

Chemotherapy-induced peripheral neuropathy (CIPN) is a frequent and disabling side effect of cancer treatment, primarily taxanes and platinum agents (Cavaletti, 2010). CIPN reduces health-related quality of life (Mols, 2014) and often results in dose delay, dose reduction, or treatment discontinuation (Speck, 2013). The prevalence of CIPN is agent-dependent, with reported rates varying from 19% to more than 85% (Fallon, 2013) and is the highest in the case of platinum-based drugs (70–100%), taxanes (11–87%), thalidomide and its analogues (20–60%), and ixabepilone (60–65%) (Banach, 2016). Toxicity may occur either with a high single dose or after cumulative exposure. Recent studies put the prevalence of CIPN at approximately 68.1% when measured in the first month after chemotherapy, 60.0% at 3 months, and 30.0% at and after 6 months (Seretny, 2014). The symptoms of CIPN are varied and presentation varies from sensory neuropathy which is the most frequent type of CIPN, primarily affecting patients treated with taxanes (docetaxel and paclitaxel), platinum derivatives (oxaliplatin, cisplatin and carboplatin), vinca alkaloids (vincristine, vinblastine and vinorelbine), thalidomide and bortezomib (Velasco, 2010) to mixed sensorimotor neuropathy and less commonly, pure motor neuropathy (Sharma, 2015). Motor neuropathy has been observed with higher doses of paclitaxel (Freilich, 1996). Paclitaxel causes more neuropathy when infused over 3 h as compared to 24 h infusion (Smith, 1999). The mechanisms of this neuropathy are usually attributed to microtubule disruption (taxanes, *Vinca* alkaloids) or a direct toxic effect of platinum compounds (Hausheer, 2006). The options of stopping treatment early or dose reducing are equally undesirable in the advanced disease setting, but may have greater implications in the adjuvant setting because taxanes have become part of the standard treatment for a wide variety of neoplasm, including breast, ovary, lung, and gastrointestinal tumors, first line as well assubsequenttherapy. Several ways have been explored to decrease the neurotoxicity associated with paclitaxel, including the use of non-steroidal anti-inflammatory agents, corticosteroids, and amifostine; and these treatments have been uniformly unsuccessful (Kottschade, 2011). Cryotherapy can reduce chemotherapy-induced complications by decreasing regional perfusion with acceptable tolerability (Kadakia,

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2014). Frozen gloves and socks prevented docetaxel-induced nail and skin toxicity in prospective, self-controlled trials that compared the protected side with the nonprotected side (Scotté, 2008). A retrospective study indicated that the occurrences of docetaxel-induced peripheral neuropathy was lower in the patients who used frozen gloves and socks compared to the patients who did not wear them (35% vs. 57%) (Eckhoff, 2013) To our best knowledge, there are no randomized controlled trials on the effect of cryotherapy on taxol- induced neuropathy in Egypt . So, the current study is the first randomized controlled study to investigate the prophylactic effect of cryotherapy on taxol- induced neuropathy in Egypt.

MATERIALS AND METHODS

Participants: In this randomized controlled study, forty patients having breast cancer were selected from the national cancer institute (NCI) ,Cairo university in the period from March 2018 to February 2019.Patients were eligible to participate in the study if they had breast cancer which has been previously diagnosed by a physician and histologically confirmed, planned to receive chemotherapy per National Cancer Institute (NCI) protocols(adjuvant or neoadjuvent therapy of weekly paclitaxel 80 mg/m^2 for one hour for 12 cycles, patients willing and ability to complete the scheduled visits and treatment plan. While patients were excluded from the study if they had history of any other neuropathy asdiabetic neuropathy, poor-healing wounds on the hands or the feet, cold intolerance, any other concurrent severe and/or uncontrolled medical condition that contraindicate patient participation, central nervous system metastases, prior treatment with taxanes, severe hypersensitivity to taxanes, pregnant and lactating womens and Raynaud's symptoms.

Design: One pre and post design study was used. A single trained investigator evaluated all patients and collected all data to eliminate inter- investigator error. Patients were randomly allocated into study group or a control group with 20 patients in each group. Study group (Group I) received the frozen mitts and slippers for 15minutes prior to treatment ,60minutes during the treatment and 15 minutes after the treatment on both sides for 12 weekly cycles while control group (Group II)received the not frozen mitts and slippers for 15minutes prior to treatment ,60 minutes during the treatment and 15 minutes after the treatment for 12 weekly cycles.

Examination: All participants underwent a pre-treatment and post treatment assessment.

The modified Total Neuropathy Score (mTNS) used to assess severity of chemotherapy induced neuropathy pre and post treatment. It includes 6 items graded from 0 to 4 according to the patients symptoms . the total grade from 0 to 24 the higher grade the worse neuropathy.it graded as mild (0:8), moderate (9:16)and(17:24) severe [16].

1) **Sensory symptoms:** tingling , numbness and burning symptoms in stocking and gloves distibution.it is graded from 0-4 according to the extent of symptoms.
2) **Motor symptoms:** ask the patient if she had motor difficulty and it is graded from non to paralysis.
3) **Pin sensibility:** using pin to determine the extent of symptoms if it only in hands or extend to the elbow or above in upper limbs and if it localised in feet or extend above. according to the level it decreased the patient had her score.
4) **Vibration sensibiltity:** using a tuning fork.
5) **Manual muscle test:** for distal muscles of both upper and lower extremities.
6) **Deep tendon reflexes:**
   - In upper limbs brachioradialis, biceps and triceps.
   - In lower limbs ankle and knees.

The modified Total Neuropathy score may raise clinicians' sensitivity to patient problems with balance, physical mobility, and QOL. Tools such as the PQAS may provide clinicians with a method to identify patients who are experiencingtaxane-induced painful peripheral neuropathy (Wampler, 2006). The sural nerve action potential amplitude SNAPA was measured pre and post treatment using the Russian electrophysiolgical equipment (Neuro Soft). Neurophysiological techniques provide objective evidence of nerve dysfunction and enable detection of physiological changes prior to clinical symptoms, as well as enhancing understanding of the neuropathological mechanisms to inform future prevention strategies (Kandula, 2017).

Intervention

All the participants received their weekly taxol. Group I wore the frozen mitts and slippers on both sides for 15 minutes pre the taxoldose, 60 minutes during the dose and 15 minutes after the dose, the total time was 90 minutes .The mitts and socks were changed every 20 minutes and the temperature was checked every 15 minutes to avoid ischemia or ice burn. Group II wore the not frozen mitts and socks on both sides for 15 minutes pre the taxoldose, 60 minutes during the dose and 15 minutes after the dose, the total time was 90 minutes.

Data analysis

- Descriptive statistics and t-test were conducted for comparison of the mean age, weight and height between the study and control groups.
- Two-way mixed MANOVA test was conducted to compare the effect of time (pre versus post) and the effect of treatment (between groups), as well as the interaction between time and treatment on mean values of sural nerves SNAPA.
- Wilcoxon Signed Ranks Test was conducted for comparison between pre and post treatment median values of mTNS© in each group.
- Mann–Whitney U test was conducted for comparison of median values of mTNS© between both groups.
- The level of significance for all statistical tests was set at $p < 0.05$.
- All statistical tests were performed through the statistical package for social studies (SPSS) version 22 for windows. (IBM SPSS, Chicago, IL, USA.

RESULTS

General characteristics: There was no significant difference between both groups in the mean age (p=0.83), weight (kg) (p=0. 68 and height (cm) (p=0.49). (Table 1).

Effect of treatment of modified Total Neuropathy Score:

Comparison between pre and post treatment within each group: There was a statistically significant increase in the median value of mTNS post treatment compared with pre treatment in both group (p = 0.0001 in both groups). (Table 2).

Table 1. Descriptive statistics and t-test for comparing the mean age, weight and height of the study and control groups

	Study group	Control group	MD	t- value	p-value	Sign
	$\bar{X}$ ±SD	$\bar{X}$ ±SD				
Age (years)	43.65 ± 6.24	44.05 ± 6.1	-0.4	-0.2	0.83	NS
Weight (kg)	71.25 ± 6.83	72.2 ± 7.64	-0.95	-0.41	0.68	NS
Height (cm)	159.15 ± 4.68	158.1 ± 4.95	1.05	0.68	0.49	NS

$\bar{x}$: mean SD: Standard deviation MD: mean difference
t value: Unpaired t valuep value: Probability value NS: Non significant

Table 2. Median mTNS© pre and post chemotherapy of the study and control groups

mTNS©	Pre	Post	Z-value	P-value	Sig
	Median	Median			
Study group	0	3	-3.63	0.0001	S
Control group	0	10.5	-3.93	0.0001	S
U-value	200	0			
P-value	1	0.0001			
Sig	NS	S			

U: Mann–Whitney U test value
Z: Wilcoxon signed ranks test value
p value: Probability value

Table 2. Mixed MANOVA for the effect treatment on the sural nerves SNAP

Mixed MANOVA	
Interaction effect (treatment * time)	
F= 27.78	*p = 0.0001*
Effect of treatment (group effect)	
F = 1.41	*p = 0.23*
Effect of time	
F= 121.9	*p = 0.0001*

Table 4. Mean right sural SNAPA pre and post chemotherapy of the study and control groups

Right sural SNAPA (μV)	Pre	Post	MD	% of change	P-value	Sig
	$\bar{X}$ ±SD	$\bar{X}$ ±SD				
Study group	8.47 ± 2.58	7.44 ± 2.21	1.03	12.16	0.002	S
Control group	8.83± 2.02	4.98 ± 1.03	3.85	43.6	0.0001	S
MD	-0.36	2.45				
P-value	0.62	0.0001				
Sig	NS	S				

$\bar{X}$: Mean, SD: Standard deviation, MD: Mean difference, P value: Probability value, S: Significant, NS: Non significant

Table 5. Mean left sural SNAPA pre and post chemotherapy of the study and control groups

Left sural SNAPA (μV)	Pre	Post	MD	% of change	P-value	Sig
	$\bar{X}$ ±SD	$\bar{X}$ ±SD				
Study group	8.28 ± 1.96	7.31 ± 1.05	0.97	11.71	0.004	S
Control group	8.96± 1.89	4.91 ± 0.9	4.05	45.2	0.0001	S
MD	-0.68	2.4				
P-value	0.26	0.0001				
Sig	NS	S				

$\bar{X}$: MeanSD: Standard deviationMD: Mean difference
p value: Probability valueS: SignificantNS: Non significant

Comparison between groups: There was no significant difference in the mTNS between both groups pretreatment (p = 1). However, there was a significant increase in the median value of the mTNS of the control group compared with that of study group post treatment (p = 0.0001). (Table 2).

Effect of treatment on the sural nerves SNAPA: There was a significant interaction effect of treatment and time (p = 0.0001). There was no significant main effect of treatment (p = 0.23). There was a significant main effect time (p = 0.0001). (Table 3).

Effect of treatment on right sural SNAPA

Comparison within each group: There was a significant decrease in right sural SNAPA in the study group post treatment compared with that pre treatment (p = 0.002). Also, There was a significant decrease in right sural SNAPA in the control group post treatment compared with that pre treatment (p = 0.0001) (Table 4).

Comparison between groups: There was no significant difference in the right sural SNAPA pre treatment between the study and control groups (p = 0.62). However, there was a significant decrease in the mean values of the right sural

SNAPA of the control group post treament compared with that of study group (p = 0.0001). (Table 4).

Effect of treatment on left sural SNAPA

Comparison within each group: There was a significant decrease in left sural SNAPA in the study group post treatment compared with that pre treatment (p = 0.004). Also, there was a significant decrease in left sural SNAPA in the control group post treatment compared with that pre treatment (p = 0.0001). (Table 5).

Comparison between groups: There was no significant difference in the left sural SNAPA pre treatment between the study and control groups (p = 0.26). However, there was a significant decrease in the mean values of the left sural SNAPA of the control group post treatment compared with that of study group (p = 0.0001). (Table 5).

DISCUSSION

The results of the current study showed that, the study group who received cooled mitts and slippers has a significant reduction in the incidence and severity of taxol-induced neuropathy than the control group who received the un cooled mitts and slippers. This results comes in agreement with the findings of Hanai *et al.* (Hanai, 2018), who found that cryotherapy resulted in a clinically and statistically significant reduction in patient-reported subjective symptoms, diminished objective signs (tactile and thermosensory), and prevention of manipulative dexterity. The results of the current study regarding the significant reduction of the incidence and severity of taxol-induced neuropathy in the study group than the control group might be explained by several mechanisms. This is because, paclitaxel promotes the formation of abnormal bundles of microtubules within the cytoplasm in vitro studies resulting in disruption of normal cell function and this is said to worsen with increased doses (Scripture, 2006), and as CIPN has a dose-related pathophysiology, this opens the possibility of devising a neuroprotective therapy through limiting deliverance of the toxic chemotherapeutic agents to the peripheral nerves, by reducing blood flow. The first explanation is related to the role of cryotherapy in reducing blood flow in which cryotherapy leads to a decrease in blood flow to 50% of the basal blood supplysecondary to local vasoconstriction (Peripheral neuropathy induced by paclitaxel). This explanation was supported by Liao *et al*. (Thorsson, 2001) who shown that hypothermia induce transient and titratable reduction in peripheral nerve blood flow and found that drop in nerve temperature from 30 °C to 20 °C results in a five-fold reduction of blood flow in the rat sciatic nerve in vivo.

Also., White and Wells (Liao, 2013), suggested that cooling causes reflexive vasoconstriction, due to increased affinity of alpha-adrenergic receptors for norepinephrine in the vascular walls and skin temperature drops rapidly in the first 1–3 min and reaches minimumtemperature around 8–9 min of cooling
Second explanation is that hypothermia may reduce cellular uptake of the chemotherapeutic agent by reducing the metabolism in the cooled regions (White, 2013). The neural conduction velocity (NCV) is a parameter related to analgesic properties, since the speed of nociceptive sensory pathways transmission is reduced by local cooling (Erecinska, 2013). So, third explanation might be attributed to role of cryotherapy in reducing NCV of pain signals. This explanation was supported by Nadler *et al*. (Herrera, 2010), who mentioned that cryotherapy induces local effects and influences the spinal cord level effects through neurological mechanismsand the cold method increases the activation of nociceptors threshold and decreases nerve conduction velocity of pain signals causing local anesthesia . Also, this explanation was confirmed with Herrera *et al*. (Erecinska, 2003 and Nadler, 2004) who observed a significant decrease in NCV after cryotherapy in posterior tibial (motor) and sural (sensory) nerves.

REFERENCES

Banach M., Juranek J.K., Zygulska A.L. Chemotherapy-induced neuropathies—A growing problem for patients and health care providers. Brain Behav. 2016;7:e00558.

Cavaletti G, Marmiroli P. Chemotherapy-induced peripheral neurotoxicity. *Nat Rev Neurol.* 2010;6(12):657–666

Eckhoff L, Knoop AS, Jensen M-B, Ejlertsen B, Ewertz M. Risk of docetaxel-induced peripheral neuropathy among 1,725 Danish patients with early stage breast cancer. *Breast Cancer Res Treat*. 2013;142(1):109–118.

Erecinska M, Thoresen M, Silver IA.Effects of hypothermia on energy metabolism in mammalian central nervous system. *J Cereb Blood Flow Metab*.2003;23:513–30.

Fallon M.T. Neuropathic pain in cancer. *Br. J. Anaesth.* 2013; 111:105–111.

Freilich RJ, Balmaceda C, Seidman AD, Rubin M, DeAngelis LM. Motorneuropathy due to docetaxel and paclitaxel. Neurology 1996; 47:115-118.

Hanai, A., H. Ishiguro, T.Sozu, M. Tsuda, I.Yano, T.Nakagawa, and T. Tsuboyama, T. 2018. Effects of cryotherapy on objective and subjective symptoms of paclitaxel-induced neuropathy: Prospective self-controlled trial. *Journal of the National Cancer Institute*. 2018; *110*(2): 141–148.

Hausheer FH, Schilsky RL, Bain S, Berghorn EJ, Lieberman F. Diagnosis, management, and evaluation of chemotherapy-induced peripheral neuropathy. *Semin Oncol* 2006; 33:15-49.

Herrera E, Sandoval MC, Camargo DM, Salvini TF. Effect of walking and resting after three cryotherapy modalities on the recovery of sensory and motor nerve conduction velocity in healthy subjects. *Rev Bras Fisioter*. 2011; 15(3):233-240.

Herrera E, Sandoval MC, Camargo DM, Salvini TF. Motor and sensory nerve conduction are affected differently by ice pack, ice massage, and cold water immersion. *Phys Ther*. 2010; 90:581-591.

Kadakia KC, Rozell SA, Butala AA, Loprinzi CL. Supportive cryotherapy: A review from head to toe. *J Pain Symptom Manage.* 2014; 47(6):1100–1115.

Kandula, T., Farrar, M. A., Kiernan, M. C., Krishnan, A. V, Goldstein, D., Horvath, L., Park, S. B. Neurophysiological and clinical outcomes in chemotherapy-induced neuropathy in cancer. *Clin Neurophysiol.* 2017; 128(7):1166-1175

Kottschade LA1, Sloan JA, Mazurczak MA, Johnson DB, Murphy BP, Rowland KM, Smith DA, Berg AR, Stella PJ, Loprinzi CL. The use of Vitamin E for the prevention of chemotherapy-induced peripheral neuropathy: Results of a randomized phase III clinical trial. Support Care Cancer. 2011;19 (11):1769-1777.

Liao LD, Orellana J, Liu YH, Lin YR, Vipin A, Thakor NV, Shen K and Wilder-Smith E. Imaging of temperature

dependent hemodynamics in the rat sciatic nerve by functional photoacoustic microscopy. Biomed Eng Online 2013;12:120–32.

Mols F, Beijers T, Vreugdenhil G, van de Poll-Franse L. Chemotherapy-induced peripheral neuropathy and its association with quality of life: A systematic review. Support Care Cancer. 2014;22(8):2261–2269.

Nadler SF, Weingand K, Kruse RJ. The Physiologic Basis and Clinical Applications of Cryotherapy and Thermotherapy for the Pain Practitioner. *Pain Physician.* 2004;7:395-399.

Peripheral neuropathy induced by paclitaxel:

Scotté F1, Banu E, Medioni J, Levy E, Ebenezer C, Marsan S, Banu A, Tourani JM, Andrieu JM, Oudard S. Matched case-control phase 2 study to evaluate the use of a frozen sock to prevent docetaxel-induced onycholysis and cutaneous toxicity of the foot. Cancer. 2008;112(7):1625–1631.

Scripture CD, Figg WD, Sparreboom A. Peripheral neuropathy induced by paclitaxel: recent insights and future perspectives. *Curr Neuropharmacol.* 2006 Apr;4(2):165-72.

Seretny M., Currie G.L., Sena E.S., Ramnarine S., Grant R., MacLeod M.R., Colvin L.A., Fallon M. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis. Pain. 2014; 155:2461–2470.

Sharma S,Venkitaraman R,Vas PRJ and Rayma G. Assessment of chemotherapy-induced peripheral neuropathy using the LDI_{FLARE} technique: a novel technique to detect neural small fiber dysfunction. *Brain Behav.* 2015 Jul; 5(7): e00354.

Smith RE, Brown AM, Mamounas EP, Anderson SJ, Lembersky BC, Atkins JH, Shibata HR, Baez L, DeFusco PA, Davila E, Tipping SJ, Bearden JD, Thirlwell MP. Randomized trial of 3-hour versus 24-hour infusion of high-dose paclitaxel in patients with metastatic or locally advanced breast cancer: National surgical adjuvant breast and bowel project protocol B-26. *J Clin Oncol* 1999;17(11):3403-3411.

Speck RM1, Sammel MD, Farrar JT, Hennessy S, Mao JJ, Stineman MG, DeMichele A. Impact of chemotherapy-induced peripheral neuropathy on treatment delivery in nonmetastatic breast cancer. *J Oncol Pract*. 2013; 9(5):e234–e240.

Thorsson O. Cold therapy of athletic injuries. Current literature review. *Lakartidningen.* 2001; 98(13):1512-3.

Vasquez, S., Guidon, M., Mchugh, E., Lennon, O., Grogan, L., & Breathnach, O. S. 2014. Chemotherapy induced peripheral neuropathy: the modified total neuropathy score in clinical practice, 53–58. https://doi.org/10.1007/s11845-013-0971-5

Velasco R, Bruna J. Chemotherapy-induced peripheral neuropathy: an unresolved issue. *Neurologia*. 2010; 25(2):116-31.

Wampler, M A, Miaskowski, C, Hamel K,Byl N, Rugo R and Topp KS. The Modified Total Neuropathy Score : A Clinically Feasible and Valid Measure of Taxane-Induced Peripheral Neuropathy in Women With Breast Cancer,.2006;4 (8):w9-w16.

White, G. E., and G. D. Wells. Cold-water immersion and other forms of cryotherapy: Physiological changes potentially affecting recovery from high-intensity exercise. *Extreme Physiology and Medicine*. 2013; *2*(1):26.

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