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Original research article

Cryotherapy for Preventing Chemotherapy-Induced Peripheral Neuropathy in Patients with Gynecologic Cancer in Thammasat University Hospital

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ABSTRACT

The aim of this study was to determine the effectiveness of cryotherapy in patients who underwent a platinum and taxane based chemotherapy regimen and developed chemotherapy induced peripheral neuropathy (CIPN). This randomized controlled trial was conducted at Thammasat University Hospital, Thailand between June 2021 and Feb 2022. Participants were patients with gynecologic cancer receiving combination chemotherapy (carboplatin plus paclitaxel). After recruitment, subjects were allocated to either the study or control group. All patients were wrapped with long socks on both legs. The study site leg had a cold pad at 20 degrees Celsius applied to it while the control site leg did not. Before and after chemotherapy administration, all cases were evaluated by patient neurotoxicity questionnaire (PNQ), tactile sensation (TS), cold sensation (CS), warm sensation (WS), vibration sensation (VS) and proprioceptive sensation (PS). A total of 36 participants (216 cycles) were enrolled with average age of 61.5 years and an average BMI of 24.7kg/m2. Leg discomfort was reduced in the study group (P-value< 0.01) even as the severity increased with each additional chemotherapy course. Tactile sensation was the worst in the group without cryotherapy (control) after the first chemotherapy cycle. Loss of thermal and vibration sensation were observed in the control group. However, change in proprioception not significant. Based on participant interviews, the leg that underwent cryotherapy had better sensation than the leg that did not. All cases participated in the study until completion, there were no participant withdrawals.

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Conclusion: Cryotherapy done in tandem with a chemotherapy regimen prevented loss of tactile sensation, temperature sensation and vibration perception.

Keywords: Chemotherapy; Cryotherapy; Gynecologic Cancer; Neuropathy

1. Introduction

The International Agency for Research on Cancer (IARC) stated that more than 19 million people were diagnosed with cancer last year and 7.2 percent of that originated from gynecological neoplasms [1]. These findings are consistent with data from the National Cancer Institute of Thailand, which shows that 22.8 percent (338/1486) of newly diagnosed cancers were gynecologic cancers [2]. Gynecologic cancer patients are often treated surgically together with chemotherapy and/or radiation therapy [3]. A combination of carboplatin and paclitaxel are commonly used for an adjuvant chemotherapy regimen after surgical treatment [4]. Serious side effects of chemotherapy (carboplatin and paclitaxel) usually result in damage to neuronal cell bodies, axons, axonal membranes, and mitochondria [5]. Chemotherapy-induced peripheral neuropathy (CIPN) was the most common complication with a prevalence of 68.1 (57.7-78.4), 60 (36.4-81.6) and 30 (6.4-53.5) percent with in the first, third and sixth month after chemotherapy, respectively [6]. CIPN burdens patients with numbness, pain, discomfort and a reduced overall quality of life (QOL), which is a concern for many physicians around the globe. The available treatment methods include massage, acupuncture, cold compression and prescription of intravenous antioxidants [7]. This study aimed to build on the ongoing study of cryotherapy for CIPN treatment/prevention.

2. Materials and Methods

This randomized self-control trial was conducted at the Gynecologic Ward, Thammasat University Hospital, Thailand between June 2021 and Feb 2022. After approval by the Thammasat Ethical Committee (IRB code: MTU-EC-OB-1-028/64), participants were informed on the study objectives and procedures therein before consent forms were completed regarding enrollment.

According to a study by Hanai, there is an odds ratio of 20 for tactile sensation differences between cryotherapy or none [8]. Five percent of type 1 error and *p*-values lower than 0.05 were considered statistically significant. The number of subjects needed for this study was 34. Compensating for case loss, the number of participants recruited for this study was 36 shown in Fig 1.

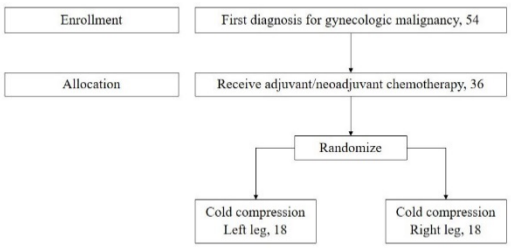

Fig 1. Flow chart of chemotherapy induced peripheral neuropathy study.

Inclusion criteria were as follows: patient was diagnosed with any gynecologic cancer that required taxane chemotherapy, and patient was aged 20 to 80 years old. Exclusion criteria were as follows: previously diagnosed with central or peripheral neuropathy, Raynaud' s phenomenon, diabetes neuropathy, cardiovascular disease, coagulopathy, limb paralysis, previously received chemo-radiation, being disabled, or unable to communicate. The recorded data contained 2 main sections, these being baseline characteristics and relevant aspects relating chemotherapy intervention.

Baseline characteristics included age, weight, height, BMI, occupation, income, educational status and gynecologic history.

This study observed 6 aspects regarding chemotherapy intervention that were patient neurotoxicity questionnaire (PNQ), tactile sensation (TS), cold sensation (CS), warm sensation (WS), vibration sensation (VS) and proprioception (PS). Participants were evaluated before each chemotherapy cycle.

PNQ is a self-evaluating form covering motor and sensorial symptoms, rating them on a scale of 0-4 to estimate neuropathy severity [8]. A score of 0 indicated no leg discomfort, while a score of 1, 2, 3 or 4 indicated a level of leg discomfort that interfered with daily life.

Tactile sensation was evaluated while the patient was blind folded, using monofilament wires of varying size. Starting from smallest size, the wire was pressed against the plantar surface at 4 locations on the feet at the big toe, and the proximal metatarsal joint of the 1st, 3rd and 5th toe. The participants then indicated if they could feel the monofilament; if there was no tactile sensation, the evaluator would then use bigger wire. The results were graded from 0 to 6, where 0 indicates loss of sensation and 6 is normal.

Cold sensation was tested while the participants were blindfolded, using 15 degree Celsius water-soaked cotton dragged against the dorsal side of both feet; participants were asked whether they felt any cold sensation and if there was any difference in the magnitude of the feeling for each leg. This process was done a total of 10 times.

Warm sensation was tested similarly but used 60 degree Celsius water instead of 15 degree Celsius.

Vibration sensation was assessed using a 128 Hz tuning fork that was struck and then pressed against the metatarsal joint of the 1st toe for 10 seconds. Participants would then indicate if they could detect a vibration sensation.

Proprioceptive sensation was tested by the evaluator holding the most distal joint of a toe on both sides with their thumb and index finger . The tip of the toe was pushed slightly up and down by the evaluator. For this test, participants were first shown a demonstration in which they watched the movement of their toe by evaluator so that they could understand the position of toe within the movement range. After that, the participants were asked to close their eyes and answer which position they thought their toe was in for each moment.

All participants underwent cold compression using a thermoregulatory machine Koolkit (Gentherm, OH, USA). Participants wore long cotton socks before being wrapped with PlastiPad (Gentherm medical, OH, USA) on either their left or right foot. They were then assigned to a study group. Site selections for either the left or right were randomized using a block size of four. The selected site for each participant remained unchanged during the study.

The cold compression started 15 minutes prior to chemotherapy administration (paclitaxel 175 mg/m2 was given for 3 hr followed by carboplatin AUC5 given for 1 hr) and then 15 minutes after the completion of chemotherapy infusion (about 4 and a half hours in total). The thermo-regulator was set at 20 degrees Celsius after being covered with PlastiPad. During cold compression, vital signs were monitored and recorded every 15 minutes. The interval of chemotherapy administration was between 3 weeks for 6 consecutive cycles. After finishing chemotherapy in each cycle, skin complications from cold compression were evaluated. The six tests (PNQ, TS, CS, WS, VS and PS) were performed before chemotherapy administration in each cycle and one month after the last course of chemotherapy by a qualified structural questionnaire interviewer.

The recorded data were analyzed using statistic package for social science (SPSS Inc. Chicago, IL USA) for Windows version 23. Categorical variables were analyzed using the Chi- square test. Continuous variables were analyzed using Mann-

Whitney U test and independent t-test. A *p*-value of less than 0.05 was classified as being statistically significant.

3. Results and Discussion

3.1 Results

Mean age was 61.5 years old with an average BMI of 24.7 kg/m2. Around one third (36.1%) of subjects were undergraduate level or above. Only around one fourth of the cases (10/36) were diagnosed with diabetes mellitus without diabetic neuropathy. Most cases (25/36) were advanced stage (stage 3-4) cancers with two thirds and one third of all participants having ovarian and endometrial cancer, respectively. Other demographic data are presented in Table 1.

Table 1. Demographic data of cancer patients who underwent chemotherapy treatment.

	n	%
Age(yrs)*	61.5	10.5
BMI(kg/m2)*	24.7	7.1
Occupation		
Employee	16	44.4
Government sector	6	16.7
Own business	3	8.3
Housewife	11	30.6
Education level		
Primary	6	16.7
Secondary	17	47.2
Graduated	13	36.1
Income(USD/month)		
<302	7	19.4
302.1-907	22	61.1
907.1-1,512	7	19.4
Underlying disease	25	69.4
Diabetes mellitus	10	27.8
Hypertension	21	58.3
Dyslipidemia	11	30.6
Single or widow	29	80.6
Tubal sterilization	32	88.9
Premenopause	31	86.1
Nulliparity	10	27.8
Site		
Ovary	24	66.7
Endometrium	12	33.3
Advance stage cancer	25	69.4

*mean ± standard deviation, BMI: body mass index

Fig 2. shows leg discomfort (numbness, pain and sharpness) comparison between the study and control group. Complaints of leg discomfort in the control group occurred significantly more than study site after the second cycle of chemotherapy (p- value < 0. 01) . The severity of leg discomfort increased with each round of chemotherapy in the control group.

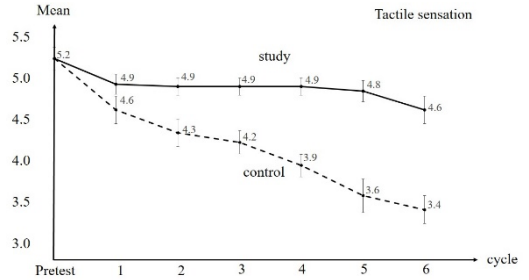

Fig. 2. Comparison curve of the tactile sensation test between cold compression leg and control group.

The tactile sensation test (TS) is depicted in Fig 3. Loss of tactile sensation at the control site occurred significantly more after the first cycle of chemotherapy, with an increasing severity of numbness for each additional chemotherapy administration.
The data from the warm test (WT) and cold test (CT) are presented in Figs 4-5, respectively. Loss of both warm and cold sensation at the control site were found after the second cycle of chemotherapy.

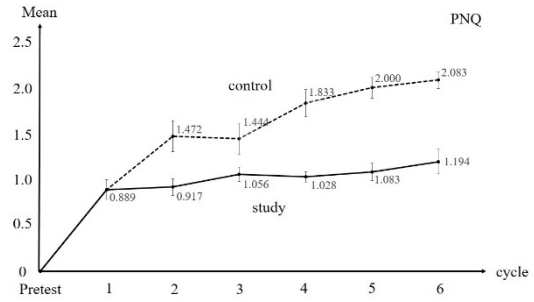

Fig. 3. Comparison curve of questionnaire test between cold compression leg and control leg.

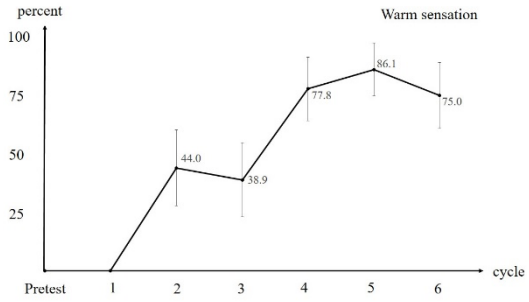

Fig. 4. Difference proportion curve of warm sensation test between cold compression leg and control leg.

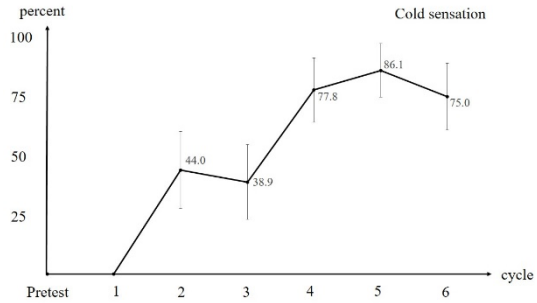

Fig. 5. Difference proportion curve of cold sensation test between cold compression leg and control leg.

Fig 6. shows data from the vibration test (VT) between the control and study groups. Loss of vibration sensation in control legs significantly increased following the third cycle of chemotherapy. Proprioception in the study and control leg were not involved during the course of chemotherapy. No distinct differences of proprioception were found in either group.

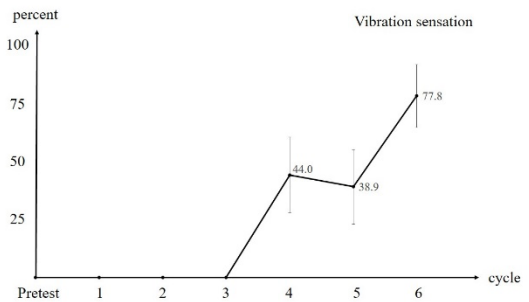

Fig. 6. Difference proportion curve of vibration sensation test between cold compression leg and control leg.

3.2 Discussion

In the present study, gynecologic cancer patients were recruited. All cases received chemotherapy for the first time (paclitaxel plus carboplatin). Around one fourth of the cases (10/36) had underlying diabetes mellitus without neuropathy. Neuropathy was the most troublesome side effect resulting from taxane and platinum (carboplatin) groups [9]. We found that almost all patients who underwent chemotherapy suffered from neuropathic side effects. Most gynecologic cancer chemotherapy regimens were composed of taxane and platinum. Carboplatin and paclitaxel are members of the platinum and taxane groups, respectively. This combination is the most common backbone chemotherapy in breast, colon and gynecologic cancers [9]. From the US, Griffiths et al. reported that from 2018-2019, CIPN was observed resulting from the prescription of carboplatin and paclitaxel in breast cancer treatment, ranging from 68 to 97 percent [10, 11].

Leg discomfort (numbness, pain and sharpness) were evaluated by monofilament test. From the current study, leg discomfort in the leg that underwent cryotherapy was lower than the control group. This finding supports Bandla's study [12]. However, the study by Ruddy et al. from the US reported that change in leg discomfort in relation to cryotherapy was insignificant. All of the participants from the Griffiths, Ruddy and Hanai studies received the same regimen of chemotherapy as the participants of the current study did. Evaluation of leg discomfort in Hanai's study was done one time after the last course of chemotherapy, while the current study was done at every course of chemotherapy. However, the leg discomfort evaluation tools in the Ruddy and Griffith studies were self- reporting questionnaires done at every course of chemotherapy. Both Ruddy and Hanai suggested that further study for the effectiveness of cryotherapy or leg

discomfort is needed. The leg discomfort evaluation in the Hanai study and the present study were questionnaires and monofilament tests. Both tests reported the same results. Comparisons of CIPN in the current study to previous studies are summarized and presented in Table 2.

Thermosensory disturbance evaluation by either cold or warm sensation test were evaluated in the current study. Both cold and warm sensation in the study leg (cryotherapy) were better than they were in the control leg (no intervention). This finding is similar to Hanai's study. Measurement in Hanai's and the current study used a thermal stimulator and cotton wool soaking. Temperature (cold/warm) in Hanai's and the current study were 3/48 and 15/60 degrees Celsius, respectively, with an equal range (45 degrees Celsius). Based on these results, cryotherapy can preserve thermosensory perception.

Cryotherapy at the effected site of chemotherapy was proposed in previous literature. Oral mucositis from 5FU was reduced by oral cryotherapy [10]. Chemotherapy-induced alopecia was prevented by scalp cooling [13]. Peripheral neuropathy, especially in lower limbs, in patients who underwent chemotherapy was reduced by frozen grove during chemotherapy administration [8, 12].

The mechanism of neuropathy prevention comes from the reduction of peripheral blood flow during chemotherapy administration [14]. Comparing the present study with previous literature was difficult as these studies only recruited taxane-treated cases and used different methods of cooling and neuropathy assessment. However, there was no long term follow up in these studies.

Neuropathy assessment was either self- reported or done by mechanical stimulation. From the current study, we used both self-reporting (questionnaire base) and mechanical stimulation. Bias from the questionnaire was the main problem. The application of a frozen sock and normal temperature or compressive sock could not blind both operator and patient. However, neuropathy prevention from cryotherapy was in lieu of data coming from the mechanical assessment. Mechanical stimulation in the current study included tiny filament picking (tactile sensation evaluation), temperature perception (cold and warm) and vibration (using a tuning fork). Tactile sensation assessment in this study was performed before and after chemotherapy administration. During the tactile sensation evaluation, the participants did not wear the sock, in order to reduce data bias. Patients in the sock group might have answered the questionnaire more positively as they understood the sock to be neuroprotective.

Temperature evaluation in the current study used a cotton ball soaked with either warm or cold water. The temperature gradient between hot and cold was 45 degrees Celsius, in accordance with Hanai's study. The Hanai study used the temperature control probe at 3 and 48 degrees Celsius, whereas the current study only used cotton balls soaked with different temperature water (15 and 60 degrees Celsius). The room temperature in the chemotherapy unit was approximately 25 degrees Celsius. Vibration perception was evaluated with a 128Hz tuning fork. The findings from the current study are in agreement with those of Hanai. Cryotherapy could prevent vibration sensation damage from chemotherapy. The proprioceptive function in the study and control limb were comparable. Whether proprioceptive function is worse after chemotherapy. Proprioceptive function is controlled by vestibular systems in the cerebellum that is not affected by chemotherapy [9].

In comparison to other studies, cold compression was well tolerated in our population as well as in Sundar's study [15]. There was no discontinuing on wearing the socks in either the current study or the study by Sundar. Both studies were conducted in hot climate countries (Thailand and

Singapore). Discontinuation of frozen sock treatment occurred at a rate between 11 to 33 percent in cold climate countries [16]. Wearing a frozen sock had a preventive effect on CIPN during chemotherapy administration and has good patient compliance among cases in the studies. However, no thermal injury was found in the current study. Cryotherapy application should be promoted and recommended to routine practice. More precise temperature control should be utilized in order to maximize the neuroprotective effect and prevent thermal injury. Cryotherapy application at the lower extremities during chemotherapy administration had a preventive effect for chemotherapy induced peripheral neuropathy. It should be added to standard care during chemotherapy administration in the future.

Table 2. Comparisons of CIPN protection of current to previous studies.

Study design	RCT,	Prospective	RCT	Pilot trial	Prospective	RCT	Present
Author	Griffiths	Hanai	Ruddy	Bandla	Kanbayashi	Beijers	Present
Year	2018	2018	2019	2019	2019	2020	2022
Country	USA	Japan	USA	Singapore	Japan	Netherland	Thailand
CMT	A+P	P	P	P,D	P	P, D, Ox	P+C
Sex	F	F	F	M/F	F	M/F	F
Site	breast	breast	breast	breast, Pros	breast	colon, breast	OV, EM
N(cases)	29	40	46	13	38	180	36
Intervention	FG + FS	FG + FS	FG + FS	FG + FS	FG + SG	FG	FS
Questionnaire	+	+	+	+	+	+	+
TS	-	+	-	-	-	-	+
Temp	-	+	-	-	-	-	+
NCS	-	-	-	+	-	-	
VS	-	+	-	-	-	-	+
PS	-	-	-	-	-	-	+
CIPN	none	NP	none	NP	none	none	NP

CIPN: chemotherapy induced peripheral neuropathy, RCT: randomize control trial, P: paclitaxel, CMT: chemotherapy, A: anthracycline, D: docetaxel, Ox: oxaliplatin, C: carboplatin, Pros: prostate, OV: ovary, EM: endometrium, F: female, M: male, FG: frozen grove, FS: frozen sock, SG: surgical grove, Questionnaire: patient neuropathy questionnaire, TS: tactile sensation, Temp: Temperature sensation, NCS: nerve conduction study, VS: Vibration sensation, PS: Proprioception sensation, NP: neuropathy protection

4. Conclusion

Patients worldwide suffer greatly from cancer and the side effects of its treatments. Despite beneficial outcomes from chemotherapy in various cancers, its adverse effects are also immense. In particular, CIPN may concern and burden a large number of patients who require combination platinum- taxane based chemotherapy. This study was done in order to help alleviate these unwanted effects by introducing cryotherapy as a standard part of some chemotherapy treatments. Cryotherapy effectiveness was tested by comparing CIPN outcomes among the participants that needed the aforementioned chemotherapy regimen. From our findings and other related studies, the data would support the use of cryotherapy for preventing CIPN.

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