Original Article

Cold Application and Exercise on Development of Peripheral Neuropathy during Taxane Chemotherapy in Breast Cancer Patients: A Randomized Controlled Trial

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ABSTRACT

Objective: Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of cancer treatment. There is no proven pharmacological application to prevent CIPN. This study was conducted to compare the effects of cold application and exercise on peripheral neuropathy development in patients with breast cancer who received taxane. **Methods:** This was a multicenter clinical trial. The study was conducted as a randomized controlled trial on breast cancer patients who had chemotherapy-induced peripheral neuropathy complaints between July 2017 and January 2018 in an outpatient chemotherapy unit of training-research and a university hospital. A standardized, home-based, 12-week exercise program involved progressive strengthening, stretching, and balance exercises. Cold packs were applied for the duration of all 12 taxane infusions and then continued at home. The standard care protocol (information about side effects) of the clinic was used for patients in the control group. Data were collected via Patient Identification Form and CIPN Assessment Tool. Demographic data were evaluated by number and percentage ratios, and the study groups' mean scores were compared by Kruskal–Wallis and Wilcoxon analyses. The data were collected at two time points including baseline (T1) and week 12 (T2). **Results:** The study was completed with a total of 90 patients, so that each of the study groups, exercise, cold application, and control groups, included 30 patients. The mean of pre- and posttest results in the cold applied group revealed an increase in hand numbness, weakness, and distress ($P < 0.05$). However, no significant difference existed between the means of the pre- and the posttests in the exercise group ($P = 0.79–0.1$). The mean scores of all the symptoms in the control group except the loss of balance increased significantly ($P < 0.05$). Exercise reduced CIPN symptoms of numbness in hands ($P = 0.009$) and in the feet ($P = 0.005$) significantly compared to the cold application and control. **Conclusions:** It was found that exercise was more effective than cold application in the management of CIPN.

Key words: Cancer, cold application, exercise, nursing, peripheral neuropathy

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Introduction

Cancer is characterized by abnormal and uncontrolled cell growth. New global cancer data suggest that the global cancer burden has risen to 18.1 million cases and 9.6 million cancer deaths. It has also been reported that breast cancer ranked the first among cancer types in women and that the number of newly diagnosed patients has reached up to 2.1 million.[1]

The aim of cancer treatment is to prevent the growth and proliferation of the main tumor with a minimized damage to patient's healthy cells. Chemotherapy medicines are among the common methods applied in the cancer treatment.[2] Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of cancer treatment. It was determined that 30%–60% of the patients receiving neurotoxic chemotherapy developed CIPN.[3] These toxic neuropathy inducing drugs are taxanes (paclitaxel and docetaxel), platinum-based drugs (oxaliplatin, cisplatin, and carboplatin), vinca alkaloids (vincristine, vinblastine, and vinorelbine), thalidomide, and bortezomib.[4] Taxanes are the most important chemotherapeutic drug groups practiced in the breast cancer treatment.[5] Symptoms of CIPN vary depending on the nerve fibers affected and the chemotherapy applied. Peripheral nerve damage can occur during or after chemotherapy. The most common symptoms are glove sock-style numbness, pinning, burning, felting, and electric shock feeling.[6]

Neuropathy primarily affects the distal organs, and the severity of the symptoms increases as the dose increase. Symptoms generally start from the limbs and then reach to the foot, wrists, and legs and then move to the fingers, to the hands, and afterward to the arms. Sensory losses that occur in patients cause burns, and loss of balance and muscle weakness cause fallings. The problem in the foot extensor muscle manifests itself by stumbling while walking.[7,8] In addition, weakness occurs in hands and ankles due to the affected motor fibers. As a result of the involvement of myelinated sensory fibers, first loss of the Achilles reflexes and then loss of other deep tendon reflexes are observed. Difficulties that arise while performing simple tasks such as buttoning, fork, and spoon using negatively affect the daily activities.[9,10]

Based on results from randomized controlled trials (RCTs), there are no effective symptomatic treatments to prevent CIPN.[11] According to the American Society of Clinical Oncology, only duloxetine could be recommended to prevent CIPN.[12,13] Amifostine, calcium gluconate, magnesium sulfate, vitamins, and other compounds with no proven pharmacological effects are being used to prevent CIPN.[14] In addition to the limited efficiency in preventing the side effects of the chemotherapeutic drugs, these agents can also produce some undesired effects.[11,13]

The use of nonpharmacological methods in the treatment of peripheral neuropathy provides advantages like controlling neuropathy with nondrug methods, as well as being cost-effective. Studies on the use of acupuncture and complementary medicine do not supply enough evidence for any clinical recommendation to treat CIPN.[15] A study by Greenlee *et al*.[16] among 48 breast cancer patients who received either electroacupuncture or sham electroacupuncture during taxane chemotherapy showed no differences between groups at treatment accomplishment. Rostock *et al*.[17] reported that there were no significant differences in terms of improvement among patients randomized to receive electroacupuncture, electroacupuncture with hydroelectric baths, high doses of Vitamin B1 and B6, or placebo for the treatment of CIPN.

A variety of rehabilitative methods, such as exercise and cold application, have been tested with positive effects in reducing the impact of CIPN symptoms and in improving the life quality of the patient.[18-23] Literature suggests that a well-planned exercise program produces safe and effective results.[19,21,23] Here, the type and frequency of the exercise is an important determinant.[18] Kleckner *et al.*[21] studied the efficacy of standard 6-week home-based low-intensity progressive walking and resistance exercise program on randomized 355 patients with primary breast cancer. After 6 weeks, exercise reduced CIPN symptoms of hot/coldness in hands/feet and numbness and tingling.

Knowing the effect of cold application as another nonpharmacological method has an important role in the symptom management. The vasoconstriction due to the local effect of the cold slows the cellular metabolism by decreased blood flow. Cold application reduces the sensitivity of pain receptors (nociceptors) by reducing the release of vasodilator substances. It also decreases the metabolic rate and cellular chemical activity via causing the capillary contraction. It also reduces muscle spasm by decreasing nerve conduction velocity and muscle excitability.[24] The expected effect of cold application depends on the application period, the temperature used, and the size of the application area. The cold application was reported to reduce the severity of neuropathy in previous studies.[20,25,26] Hanai *et al*.[26] indicated that the occurrences of paclitaxel-induced peripheral neuropathy were less frequent in the patients who used frozen gloves and socks.

Side effects of cancer and chemotherapy interfere with the daily life activities of the patients and adversely affect their life quality. In addition to these negativities, it also increases the health expenditures. Timely recognition of the

possible toxicities is influential on the treatment outcome.[27] Since CIPN influences the individual not only physically but also psychologically and socially, the nurse should plan the patient's private intervention by periodic evaluations in the treatment process. Although there is no standardized treatment protocol in the literature for the management of CIPN, these symptoms have been reported most likely to be under considerable control with good nursing care. Prevention of peripheral neuropathy due to drugs would positively affect the treatment process of patients and increase the quality of life.[28] This study was conducted to compare cold application and exercise on peripheral neuropathy development in taxane receiving breast cancer patients.

Research hypotheses

H0: Exercise and cold application are not superior to each other in reducing CIPN symptoms in breast cancer patients receiving chemotherapy.

Methods

Research design

A three-arm parallel RCT (two intervention arms and one control arm) was used to compare the effectiveness of exercise and cold application in breast cancer patients undergoing chemotherapy.

Participants and setting

The population of the study included patients with breast cancer admitted to Ankara University, School of Medicine, Cebeci Hospital's Outpatient Chemotherapy Unit and Gülhane Training and Research Hospital's Day Chemotherapy Unit between July 1, 2017, and January 20, 2018, who also met the study inclusion criteria.

The study inclusion criteria required research participants to:

- Be able to comprehend and speak in Turkish
- Be older than 18 years
- Be taking taxane group chemotherapy treatment at the outpatient chemotherapy clinics
- Have at least 1 neuropathy symptom according to CIPN Assessment Tool (CIPNAT)
- Be breast cancer patients with histologically proven Stage II to IV
- Be receiving planned administration of weekly taxane group chemotherapy infusion dose (70–99 mg/m², 100–129 mg/m², 130–159 mg/m², 160 mg/m², and above) and completed 12 cycles of curing
- Be voluntarily participate in the study.

The study exclusion criteria excluded those people:

- Who have central nervous system problems, such as movement and balance
- Coordination and feeling (sensation)
- Having any skin infection, scar tissue, inflammation, and incision in the hand and ankle
- Having intolerance to cold.

Sample size

Twenty-eight patients per arm were required to achieve significance level of 0.05 and power of 0.90, and the effect size was considered to be $f = 0.35$ in a three-group study. Patients were allocated to study groups in a 1:1:1 ratio through computer-generated randomization. Randomization considered the cancer stage and receiving chemotherapy dose. One hundred and twenty-six patients were evaluated with the research criteria for compliance. These 126 patients attended the study with simple sampling method. Patients were assigned to the exercise group, cold application group, and the control group, using a randomization list prepared by the computer. During the study, some of the patients did not attend the exercise or cold application, some of them did not complete the questionnaires, some of them changed mind, and some patients changed treatment protocol. Hence, the study was completed with 90 patients: 30 in the exercise group, 30 in the cold application group, and 30 in the control group [Figure 1].

The standard care protocol (informing about side effects) of the clinic was used for patients in the control group. This group was offered to do exercise to reduce their CIPN at the end of the trial after they completed week 12 assessments.

In this study, it was not possible to blind participants or researchers due to the nature of the intervention.

Primary outcome

The primary outcome measure was the total neuropathy score assessed by the researcher. CIPN symptoms (numbness, tingling, burning, etc.) seen in the patients were recorded by questionnaire. CIPN was measured using the CIPNAT. Patients were asked to describe how heavily they were affected at the respective point in time from CIPN disturbance altogether and to rate the severity of neuropathic symptoms on a rating scale ranging from 0 (no disturbance) to 10 (highest disturbance).

Secondary outcomes

The researcher evaluated the intensity of the CIPN complaints by classification according to the CIPNAT, while the follow-up interview after 12 weeks was done in writing, via questionnaires sent to the patients' homes.

Data collection

Data of the study were collected using "Patient identification form for the determination of neuropathy

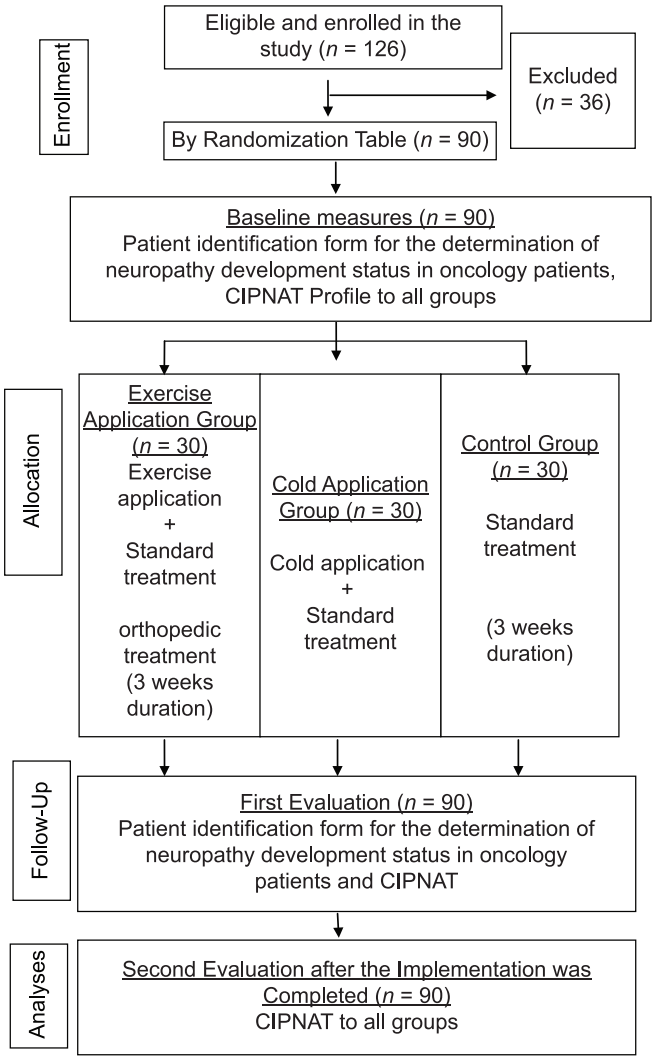

Figure 1: Flowchart

development status in oncology patients" and CIPNAT.[29]

Patient identification form for the determination of neuropathy development status in oncology patients

The form named "Patient identification form for the determination of neuropathy development status in oncology patients," prepared in accordance with the literature, consists of three parts.[18,29,30]

The first part collects information on the patient's age, educational status, occupation, marital status, average monthly income, place of permanent residence, cancer diagnosis in the family, current status of the patient, smoking and alcohol use history, and chronic illness status assessment.

The second part contains questions related to following items;

- The patient's primary diagnosis and its date;
- Disease stage;
- The previous treatments; its date and type, radiotherapy receiving status;
- Current treatment; chemotherapeutic drugs and the number of cures if chemotherapy received;
- Treatment status to prevent peripheral neuropathy; the name of the medicine, the doses, route of administration.

The probable problems during or after chemotherapy treatment such as dizziness, loss of balance, falling, increased sensitivity to cold, tingling, numbness, burning sensation, swallowing difficulty, and weakness and the locations of these problems such as fingers of hands and feet, hands, feet, legs, or other areas of the body were questioned in the third part. Besides, if there were any of these problems, the timing and frequency of experiencing the problems were evaluated. Whether these problems happened during chemotherapy, in the morning, afternoon, evening, night and whether they were experienced continuously or in times other than mentioned above were also evaluated.

Chemotherapy-induced peripheral neuropathy assessment tool

CIPNAT is a Likert-type scale developed by Tofthagen *et al*.[31] It consists of two parts. In the first part, questions about sensory and motor issues as numbness, itching, burning, discomfort, cold sensitivity, pain, weakness, and balance disorder were answered. If the question A (Over the last week, have you experienced) was answered as "Yes," then the participant also answered questions B (How severe was it?), C (How distressing emotionally upsetting was it?), and D (How frequently did you have it?) that are located on the right of A. Each category was scored between 0 and 10. A higher score indicated a higher level of neuropathy due to chemotherapy. In the second part of the form, the problems encountered in the daily life activities of the patients (dressing, walking, picking up objects, holding onto objects, driving, working, participating in hobbies or leisure activities, exercising, sleeping, sexual activity, relationships with other people, writing, usual household chores, and enjoyment of life) were evaluated and scored between 0 and 10. The reliability and validity of the Turkish version of the scale were done by Yükseltürk Şimşek and Demir in patients with breast cancer. The sample of the scale consisted of 430 breast cancer patients receiving taxane treatment between April and December 2017, and the Cronbach's alpha value was calculated as 0.87. The test–retest reliability of the CIPNAT rating scale was found to be 0.90–0.96 for all dimensions.[29]

Intervention

Preapplication evaluation and training

First, the aim of the study was explained to all patients who were included in the exercise application,

cold application, or control group. After obtaining the written informed consent to participate in the study, the demographic and clinical data were collected. Information on medical characteristics was obtained from the patient file. In the study, CIPNAT, which reliability and validity study had been done for Turkish version, was applied to determine the effect of taxane on the development of peripheral neuropathy in breast cancer patients. CIPNAT was applied to all patients who met the inclusion criteria and who were found to have peripheral neuropathy during the first interview. The tool was re-applied to the control, exercise, and cold groups after 12 weeks.

Cold application protocol

- Cold application started the week when the first neuropathy symptom developed and continued for 12 weeks;
- Cold application was done by the researcher when the patients came to the hospital;
- All controlled cold applications were performed at home after chemotherapy and done by the help of relatives. When they came for chemotherapy treatment the next week, they were questioned whether they could do the treatment for 24 h or not. The cold packs were prepared specifically for each patient in the freezer;
- The procedure was explained to the patient and the family, and the area to be treated was checked for infection, scar tissue, inflammation, and incision;
- Application area was opened and the patient was given the proper position while caring the privacy of the patient's body;
- Cold packs were used in the sizes of 30 cm × 20 cm for ankles and 20 cm × 10 cm for wrists [Figure 2];
- The compress pack was kept in the freezer for a minimum of 2 h (−20°C/−30°C) before using;
- The application areas were wrapped with nonsterile gauze compress (10 cm × 10 cm) to prevent direct contact with cold;

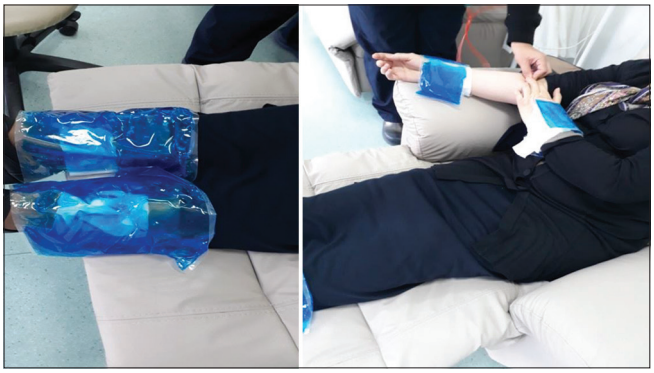

Figure 2: Cold packs

- Frozen cold compress packages were applied for 15 min before infusion and 15 min during chemotherapy totaling up to a total of 30 min;
- There were 45-min breaks between each application;[25,26,32]
- Adherence to cold application, pain, aberrant sensation; and other discomforts due to cold application were checked during every intervention;
- Patients sent home with these compresses and instructed to freeze them at home before using them;
- The application continued for 24 h during and after the chemotherapy infusion;
- The researcher made a weekly home visit;
- Patients are recommended to avoid the consumption of cold drinks, contact with hot water for 72 h, and consumption of hot food and beverages.[33]

Exercise protocol

- Exercise program started the week when the first neuropathy symptom developed and continued for 12 weeks;
- Since there is no standard exercise program used for peripheral neuropathy, the exercise program to be applied was prepared with a physiotherapist counsel;
- All training sessions were conducted at first by the researcher who had previously learned the exercise program given by a physiotherapist;
- All supervised exercises were conducted at home and inspected once a week by the researcher. A brochure about the exercise program was prepared and given to the patients [Supplementary Figure S1]. The exercise program consisted of strengthening, stretching, and balance exercises. The stated exercise program was progressive depending on exercise tolerance. The program was described according to the frequency (number of sessions per week), intensity, time (duration of exercise), and type of exercise. The patients and their relatives in the exercise group were informed about how to perform the application on the day of the chemotherapy;
- The exercise program was planned for the outpatient;
- The 15–30-min exercise program was planned as 5 times per week and continued for 12 weeks;
- The program was first started in the form of strengthening and stretching exercises (foot dorsiflexion, foot plantar flexion, gastrocnemius stretching, hamstring stretching, quadriceps exercises, biceps, and hand flexion-extension) followed by balance exercises (hip flexion, hip extension, hip abduction, and knee flexion);
- The program was started by 10 repetitions for the first 3 weeks, the repetitions were increased to 20 for 4, 5, 6 weeks, and to 30 repetitions for 7, 8, 9 weeks;
- There was no repetition for stretching exercises;[34]

- The exercise program was practiced by two 500 cc water bottles, and sheets and towels were used as supportive equipment.

Ethical approval

The permission, with the decision of the Council of 85434274-050.04.04/5510 dated January 23, 2017, was approved by the authors' university ethics review board. Permissions dated April 14, 2017, No. 59137464-663.08-4027 from the University Hospital, and dated February 21, 2017, and numbered 59137464-663.08-E.1347 from Education and Research Hospital were also obtained. Informed consent from each patient was obtained after the study was explained to them.

Statistical analysis

Statistical analysis of the data were run in the IBM SPSS statistics 24 program. Numbers and percentages were used in the evaluation of demographic data of the exercise, cold application, and control groups such as educational status and working status. The Shapiro–Wilk test was used to determine whether the study groups showed normal distribution or not. The Shapiro–Wilk test is one of the commonly preferred normality tests if the sample size is lower than 50.[35] Shapiro–Wilk test resulted in the deviation from normal in the subdimensions of the scale ($P < 0.05$), so nonparametric tests (Kruskal–Wallis and Wilcoxon analysis) were applied for data analyses. CIPNAT scale pre- and posttest mean scores of the study groups were compared with Kruskal–Wallis tests. The pre- and posttest results of the study groups were analyzed with the Wilcoxon signed-rank test. Furthermore, eta square (η2) was used to calculate the effect size of each variable to assist in determining the degree to which group means differed. The effect size and named eta square indicate how much the independent variable or factor explains the variance in the dependent variable and ranges between 0.00 and 1.00. In this study, the value of η2 was 0.06 or less and it means that the mean differences were moderate or less.

Results

Information about the medical characteristics and information about the 90 participated patients in the study are given in Tables 1 and 2.

Information on the problems experienced by 90 patients participating in the study is given in Table 3.

A comparison of the mean posttest scores of the CIPNAT scale of the study groups is presented in Table 4. Three groups differed in the symptoms of hand numbness and foot numbness. There was a difference between the exercise and control groups, especially among these three groups ($P < 0.05$). There was no significant difference between the groups for other symptoms [Table 4].

The mean of the pre- and posttest results of all groups is presented in Table 5. There was no significant difference when the mean scores of the pre- and posttest results of the exercise group were compared. When Table 5 is examined, there was no increase in the symptoms of neuropathy. This suggested that exercise has been effective in reducing the severity of CIPN. The mean scores of the pre- and posttest results of the cold application group are presented in Table 6. The cold application used in the management of peripheral neuropathy was effective in alleviating some symptoms. The mean scores of the control group pre- and posttest results are presented in Table 7. All symptoms of the control group except balance state had a significant mean increase in Figure 3. This supported the literature that neuropathy is a dose-dependent chemotherapy-drug toxicity and increases the risk of developing peripheral neuropathy development.

Discussion

Although there are many applications in the literature for CIPN (cold application, massage, acupuncture, tens, etc.), there is no study comparing the effectiveness of cold application and exercise in studies.

According to our research findings, it was found that there was a difference in the means of posttest scores between the cold application, exercise, and control groups used in the prevention of CIPN in patients with breast cancer who received taxane ($P < 0.05$). Consequently, H0 hypothesis was rejected.

At the end of the study, it was found that there was a significant difference between the pre- and posttest mean scores of the studied patients ($P < 0.05$). As a result of the statistical analysis, it was determined that this difference was mainly caused by the exercise group and there was no increase in neuropathy rate of the patients in the exercise group when compared to the control group. The comparisons of the two groups indicated that the exercise method was significantly

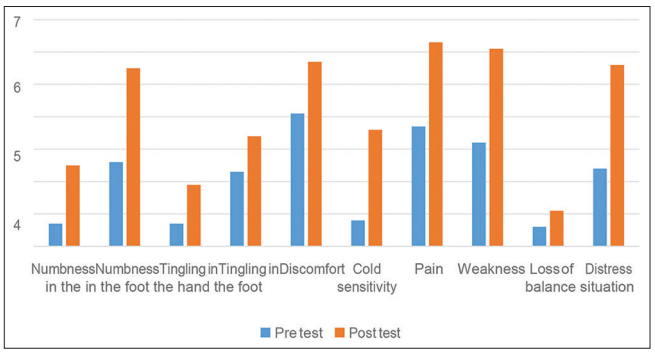

Figure 3: Comparison of pre- and posttest results of control group

Table 1: Sociodemographic characteristics (n=90)

Sociodemographic characteristics	Exercise group (n=30), n (%)	Cold application group (n=30), n (%)	Control group (n=30), n (%)	Total (n=90), n (%)
Age (years)				
20-39	4 (13.4)	5 (16.7)	8 (26.7)	17 (18.9)
40-59	14 (46.6)	20 (66.6)	16 (53.3)	50 (55.5)
60 and more	12 (40.0)	5 (16.7)	6 (20.0)	23 (25.6)
Education				
Illiterate	5 (16.6)	1 (3.3)	0	6 (6.7)
Elementary school	13 (43.4)	13 (43.4)	13 (43.3)	39 (43.3)
Secondary school	7 (23.3)	2 (6.7)	0	9 (10.0)
High school	4 (13.4)	10 (33.3)	8 (26.7)	22 (24.4)
University and higher	1 (3.3)	4 (13.3)	9 (30.0)	14 (15.6)
Employment				
Unemployed	24 (80.0)	24 (80.0)	20 (66.7)	68 (75.6)
Retired	4 (13.3)	5 (16.7)	10 (33.3)	19 (21.1)
Employed	2 (6.7)	1 (3.3)	0	3 (3.3)
Marital status				
Married	25 (83.3)	27 (90.0)	22 (73.3)	74 (82.2)
Single	5 (16.7)	3 (10.0)	8 (26.7)	16 (17.8)
Average monthly income				
Low	19 (63.3)	12 (40.0)	16 (53.3)	47 (52.2)
Intermediate	11 (36.7)	17 (56.7)	14 (46.7)	42 (46.7)
High	0	1 (3.3)	0	1 (1.1)
Number of people in the family				
1-3	19 (63.3)	13 (43.3)	19 (63.3)	51 (56.7)
4-6	11 (36.7)	16 (53.4)	11 (36.7)	38 (42.2)
7 and more	0	1 (3.3)	0	1 (1.1)
Children number				
0-3	22 (73.3)	24 (80.0)	25 (83.3)	71 (78.9)
4-7	8 (26.7)	6 (20.0)	5 (16.7)	19 (21.1)
Place of permanent residence				
In Ankara	19 (63.3)	21 (70.0)	21 (70.0)	61 (67.8)
Out of Ankara	11 (36.7)	9 (30.0)	9 (30.0)	29 (32.2)

more effective than the cold application in reducing the peripheral neuropathy symptoms. This showed that exercise applied to the patients, who developed neuropathy due to taxane treatment, reduced the symptoms of neuropathy. In the literature, it was seen that the neuropathy in the chemotherapy patients was reduced after the exercise program.[22,30,36] In the study of Kleckner *et al.,*[21] exercise has been reported to reduce CIPN symptoms in patients receiving taxane, platinum, or vinca alkaloid-based chemotherapy. In a study by Streckmann *et al.,*[37] exercise was found to reduce the limitations associated with peripheral neuropathy and to increase the balance control and physical performance of the patients. The study of Zimmer *et al.*[22] showed that an 8-week exercise program increased balance and strength in patients with CIPN. Many researches have shown beneficial effects of exercise in cancer treatment-related toxicities as well as enhancing the quality of life of the patients. Exercise programs should be designed to help patients maintain their independent functioning.[22,30]

Studies to date have included varying cancer patients and treatment protocols, as well as different outcome measures and intervention designs. In a study by Beijers *et al.,*[38] 90 patients receiving taxane and platinum between 2013 and 2016 had reduced symptoms of neuropathy after wearing frozen gloves during chemotherapy. In a different study by Scotte *et al.,*[32] frozen gel gloves were worn to the right hand of the patients who took 75 mg/m² taxane 15 min before chemotherapy, 60 min during chemotherapy, and 15 min after chemotherapy, total application duration adding up to 90 min. Routine care was applied to the left hand of the patients, and nail changes on both hands were assessed using the NCI-CTCAE and 4.03 toxicity criteria. At the end of the study, that nail changes were significantly lower in the cold applied group than in the control group.[32] Contrary to the expectations, McCarthy *et al.*[39] found that cryotherapy applied in the form of frozen gel gloves did not provide significant benefit on hand and nail toxicities. Similarly, in the study of Can *et al.*, patients who received at least three cures of taxane infusion were dressed in elastogel gloves (frozen for 3 h at −18°C and −20°C) for 15 min. At the end of the study, there was no difference in nail change between the application and

Table 2: Patient medical characteristics (*n*=90)

Patient medical characteristics	Exercise group (*n*=30), *n* (%)	Cold application group (*n*=30), *n* (%)	Control group (*n*=30), *n* (%)	Total (*n*=90), *n* (%)
Family history of cancer				
Yes	15 (50.0)	13 (43.3)	12 (40.0)	40 (44.4)
No	15 (50.0)	17 (56.7)	18 (60.0)	50 (55.6)
Smoking				
Yes	1 (3.3)	4 (13.3)	3 (10.0)	8 (8.9)
No	29 (96.7)	26 (86.7)	27 (90.0)	82 (91.1)
Alcohol				
Yes	0	1 (3.3)	0	1 (1.1)
No	30 (100.0)	29 (96.7)	30 (100.0)	89 (98.9)
Chronic disease				
Diabetes	7 (38.9)	0	1 (9.1)	8 (22.2)
Hypertension	5 (27.8)	4 (57.1)	7 (63.6)	16 (44.4)
Heart failure	5 (27.8)	3 (42.9)	3 (27.3)	11 (30.6)
Other	1 (5.5)	0	0	1 (2.8)
Stage of cancer				
II	12 (40.0)	14 (46.7)	12 (40.0)	38 (42.2)
III	15 (50.0)	12 (40.0)	14 (46.7)	41 (45.6)
IV	3 (10.0)	4 (13.3)	4 (13.3)	11 (12.2)
Operation				
Yes	13 (43.3)	14 (46.7)	19 (63.3)	46 (51.1)
No	17 (56.7)	16 (53.3)	11 (36.7)	44 (48.9)
Operating region				
Right mastectomy	7 (53.8)	7 (50.0)	10 (52.6)	24 (52.2)
Left mastectomy	5 (38.5)	6 (42.8)	9 (47.4)	20 (43.4)
Bilateral mastectomy	1 (7.7)	1 (7.2)	0	2 (4.4)
Radiotherapy				
Yes	3 (10.0)	4 (13.3)	7 (23.3)	14 (15.6)
No	27 (90.0)	26 (86.7)	23 (76.7)	76 (84.4)
Taxane dose (mg)				
70-99	3 (10.0)	4 (13.3)	1 (3.3)	8 (8.9)
100-129	12 (40.0)	8 (26.7)	10 (33.3)	30 (33.3)
130-159	15 (50.0)	16 (53.3)	16 (53.4)	47 (52.2)
160 and more	0	2 (6.7)	3 (10.0)	5 (5.6)
Received cures				
1-4	14 (46.7)	16 (53.3)	24 (80.0)	54 (60.0)
5-8	12 (40.0)	14 (46.7)	6 (20.0)	32 (35.6)
9-12	4 (13.3)	0	0	4 (4.4)
Total cures				
<12	0	0	0	0
12	26 (86.7)	30 (100.0)	30 (100.0)	86 (95.6)
>12	4 (13.3)	0	0	4 (4.4)

Table 3: Problems experienced during or after chemotherapy (*n*=90)

Problem	Exercise group (*n*=30), *n* (%)	Cold application group (*n*=30), *n* (%)	Control group (*n*=30), *n* (%)	Total (*n*=90), *n* (%)
Dizziness	3 (10.0)	2 (6.7)	3 (10.0)	8 (8.9)
Loss of balance	3 (10.0)	2 (6.7)	1 (3.3)	6 (6.7)
Fall	1 (3.3)	0	0	1 (1.1)
Cold sensitivity	9 (30.0)	5 (16.7)	4 (13.3)	18 (20.0)
Tingle	27 (90.0)	23 (76.7)	25 (83.3)	75 (83.3)
Numbness	22 (73.3)	16 (53.3)	13 (43.3)	51 (56.7)
Burning	5 (16.7)	4 (13.3)	9 (30.0)	18 (20.0)
Swallowing difficulty	2 (6.7)	0	0	2 (2.2)
Weakness	18 (60.0)	13 (43.3)	15 (50.0)	46 (51.1)

Table 4: Comparison of posttest results of experimental and control groups

Problem	Groups	*n*	$\bar{x}$	SS	χ^{2**}	*P**
Numbness in the hand	Exercise	30	1.9	1.9	9.32	0.009*
	Cold application	30	3.0	2.0		
	Control	30	3.1	2.0		
Numbness in the foot	Exercise	30	3.8	1.8	10.47	0.005*
	Cold application	30	4.0	1.5		
	Control	30	5.5	1.7		
Tingling in the hand	Exercise	30	0.7	1.1	2.70	0.26
	Cold application	30	0.8	1.3		
	Control	30	1.9	2.3		
Tingling in the foot	Exercise	30	1.4	1.6	1.73	0.42
	Cold application	30	1.2	1.5		
	Control	30	3.4	2.5		
Discomfort	Exercise	30	3.5	1.5	2.13	0.35
	Cold application	30	4.4	1.2		
	Control	30	5.7	1.7		
Cold sensitivity	Exercise	30	1.9	1.8	1.5	0.47
	Cold application	30	1.4	1.7		
	Control	30	3.5	2.0		
Pain	Exercise	30	3.4	2.2	1.97	0.37
	Cold application	30	3.5	1.4		
	Control	30	6.3	1.5		
Weakness	Exercise	30	3.0	2.8	0.05	0.98
	Cold application	30	3.9	2.2		
	Control	30	6.1	1.3		
Loss of balance	Exercise	30	0.8	1.5	0.29	0.87
	Cold application	30	0.8	1.8		
	Control	30	1.1	2.3		
Distress situation	Exercise	30	3.8	1.1	3.44	0.18
	Cold application	30	3.6	1.3		
	Control	30	5.6	1.2		

*P<0.05. **Kruskal-Wallis tests

Table 5: Comparison of pre- and posttest results of exercise groups

Problem	Groups	*n*	$\bar{x}$	SS	*Z**	*P*
Numbness in the hand	Pretest	30	2.2	2.3	−0.64	0.52
	Posttest	30	1.8	1.9		
Numbness in the foot	Pretest	30	4.0	2.2	−0.87	0.39
	Posttest	30	3.8	1.8		
Tingling in the hand	Pretest	30	0.7	1.2	−0.11	0.92
	Posttest	30	0.7	1.1		
Tingling in the foot	Pretest	30	1.5	1.9	−0.28	0.78
	Posttest	30	1.3	1.6		
Discomfort	Pretest	30	4.1	1.8	−2.5	0.01
	Posttest	30	3.5	1.5		
Cold sensitivity	Pretest	30	1.5	2.3	−1.1	0.25
	Posttest	30	1.9	18.0		
Pain	Pretest	30	4.1	2.7	−1.2	0.23
	Posttest	30	3.4	2.2		
Weakness	Pretest	30	3.2	3.1	−0.37	0.72
	Posttest	30	3.0	2.8		
Loss of balance	Pretest	30	0.6	1.2	−0.63	0.53
	Posttest	30	0.8	1.5		
Distress situation	Pretest	30	31.0	1.8	−1.5	0.13
	Posttest	30	3.8	1.1		

*Wilcoxon signed-rank test

control groups.[40] As can be seen in the studies above, it was seen that the cold application had different effects on neuropathy. There were differences in regimens and the use of concomitant chemotherapy. In our study, the numbness of the hand and feet of the patients in the cold application group was minimally decreased compared to the control group. The incidence of other symptoms was also reduced, but these findings were not statistically significant. Thus, understanding the reasons for such variance in cold application and whether adjustments to the cold application would improve this effect is worthwhile investigating.

When we compared the pre- and posttest mean scores of the patients in the exercise group, there was no significant difference. The degree of peripheral neuropathy associated with chemotherapy depends on the chemicals (drugs) and the dose applied. In the literature, the severity of neuropathy increases with the dose.[15,41] In a study on chemotherapy drugs that cause peripheral neuropathy, 59%–78% of the paclitaxel-treated patients were reported to develop sensory-motor neuropathy due to dose and infusion rate.[41] No increase in the severity of symptoms of neuropathy despite the dose increase in our study showed that exercise was effective in alleviating symptoms of treatment-induced neuropathy. One purpose of this study was to determine whether home-based exercise program was beneficial to reduce symptoms of CIPN or not. However, these outcomes only included single-item questions evaluated on a 0–10 scale. Patients were encouraged to progressively increase the total number of repetitions each week. In our study, no increase was observed in the number of symptoms of neuropathy despite the increased therapy dose, which showed that exercise was effective in alleviating symptoms of neuropathy due to the treatment. It should also be noted that the exercise program was not a professional one.

When the pre- and posttest mean scores of the patients in the cold application group were compared, there was a significant increase in the subthemes such as hand numbness, weakness, and distress. There were different conclusions in the literature about the effect of cold application on peripheral neuropathy due to chemotherapy.[32,38,39] The increase observed in some symptoms in our study may be due to the variability of the cold application techniques used, the duration of the application, and the risk factors in chemotherapy-related peripheral neuropathy. The characteristics of the sample group included in the study may have affected the significance as well.

Patients in the control group had a significant difference in the pre- and posttest mean scores ($P < 0.05$). CIPN was found to be 20%–100% in cancer patients.[42]

Table 6: Comparison of pre- and posttest results of cold application group

Problem	Groups	*n*	x̄	SS	*Z***	*P**
Numbness in the hand	Pretest	30	1.8	1.9	−3.98	<0.0001
	Posttest	30	2.8	1.7		
Numbness in the foot	Pretest	30	3.6	2.1	−1.32	0.2
	Posttest	30	4.0	1.5		
Tingling in the hand	Pretest	30	0.9	1.7	−0.46	0.6
	Posttest	30	0.8	1.3		
Tingling in the foot	Pretest	30	1.6	2.2	−1.82	0.07
	Posttest	30	1.2	1.5		
Discomfort	Pretest	30	4.0	1.9	−1.6	0.1
	Posttest	30	4.4	1.2		
Cold sensitivity	Pretest	30	1.5	2.2	−0.26	0.79
	Posttest	30	1.4	1.7		
Pain	Pretest	30	3.5	2.4	−0.48	0.63
	Posttest	30	3.5	1.4		
Weakness	Pretest	30	3.2	2.4	−3.85	<0.0001
	Posttest	30	3.9	2.2		
Loss of balance	Pretest	30	0.7	1.7	−1.60	0.11
	Posttest	30	0.8	1.8		
Distress situation	Pretest	30	2.8	1.9	−4.08	<0.0001
	Posttest	30	3.6	1.3		

*P<0.05, **Wilcoxon signed-rank test

Table 7: Comparison of pre- and posttest results of control group

Problem	Groups	*n*	x̄	SS	*Z***	*P**
Numbness in the hand	Pretest	30	0.7	1.8	−4.3	<0.0001
	Posttest	30	2.5	2.1		
Numbness in the foot	Pretest	30	2.6	2.1	−4.8	<0.0001
	Posttest	30	5.5	1.7		
Tingling in the hand	Pretest	30	0.7	2.0	−3.6	<0.0001
	Posttest	30	1.9	2.3		
Tingling in the foot	Pretest	30	2.3	2.4	−3.8	<0.0001
	Posttest	30	3.4	2.5		
Discomfort	Pretest	30	4.1	1.8	−4.7	<0.0001
	Posttest	30	5.7	1.7		
Cold sensitivity	Pretest	30	0.8	1.8	−4.5	<0.0001
	Posttest	30	3.6	2.0		
Pain	Pretest	30	3.7	2.7	−4.8	<0.0001
	Posttest	30	6.3	1.5		
Weakness	Pretest	30	3.2	2.6	−4.8	<0.0001
	Posttest	30	6.1	1.3		
Loss of balance	Pretest	30	0.6	1.5	−2.4	0.02
	Posttest	30	1.1	2.3		
Distress situation	Pretest	30	2.4	1.8	−4.8	<0.0001
	Posttest	30	5.6	1.2		

*P<0.05, **Wilcoxon signed-rank test

The agents that cause neuropathy, such as docetaxel and paclitaxel, were found to cause peripheral neuropathy in 64% of the patients.[7,41] The daily living activities of the patients were affected negatively by related developing CIPN.[43,44] The results of our study were in accordance with the findings of these studies. The difficulties experienced by the patients in the control group were significantly higher than the evaluation on the 1st day of the study.

Limitations

This trial has several limitations. First, we only had access to simple patient-reported measures of CIPN symptoms instead of a clinical assessment. One limitation of the study was that it was done on only taxane-receiving breast cancer patients. Second, we could not evaluate whether patients were able to apply the practice correctly at home. Tolerability of extremity hypothermia could not be measured. In addition, the patients showed resistance to using the cold package in cold conditions.

Conclusions

This study contributes to efforts for developing effective strategies to improve the physical health of breast cancer patients. Increasing the life quality of patients receiving chemotherapy requires controlling the symptom. Nurses who play an active role in the application of chemotherapy drugs have an important role in alleviating side effects that may develop during treatment. Nurses should be aware of the symptoms of chemotherapy, develop effective practices to prevent symptoms, and support patient adherence to interventions for good results. As a result of the study, exercise was determined to be more effective than cold application in prevention of peripheral neuropathy among patients with breast cancer under taxane treatment. Nurses should evaluate the physical condition of the patient to prevent CIPN development. In the evaluation, it should be determined whether the individual has a condition that restricts or prevents the application. It is recommended that nurses guide patients by taking into consideration the advantages and disadvantages of the method and they should play an active role in the controlling of CIPN symptoms.

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Conflicts of interest

There are no conflicts of interest.

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