H.Ü. Sağlık Bilimleri Fakültesi Dergisi
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Original Research

Effect of Reflexology Massage on Chemotherapy Induced Peripheral Neuropathy in Breast Cancer Patients Receiving Taxanes: A Randomized Controlled Study

Neriman Yükseltürk Şimşek[1], Barış Nacır[2] ,Ayten Demir[3]

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Abstract

Objectives: This study was conducted as a randomized controlled trial of the efficacy of reflexology in reducing chemotherapy induced peripheral neuropathy in breast cancer women receiving taxanes.
Methods: The research was carried out at the hospitals' outpatient chemotherapy unit during the period spanning from June 1st to December 30th. Data were assessed using the Chemotherapy- Induced Peripheral Neuropathy Assessment Tool (CIPNAT), Patients' Information on Disease Variables and the Patient Information Form. Analysis was performed by number, percentage, independent t-test, chi-square test and one-way analysis of variance test for repeated measures.
Results: The participants were divided randomly into two groups: experimental (n=29) and control (n=29). During the 6-week intervention period, foot reflexology was administered to the experimental group, while the control group followed the clinic's standard protocol. Following the intervention, the average neuropathy symptom scores of the female participants in the experimental group did not increase significantly ($p < 0.05$).
Conclusions: The results of this study indicate that the administration of foot reflexology has a positive impact on symptoms of peripheral neuropathy.

Keywords: *Chemotherapy, Peripheral Neuropathy, Randomized Controlled Study, Reflexology, Nursing*

[1]**Neriman YÜKSELTÜRK ŞİMŞEK (Corresponding Author).** Gülhane Training and Research Hospital, Ankara/Turkiye, Phone: 05363226541 e-mail: nyukselturk007@hotmail.com
[2]**Barış NACIR.** Ankara Training and Research Hospital, Ankara/Turkiye, Phone: 05327278724 e-mail: baris.nacir@sbu.edu.tr
[3]**Ayten DEMİR** Ankara University, Faculty of Nursing, Ankara/Turkiye, Phone: 05325497927 e-mail: aytendemirankara@gmail.com

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Introduction

Chemotherapy is employed in certain stages of breast cancer. Taxanes are the chemotherapeutic agents frequently used in breast cancer (Windebank & Grisold, 2008; Cunningham et al, 2011; Denduluri et al, 2018; Colvin, 2019; Noh & Park, 2019). The most commonly side effects seen in patients taking paclitaxel and docetaxel are peripheral neuropathy. The reduction of dosage and adverse effects on the quality of life of patients are significant consequences of chemotherapy-induced peripheral neuropathy (CIPN) (Seretny et al, 2014; Cunningham et al, 2011; Tofthagen et al, 2011; Starobova et al, 2017; Wadia et al, 2018; Colvin, 2019; Zhi et al, 2019).

The incidence of taxane-related peripheral neuropathy varies between 61-92% (Colvin, 2019). Many factors affect the incidence and intensity of CIPN are associated with factors like the duration of drug administration, the use of multiple agents and cumulative dose (Cunningham et al, 2011; Tofthagen et al, 2011; Seretny et al, 2014; Caveletti et al, 2019). It is stated that individuals with a cumulative drug dose of approximately 300 mg/m² have a high risk of developing neuropathy, whereas those with existing neuropathy experience more severe neuropathic complaints (Park et al, 2013). Peripheral neuropathy can also affect different body parts and the symptoms initially start feet and hands. The main symptoms of chemotherapy induced peripheral neuropathy is characterized by numbness, tingling, burning, coldness and electric shock sensation (Wu et al, 2019; Şimşek & Demir, 2021).

According to the results of randomized controlled trials (RCTs), there is no pharmacological agent with proven efficacy other than duloxetine is recommended by the American Society of Clinical Oncology (ASCO) for the treatment of peripheral neuropathy (Windebank & Grisold, 2008; Smith et al, 2013; Loprinzi et al, 2020; Shigematsu et al, 2020). It has been determined that antiepileptics, antidepressants, vitamin E, vitamin B, calcium and magnesium infusions can provide a preventive effect for peripheral neuropathy caused by paclitaxel in breast cancer patients. However, a limited number of studies have been done to support, these agents effectiveness in coping with CIPN (Park et al, 2021; Şimşek & Demir, 2021).

Complementary and alternative medicines are used to reduce the side effects of cancer treatment (Cassileth et al, 2010; Tofthagen et al, 2013; Park & Park, 2015; Gholamzadeh et al, 2019). A variety of a complementary therapies, such as reflexology, have been tried to have a positive effects in management of CIPN. Reflexology is effective in improving muscle strength and tone, reducing migraine pain, chronic back pain, neck pain, muscle pain and advanced cancer pain, regression in sensory and urinary symptoms, relieving nausea-vomiting

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and decreasing the severity of chemotherapy -related side effects. In a limited number of studies conducted among patients undergoing chemotherapy, the effectiveness of reflexology was evaluated (Embong et al, 2015; Ben-Horin et al, 2017; Kurt & Can, 2018; Noh and Park, 2019). In a study highlighted that massage applied for six weeks to a esophageal adenocarcinoma patient treated with docetaxel and cisplatin reduced the numbness and tingling sensation caused by CIPN (Cunningham et al, 2011). Özdelikara and Tan's study demonstrated that reflexology application was an effective approach in reducing the symptom severity of patient with breast cancer undergoing chemotherapy (Özdelikara & Tan, 2017).

Reflexology is a non-invasive and beneficial intervention that includes simple techniques. This situation revealed the responsibilities of nurses to improve their knowledge and practices on the subject by evaluating patients' use of complementary therapy (Vardanjanı et al, 2013). CIPN influences the person not only psychologically but also physically and socially. Incorporating reflexology, a complementary and alternative practice, by nurses to manage symptoms may provide the quality of life and relief in patients. Furthermore, utilizing reflexology as a symptom treatment not only provides protection against drug side effects but can also be cost-effective (Gholamzadeh et al, 2019; Fritz & Fritz, 2020).

Research Hypothesis

H0: Reflexology is not an effective approach to reduce the symptoms of CIPN during taxane in breast cancer patients.

H1: Reflexology is an effective approach to reduce the symptoms of CIPN during taxane in breast cancer patients.

Methods

Setting and participants

This multicenter randomized trial was carried out in the chemotherapy outpatient clinic of Gülhane Training and Research Hospital and Ankara Training and Research Hospital's outpatient chemotherapy unit.

Sample Size

The size of the samples in this study was determined using the G*Power program (NCSS-PASS, https://www.ncss. com). Yükseltürk Şimşek and Demir (2021) reported a change in hands and the feet scores measured by Chemotherapy-induced peripheral neuropathy assessment tool in patients with breast cancer. Based on the difference in the Chemotherapy-Induced Peripheral Neuropathy Assessment Tool between the study groups in

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this study, the power (1-β) = 0.90 with type-1 error (α) = 0.05 the sample size was calculated as 58 people (Şimşek & Demir, 2022).

Randomization

Firstly the researcher evaluated the participants based on eligibility criteria. Then we conducted group assignments by computer-generated permuted block randomization using the link http://www.randomization.com. Participants were allocated in the control (n=29) and experimental (n=29) groups (Figure1).

Inclusion Criteria

Eligible women included the study were those who diagnosed with stage III breast cancer had already taken 4-7 cycles of taxane group chemotherapy regimen; consisted of weekly paclitaxel 80-140 mg/m2 administered intravenously per completion of the 12 weeks of chemotherapy; were describing the chemotherapy-induced neuropathy symptom with Chemotherapy-Induced Peripheral Neuropathy Assessment Tool, such as glove sock- style numbness, pinning, burning, felting; had not a nerve damage in history, psychiatric illness, a central nervous system metastasis or disease, irritation in the skin area, deep vein thrombosis history; and didn't using anticoagulant drugs.

Exclusion Criteria

Patients whose taxane treatment protocol was changed were excluded from the study.

Data Collection Tools

The sociodemographic data form and the CIPNAT assessment scale were used to collect research data.

Sociodemographic Data Form

The sociodemographic data form consisted of two parts (Vardanjani et al, 2013; Özdelikara & Tan, 2017; Yükseltürk Şimşek & Demir, 2018). In the first section of the questionnaire consisted of descriptive characteristics, in the second part, there were problems related to peripheral neuropathy during or after chemotherapy and questions about the relevant body region.

Chemotherapy-Induced Peripheral Neuropathy Assessment Tool –CIPNAT

The data collection scale used in this study was the Chemotherapy-Induced Peripheral Neuropathy Assessment Tool (CIPNAT) developed by Tofthagen et al. (2011). The scale consists of two sections. The first section consists of nine symptoms asking the frequency, severity and discomfort of the symptoms. The second part consists of 14 items that enable the evaluation of which neuropathy affects daily living activities. After each question answered as yes, the frequency, severity and discomfort of each symptom is scored and evaluated with a 0-

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10 numerical rating scale. The increase in the score on the scale indicates that the neuropathy associated with chemotherapy is high (Tofthagen et al, 2011).

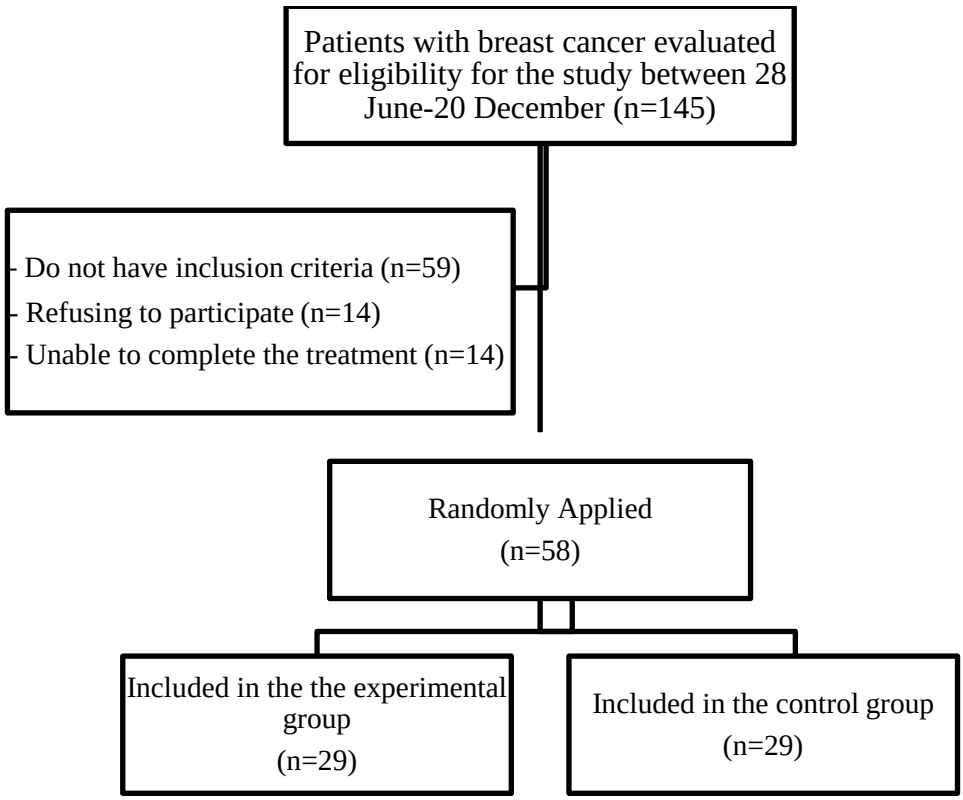

Figure 1: Flow chart of the research

The Turkish reliability and validity of this tool was done by Yükseltürk Şimşek & Demir (2018) with breast cancer patients (n = 430) who took taxanes. In the first section, questions about the motor and sensory problems experienced by the patients are replied. For each issue A (which of the following negativities did you experience last week?), Which is answered as "yes", questions B (how uncomfortable did you feel?), C (how sensually uncomfortable?) and D (how often did you feel?) are answered. Each item is scored between 0-10. Answers to questions; if 0, 1, 2 “very little”; if 8, 9, 10 is evaluated as “too much”. In the second section of the form, the troubles in the patients' daily life activities are scored between 0 and 10 and evaluated. The total Cronbach's alpa value of the scale was 0.87, and test-retest reliability of the CIPNAT was between 0.90-0.96 for all dimensions. These findings showed that the Turkish version of the CIPNAT was a reliable and valid instrument for identifying of chemotherapy-induced peripheral neuropathy (Yükseltürk Şimşek & Demir, 2018).

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Study Procedure

According to the chemotherapy protocol of both hospitals, patients were treated with taxane (80–140 mg/m²) infusion weekly for 12 dose. All patients received the same chemotherapy course at 7-day intervals. Reflexology application was started simultaneously with chemotherapy infusion.

According to 31 studies involving 4179 patients, the prevalence of CIPN increases to 68% at the first month, 60% after 3 months and up to 30% after 6 months (Seretny et al, 2014). Neuropathy symptoms as measured by CIPNAT using a patient questionnaire. After being provided with the necessary information about the study, the patients who took part in the research provided written informed consent. "Patient Introduction Form and CIPNAT" was administered by the researcher within 24 hours of coming to the Daytime Chemotherapy Unit for 4-7th cure chemotherapy treatment. The forms were filled out once a week, with a face-to-face interview technique for a total of six weeks. Researcher visited patient's home and filled forms with face-to face interview within the first 24 hours after CIPNAT reflexology application. None of the participants experienced unexpected side effects of reflexology during weekly taxane therapy. Patients in the control group received usual care of the clinic.

In order to learn the definition of reflexology, mechanism of action, indications and contraindications, therapeutic effects, application methods and application areas, the researcher was held at Biruni University on March 02-03, 2019 for a total of 16 hours of practice, four hours of theoretical and 12 hours of practice. She participated in the Foot Analysis Certificate Program and received a certificate.

Reflexology Intervention

The reflexology treatment was administered by a licensed massage therapist and commenced simultaneously with the chemotherapy infusion. The treatment was comprised of a total of six sessions, each lasting approximately 40 minutes, with 20 minutes dedicated to each foot. The reflex areas were manipulated using techniques such as scrubbing, patting, and pressure. To facilitate lubrication, olive oil was used to the patient's feet using bare hands. The procedure began with a 5-minute general massage of the feet, followed by finger manipulation of the reflex areas. The intensity of the massage pressure was gradually increased per patient tolerance. The researcher placed four fingers on the dorsal surface of the patient's feet, followed by applying effleurage to the sole of the foot and then to the back of the feet and toes. To stretch the toes, the fingers were grasped with one hand and bent slightly back and forth. Foot surface massage applied to each point on the thumb, soles and dorsum of the feet.

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The thumb, soles and dorsum of the feet were also gently massaged with the index finger. Afterwards, the inner edge of the foot was pressed all along (Figure 2). After the whole foot was massaged with the finger, the "solar plexus" area was pressed 8-10 times with the thumb of one hand (Vardanjanı et al, 2013; Soutar, 2016; Wyatt et al, 2017; Wyatt et al, 2021). The patient was given the opportunity to relax by wrapping their feet in a warm towel.

Figure 2: Reflexology

Ethical Aspect of the Research

Approval to conduct the study was received from the Ankara University Faculty of Medicine Clinical Research Ethics Committee (decision number 1-25-19) and the General Directorate of Health Services, Department of Traditional and Complementary Medicine Practices (decision number 77979112), and was authorized by the Ministry.

Data Analysis

Statistical analysis was performed using the software program Statistical Package for Social Sciences version 23.0 for Windows. The Shapiro-Wilk test was used to assess normal distribution. Descriptive statistics such as mean and standard deviation were used to analyze the data, while categorical variables were presented as numbers and percentages. The independent sample t-test was used to compare differences between the experimental and control groups. Repeated Measures Analysis of Variance (ANOVA) was utilized to compare variable differences among the groups. The chi-square test was used to examine associations among two independent categorical variables. We considered p value less than 0.05 to be significant.

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Results

Table 1 provides details concerning the sociodemographic and medical characteristics of the patients in both the experimental and control groups. The mean ages of the patients in the experimental and control group were 51.06 (28-77) and 51.48 (29-77) years old. Majority of the patients in both the groups had completed elementary school (Experimental=44.8%, Control=37.9%). More than of the patients (69%) in the experimental and 51.7% in the control group recieved a taxane chemotherapy dose of 80–120 mg. It was observed that 89.7% of the patients in experimental group didn't receive radiotherapy. It was found that 55.2% of the patients in experimental hadn't surgery. In addition, 82.8% of the patients did not recieve radiotherapy and 55.2% hadn't surgery in control group. There were no statistical differences in the sociodemographic and medical characteristics between the two groups ($p>0.05$).

Table 1: Sociodemographic and medical characteristics (n=58)

Characteristics	**Experimental (n=29)**		**Control (n=29)**		**Test value* and Significance**
	n	**%**	**n**	**%**	
Age (years)					
25-39	5	17.2	6	20.7	χ^2=0.75
40-54	11	37.9	13	44.8	p=0.691
55-↑	13	44.8	10	34.5	
Education					
Elementary school	13	44.8	11	37.9	χ^2=0.85
High school	11	37.9	1	3.4	p=0.324
University	5	17.3	17	58.6	
Time Since Diagnosis*					
0-6 months	6	20.6	7	24.2	
7-12 months	19	65.6	14	48.2	χ^2=3.13 p=0.214
13 months and more	4	13.8	8	27.6	
Chronic disease (Diabetes, Hypertension, Heart failure)					
Yes	11	37.9	10	34.5	χ^2=0.08
No	18	62.1	19	65.5	p=0.501
Taxane regimen					
80-120 mg	20	69	15	51.7	χ^2=0.67
≥121 mg	9	31	14	48.3	p=0.29
Radiotherapy					
Yes	3	10.3	5	17.2	χ^2=0.58
No	26	89.7	24	82.8	p=0.353
Operation					
Yes	13	44.8	13	44.8	χ^2=0.001
No	16	55.2	16	55.2	p=0.602

* Chi-square test

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Patients' Information on Disease Variables

Table 2 presents information on the disease variables and symptom status of patients in both the experimental and control groups. It was found that 93.1% of patients in the experimental group and 79.3% of patients in the control group described the sensation of tingling the most. Also, 62.1% of patients in the experimental group and 37.9% of patients in the control group stated that the symptoms of neuropathy manifested in the toes. In addition, 20.7% of patients in the experimental group and 10.3% of patients in the control group reported symptoms of neuropathy in their hands. There wasn't any significant difference in disease variables and symptom status ($p>0.05$).

Table 2: Disease variables and symptom status of patients

Disease Variable	**Experimental (n=29)**		**Control (n=29)**		**Test value* and Significance**
	n	**%**	**n**	**%**	
Neuropathy-Related Problems **					
Tingle	27	93.1	23	79.3	χ^2=2.3 p=0.132
Numbness	23	79.3	10	34.5	χ^2=1.4 p=0.204
Cold sensitivity	14	48.3	12	41.4	χ^2=0.62 p=0.301
Burning	10	34.4	19	65.5	χ^2=0.00 p=0.612
Weakness	9	31.1	8	27.6	χ^2=0.08 p=0.502
Pain	9	31.1	12	41.4	χ^2=0.67 p=0.294
Loss of balance	3	10.3	2	6.9	χ^2=0.22 p=0.504
Dizziness	2	6.9	1	3.4	χ^2=0.35 p=0.503
Neuropathy-Related Problem Area **					
Toes	18	62.1	11	37.9	χ^2=0.34 p=0.061
Foot	13	44.8	5	17.2	χ^2=0.62 p=0.302
Hand	6	20.7	3	10.3	χ^2=1.2 P=0.243
Arm	2	6.9	2	6.9	χ^2=0.001 P=0.692
Leg	1	3.4	2	6.9	χ^2= 0.35 P=0.501

* Chi-square test ** Multiple answers were given to the question and the percentages were evaluated on "n"

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Comparison of Experimental and Control Groups' CIPNAT Item Score Averages

Table 3 presents a comparison of the average CIPNAT item scores between patients in the experimental and control groups. It was observed that the mean scores of numbness, tingling, discomfort, sensitivity to cold, and muscle or joint pain in the fingers and toes of the patients in the intervention group decreased statistically significantly in the last week compared to the mean item score of the baseline ($p<0.05$). When we look at the impact on daily activities; patients in intervention and control groups, dressing, picking up objects, holding onto objects and sexual activity were not found to be significant between beginning and the other weeks ($p>0.05$). However, while the mean "sleeping" score for patients in the intervention group was 4.41 initially, it dropped to 3.72 at week 6, and the difference was statistically significant ($p<0.05$). When the mean CIPNAT scores between groups were observed, only the average scores of "discomfort in the fingers/hand or toes/foot" were found to be significant($p<0.05$). When the effects on daily life activities were examined between the groups, the mean scores for "sleeping" and "relationships with other people" were found to be statistically significant $p<0.05$).

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Table 3. Comparison of Intervention and Control Groups' CIPNAT Item Score Averages

CIPNAT		Beginning x̄±SS	First week x̄±SS	Second week x̄±SS	Third week x̄±SS	Fourth week x̄±SS	Fifth week x̄±SS	Sixth week x̄±SS	Analysis**
Numbness in the hand	Intervention	0.51±1.35	0.51±1.35	0.51±1.35	0.51±1.35	0.51±1.35	0.55±1.45	0.55±1.45	F=0.21 p=0.672
	Control	0.24±0.91	0.24±0.91	0.24±0.91	0.37±1.20	0.58±1.40	0.65±1.56	0.65±1.56	F=4.17 p=0.041
	Between Groups t* p	t=-0.91 p=0.67	t=-0.91 p=0.367	t=-0.91 p=0.367	t=-0.41 p=0.684	t=0.19 p=0.850	t=0.26 p=0.795	t=0.26 p=0.795	
Numbness in the foot	Intervention	3.75±2.04	3.75±2.04	3.75±1.99	3.72±1.96	3.68±1.96	3.65±1.96	3.51±1.88	F=2,33 p=0.089
	Control	3.06±1.88	3.06±1.88	3.10±1.89	3.24±1.99	3.34±2.02	3.48±2.16	3.51±2.18	F=8.09 p=0.002
	Between Groups t* p	t=-1.33 p=0.188	t=-1.33 p=0.188	t=-1.28 p=0.205	t=-0.92 p=0.357	t=-0.65 p=0.513	t=-0.31 p=0.752	t=0.001 p=1.0001	
Tingling in the hand	Intervention	0.72±1.50	0.58±1.15	0.58±1.15	0.55±1.12	0.72±1.50	0.68±1.36	0.68±1.36	F=1.07 p=0.321
	Control	0.65±1.26	0.65±1.26	0.65±1.26	0.82±1.53	0.89±1.54	1.06±1.81	1.10±1.85	F=6.17 p=0.008
	Between Groups t* p	t=-0.19 p=0.851	t=0.21 p=0.829	t=0.21 p=0.829	t=0.78 p=0.438	t=0.21 p=0.669	t=0.90 p=0.372	t=0.96 p=0.338	
Tingling in the foot	Intervention	4.51±1.24	4.51±1.24	4.48±11.8	4.37±1.08	4.41±1.15	4.31±1.07	4.27±1.09	F=1.15 p=0.322
	Control	3.93±0.52	3.89±0.55	3.96±05.6	4.20±0.72	4.44±0.68	4.62±07.2	4.65±0.76	F=19.45 p=0.0001
	Between Groups t* p	t=-2.33 p=0.053	t=-2.33 p=0.053	t=-2.12 p=0.380	t=-0.71 p=0.479	t=0.14 p=0.890	t=1.29 p=0.203	t=-1.52 p=0.133	
Discomfort	Intervention	4.68±1.00	4.72±0.95	4.65±0.81	4.62±0.77	4.55±0.82	4.20±0.90	4.20±0.90	F=5.34 p=0.008
	Control	3.93±0.65	3.96±0.62	4.13±0.69	4.41±0.82	4.68±0.80	4.79±0.90	4.96±0.77	F=26.02 p=0.0001
	Between Groups t* p	t=-3.41 p=0.001	t=-3.56 p=0.001	t=-2.60 p=0.012	t=-0.98 p=0.029	t=-0.64 p=0.023	t=2.47 p=0.016	t=3.43 p=0.001	

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Table 3. (Continue) Comparison of Intervention and Control Groups' CIPNAT Item Score Averages

Cold sensitivity	**Intervention**	**2.48±2.27**	**2.48±2.27**	**2.41±2.30**	**2.37±2.27**	**2.31±2.28**	**2.17±2.15**	**2.13±2.16**	**F=4.23 p=0.021**
	Control	1.44±1.90	1.48±1.95	1.58±1.95	1.72±2.16	1.79±2.24	1.89±2.38	2.03±2.39	F=5.42 p=0.008
	Between Groups t*	t=-1.87	t=-1.79	t=-1.47	t=-1.12	t=-0.87	t=-0.46	t=-0.17	
	p	p=0.066	p=0.078	p=0.146	p=0.266	p=0.388	p=0.645	p=0.864	
Pain	Intervention	3.17±2.30	3.34±2.25	3.31±2.18	3.24±2.14	3.17±2.05	2.93±1.92	2.86±1.86	F=4.22 p=0.012
	Control	3.13±1.76	3.20±1.82	3.24±1.82	3.68±1.87	3.96±16.3	4.20±1.52	4.31±1.56	F=18.19 p=0.004
	Between Groups t*	t=-0.06	t=-0.25	t=-0.13	t=0.84	t=1.62	t=2.80	t=3.20	
	p	p=0.949	p=0.799	p=0.897	p=0.401	p=0.109	p=0.007	p=0.002	
Weakness	Intervention	2.27±2.10	2.37±2.06	2.37±2.04	2.17±1.89	2.10±1.85	2.03±1.82	1.93±1.73	F=6.02 p=0.003
	Control	2.27±2.18	2.27±2.18	2.34±2.20	2.31±2.18	2.44±2.16	2.44±2.16	2.58±2.13	F=1.64 p=0.203
	Between Groups t*	t=0.001	t=-0.18	t=-0.06	t=0.25	t=0.65	t=0.78	t=-1.28	
	p	p=1.0001	p=0.854	p=0.951	p=0.798	p=0.518	p=0.434	p=0.204	
Loss of balance	Intervention	0.20±0.77	0.20±0.77	0.20±0.77	0.20±0.77	0.20±0.77	0.20±0.77	0.20±0.77	F=2.07 p=1
	Control	0.06±0.37	0.06±0.37	0.06±0.37	0.06±0.37	0.06±0.37	0.06±0.37	0.10±0.55	F=1 p=0.331
	Between Groups t*	t=-0.86	t=-0.86	t=-0.86	t=-0.86	t=-0.86	t=-0.86	t=0.24	
	p	p=0.390	p=0.390	p=0.390	p=0.390	p=0.390	p=0.390	p=0.561	
Effect On Daily Life Activities									
Dressing	Intervention	0.68±1.44	0.68±1.44	0.62±1.34	0.62±1.34	0.58±1.29	0.58±1.29	0.58±1.29	F=2.49 p=0.111
	Control	0.55±1.12	0.55±1.12	0.58±1.18	0.62±1.26	0.62±1.26	0.62±1.26	0.68±1.39	F=1.34 p=0.277
	Between Groups t*	t=-0.40	t=-0.40	t=-0.10	t=0.001	t=0.10	t=0.10	t=0.29	
	p	p=0.686	p=0.686	p=0.918	p=1.0001	p=0.919	p=0.919	p=0.771	
Walking	Intervention	1.65±1.98	1.75±1.97	1.75±1.97	1.79±1.89	1.79±1.91	1.72±1.88	1.68±1.83	F=0.51 p=0.611
	Control	0.93±1.46	0.93±1.46	1.06±1.57	1.20±1.80	1.20±1.80	1.27±1.86	1.37±1.87	F=4.61 p=0.012
	Between Groups t*	t=-1.58	t=-1.81	t=-1.46	t=-1.20	t=-1.20	t=-0.90	t=-0.63	
	p	p=0.120	p=0.075	p=0.148	p=0.232	p=0.235	p=0.367	p=0.527	

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Table 3. (Continue) Comparison of Intervention and Control Groups' CIPNAT Item Score Averages

Picking up objects	Intervention	0.58±1.21	0.68±1.28	0.65±1.23	0.65±1.23	0.62±1.17	0.55±1.15	0.55±1.15	F=0.89 p=0.423
	Control	0.31±0.92	0.31±0.92	0.31±0.92	0.31±0.92	0.31±0,92	0.31±0.92	0.31±0.92	F=0.72 p=1
	Between Groups t*	t=-0.97	t=-1.28	t=-1.20	t=-1.20	t=-1.11	t =-0.87	t=-0.87	
	Between Groups p	p=0.335	p=0.203	p=0.234	p=0.234	p=0.270	p=0.384	p=0.384	
Holding onto objects	Intervention	0.86±1.59	0.86±1.59	0.93±1.60	0.89±1.54	0.86±1.50	0.86±1.50	0.86±1.50	F=0.39 p=0.601
	Control	0.44±1.15	0.44±1.15	0.44±1.15	0.51±1.35	0.51±1.35	0.58±1.52	0.58±1.52	F=2.07 p=0.152
	Between Groups t*	t=-1.13	t=-1.13	t=-1.31	t=-0.99	t=-0.91	t=-0.69	t=-0.69	
	Between Groups p	p=0.263	p=0.263	p=0.193	p=0.324	p=0.363	p=0.491	p=0.491	
Driving	Intervention	3.41±2.17	3.44±2.18	3.41±2.04	3.41±1.80	3.55±1.84	3.51±1.84	3.48±1.82	F=0.31 p=0.65
	Control	1.82±1.83	1.82±1.83	2.34±1.85	2.89±1.79	3.27±1.70	3.48±1.84	3.58±1.89	F=21.92 p=0.0001
	Between Groups t*	t=-2.99	t=-3.06	t=-2.08	t =-1.09	t=-0.59	t=-0.07	t=-0.21	
	Between Groups p	p=0.054	p=0.053	p=0.042	p=0.279	p=0.557	p=0.943	p=0.833	
Working	Intervention	2.41±2.17	2.44±2.19	2.65±2.09	2.72±1.98	2.89±1.83	2.82±1.77	2.79±1.73	F=2.03 p=0.155
	Control	1.89±1.95	1.96±1.89	2.17±1.94	2.48±2.08	2.79±2.04	3.06±2.10	3.10±2.09	F=13.49 p=0.0001
	Between Groups t*	t=-0.95	t=-0.89	t=-0.91	t=-0.45	t=-0.20	t=0.47	t=0.61	
	Between Groups p	p=0.345	p=0.375	p=0.367	p=0.653	p=0.840	p=0.638	p=0.542	
Participating in hobbies or leisure activities	Intervention	3.20±2.12	3.24±2.13	3.34±2.04	3.34±1.89	3.48±1.90	3.44±1.88	3.34±1.87	F=1.06 p=0.35
	Control	2.58±1.78	2.79±1.65	3.34±1.44	3.58±1.37	3.93±1.38	4.24±1.40	4.41±1.11	F=26.44 p=0.0001
	Between Groups t*	t=-1.20	t=-0.89	t=0.001	t=0.55	t=1.02	t=1.81	t=2.63	
	Between Groups p	p=0.234	p=0.375	p=1.0001	p=0.581	p=0.309	p=0.074	p=0.011	
Exercising	Intervention	3.96±1.70	3.93±1.68	3.96±1.67	3.93±1.62	4.27±1.25	4.34±1.23	4.34±1.23	F=3.4 p=0.074
	Control	2.93±1.79	3.03±1.74	3.37±1.61	3.68±1.56	4.03±1.42	4.24±1.40	4.34±1.39	F=18.65 p=0.0001
	Between Groups t*	t=-2.25	t=-1.99	t=-1.35	t=-0.57	t=-0.68	t=-0.29	t=0.001	
	Between Groups p	p=0.028	p=0.051	p=0.181	p=0.566	p=0.496	p=0.767	p=1.0001	

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Table 3. (Continue) Comparison of Intervention and Control Groups' CIPNAT Item Score Averages

Sleeping	Intervention	4.41±1.80	4.44±1.82	4.34±1.69	4.13±1.61	4.03±1.63	3.82±1.64	3.72±1.66	F=9.01 p=0.0001
	Control	3.27±1.84	3.27±1.84	3.58±1.65	4.03±1.37	4.44±1.12	4.82±0.65	4.89±0.61	F=19.85 p=0.0001
	Between Groups t*	t=-2.37	t=-2.43	t=-1.72	t=-0.26	t=1.12	t=3.03	t=3.55	
	Between Groups p	p=0.021	p=0.018	p=0.001	p=0.004	p=0.046	p=0.004	p=0.001	
Sexual activity	Intervention	0.96±1.49	0.96±1.49	0.96±1.49	0.93±1.46	0.93±1.46	0.93±1.46	0.82±1.41	F=1.29 p=0.272
	Control	0.75±1.40	0.75±1.40	0.86±1.45	0.96±1.67	1.06±1.70	1.06±1.70	1.06±1.70	F=2.89 p=0.074
	Between Groups t*	t=-0.54	t=-0.54	t=-0.26	t=-0.08	t=0.33	t=0.33	t=0.58	
	Between Groups p	p=0.590	p=0.590	p=0.791	p=0.934	p=0.743	p=0.743	p=0.561	
Relationships with other people	Intervention	1.17±1.69	1.17±1.69	1.17±1.69	1.17±1.69	1.17±1.69	1.17±1.69	1.10±1.61	F=1 p=0.332
	Control	0.41±1.08	0.41±1.08	0.41±1.08	0.41±1.08	0.41±1.08	0.41±1.08	1.17±1.69	F=7.16 p=0.012
	Between Groups t*	t=-2.03	t=-2.03	t=-2.03	t=-2.03	t=-2.03	t=-2.03	t=0.59	
	Between Groups p	p=0.047	p=0.047	p=0.047	p=0.047	p=0.047	p=0.047	p=0.874	
Writing	Intervention	0.37±1.17	0.37±1.17	0.37±1.17	0.37±1.17	0.37±1.17	0.37±1.17	0.37±1.17	F=0 p=1
	Control	0.20±0.81	0.20±0.81	0.20±0.81	0.20±0.81	0.20±0.81	0.20±0.81	0.65±1.34	F=4.39 p=0.045
	Between Groups t*	t=-0.64	t=-0.64	t=-0.64	t=-0.64	t=-0.64	t=-0.64	t=0.83	
	Between Groups p	p=0.520	p=0.520	p=0.520	p=0.520	p=0.520	p=0.520	p=0.409	
Usual household chores	Intervention	3.72±2.03	3.75±2.02	3.86±1.90	3.82±1.85	4.06±1.53	4.06±1.53	4.06±1.53	F=1.87 p=0.182
	Control	2.48±2.14	2.55±2.09	3.03±1.97	3.13±1.86	3.48±1.84	3.62±1.87	3.79±1.93	F=12.12 p=0.0001
	Between Groups t*	t=-2.26	t=-2.22	t=-1.62	t=-1.41	t=-1.31	t=-0.99	t=-0.60	
	Between Groups p	p=0.028	p=0.030	p=0.110	p=0.163	p=0.194	p=0.324	p=0.550	
Enjoyment of life	Intervention	4.03±1.84	4.10±1.79	4.06±1.77	3.96±1.61	4.06±1.43	4.03±1.37	3.96±1.40	F=0.19 p=0.762
	Control	3.55±1.55	3.50±1.73	3.65±1.75	3.89±1.69	4.41±1.35	4.79±1.29	4.86±1.30	F=17.60 p=0.0001
	Between Groups t*	t=-1.04	t=-1.28	t=-0.89	t=-0.15	t=0.94	t=2.16	t=2.52	
	Between Groups p	p=0.299	p=0.203	p=0.376	p=0.875	p=0.350	p=0.035	p=0.014	

* Independent sample t-test, ** Repeated Measures ANOVA

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Discussion

This randomized controlled trial aims to determine the effect of six sessions of reflexology on peripheral neuropathy in breast cancer patients taking taxane infusion 80–140 mg/m2 in outpatient chemotherapy units. This study reported that while the mean scores of numbness in the finger or hand and itchy-burning neuropathy did not change in the experimental group, it was reported that the mean scores of numbness in the toes, feeling of discomfort and sensitivity to cold, and weakness decreased. In the control group, numbness, burning, itching and finger discomfort, cold intolerance, muscle and joint pain were observed to increase. In addition, these symptoms were found to affect the daily activities of the participants in the control group, such as walking, driving, working, participating in activities they like, playing sports, sleeping, communicating, writing, participating in ordinary housework and enjoying life. According to the results of this study, the hypothesis "Reflexology is an effective approach to reduce the symptoms of CIPN during taxane in breast cancer patients" was accepted and the hypothesis "Reflexology is not an effective approach to reduce the symptoms of CIPN during taxane in breast cancer patients" was rejected. This study demonstrated that reflexology was effective in reducing CIPN-related symptoms.

CIPN is a potentially dose-limiting side effect caused by anticancer drugs, including taxane and platinum. The neuropathy that develops is often dose-dependent and affects the nerves in the distal and proximal parts of the extremities (Salehifar et al, 2020; Salgado et al, 2020; Tofthagen et al, 2020). Peripheral neuropathy symptoms are predominantly sensory, like burning, numbness and tingling. Sometimes there are motor symptoms like weakness and autonomic neuropathy like dizziness (Starobova et al, 2017; Salgado et al, 2020). Timmins et al. (2020) studied patients who took taxanes, it was reported that patients frequently experienced numbness (82%) and tingling (64%) in their fingers or toes. In another study by Pachman et al. (2016), it was shown that patients experienced similar neuropathy symptoms in their hands and feet while receiving taxane therapy. Similar to the literature, our study found that the most common neuropathy symptoms were tingling (93.1%), burning (34.4%), numbness (79.3%), increased sensitivity to cold (48.3%), pain (31.1%) and weakness (31.1%) in experimental group. Additionally, the symptoms of chemotherapy-induced neuropathy were found to be mainly in the toes (62.1%), feet (44.8%) and hands (20.7%).

Although these symptoms may seem minor at first, they gradually increase with continued chemotherapy and affect the patient's daily living activities. In addition to

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pharmacological methods, non- pharmacological approaches are also being used to control symptoms in breast cancer patients. One of the non-pharmacological methods that has a positive effect on the symptoms developing in cancer patients is reflexology (Noh & Park, 2019). Effect of foot reflexology on peripheral neuropathy; it is explained by the stimulation of large nerve fibers, suppression of pain perception and suppression of the sympathetic nervous system (Noh & Park, 2019; Mackey, 2001).

There are very few reports focusing on cancer patients among studies on the effect of reflexology for treatment of peripheral neuropathy (Se Young et al, 2012; Ben-Horin et al, 2017; Noh and Park, 2019). Noh & Park (2019) reported that the peripheral neuropathy symptoms of the participants in the experimental group decreased after the application, while the neuropathy symptoms of the patients in the control group increased by an average of 0.30 ± 0.40 points. Ben-Horin et al. (2017) studied that the effect of reflexology and acupuncture on the alleviation of CIPN in breast cancer patients received average cumulative dose 1407 mg taxane, a total of 26 patients (93%) reported conclude improvement in CIPN findings. In the study, only two (10%) of 20 patients with stage I-II neuropathy stated that their symptoms were still continuing at 12 months. After applying a total of 16 massages to colorectal cancer patients taking oxaliplatin, Arikan (2014) assessed the symptoms experienced by patients using the American National Cancer Institute's Neurotoxicity Scale (NIC CTC, version 2.0). As a result of the study, it was found that neuropathic symptoms and complaints, such as pain, insomnia and fatigue, decreased in patients (Arıkan, 2014). Lee et al. (2012) evaluated the effect of foot reflexology on peripheral neuropathy and its effect on quality of life, and it was shown that the reflexology group experienced less neuropathy symptoms. In a randomized study with a diabetic patient group it was found that foot reflexology had a positive impact on symptoms of diabetic neuropathy (Çiçek et al; 2021). İbrahim and Rizk concluded that reflexology intervention lowered pain levels (İbrahim & Rizk, 2018). Considering the development of peripheral neuropathy in the experimental and control groups in our study; while there was no significant difference between groups in the initial and other weeks of patients in the intervention group, a statistically significant difference was found in the control group compared to weeks. In addition, while there was no difference between the average daily living activity scores of patients in the intervention group, it was determined that in patients in the control group, they increased from the initial measurement and they were negatively affected.

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Contrary to existing studies, Kurt & Can (2018) indicated that there was no statistically significant difference with control and experimental groups. Another finding of this study was that the sensory functions in the patients of the experimental group who underwent foot reflexology were higher. Contradictory results of the present study can be due to different sample size, different sessions of reflexology and individual differencesin response to the intervention and its impact. On the other hand, there may be differences in the practice of reflexology technique between researchers, which can affect the results.

Limitations of the Study

Firstly, this study only applied to women with breast cancer who received taxane, the results of the study cannot be generalized to other patients receiving neurotoxic chemotherapy. Secondly, we only had access to patient-reported measures of CIPN symptoms. Thirdly, lack of blinding in this study constituted the limitation of the study.

Conclusions

Consequently, based on our study findings, the Comparison of Intervention and Control Groups' CIPNAT Item Score Averages outcomes supported our H1 hypothesis that reflexology has positive effects on the prevention of CIPN. Non-pharmacological treatments are known to be effective in managing symptoms in patients with chronic illnesses; however, further research is needed to evaluate the efficacy of foot massage.

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Conflict of interest

We have no conflict of interest related to this work.

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