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Prevention of chemotherapy-induced peripheral neuropathy with classical massage in breast cancer patients receiving paclitaxel: An assessor-blinded randomized controlled trial

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ABSTRACT

Purpose: This assessor-blinded, prospective, randomized controlled clinical trial aimed at investigating the effect of classical massage on chemotherapy induced peripheral neuropathy and the quality of life (QOL) in breast cancer patients receiving adjuvant paclitaxel.

Methods: A total of 40 female breast cancer patients were randomly allocated to the classical massage group (CMG) or the control group (CG). Classical massage was applied to the patients in the CMG before each paclitaxel infusion. The CG received only usual care. Presence of peripheral neuropathic pain and QOL were assessed at baseline and weeks 4, 8, 12, and 16. Nerve conduction studies (NCS) findings were also recorded at baseline and week 12.

Results: The peripheral neuropathic pain was lower in the CMG compared to the CG at week 12 ($p < 0.05$). The sensory and motor sub-scale scores of the QOL measure showed statistically significant differences over time in favor of the CMG ($p < 0.05$). Sensory action potential amplitude of the median nerve was significantly higher and the tibial nerve latency was significantly shorter in the CMG compared to the CG at week 12.

Conclusions: This study suggested that classical massage successfully prevented chemotherapy-induced peripheral neuropathic pain, improved the QOL, and showed beneficial effects on the NCS findings.

1. Introduction

Taxanes (paclitaxel and docetaxel) are among the widely-accepted adjuvant antineoplastic agents which increase the likelihood of cure and improve the disease-free survival in breast cancer patients (Gandhi et al., 2014). However, patients may experience numerous side effects, including myelosuppression, myalgia, arthralgia, hypersensitivity reactions, and chemotherapy-induced peripheral neuropathy (CIPN) (Ho and Mackey, 2014; Tao et al., 2015). CIPN is one of the most common and dose-limiting toxicities related to paclitaxel. Approximately 32%–98% of the breast cancer patients receiving paclitaxel suffer from CIPN (Song et al., 2017; Tanabe et al., 2013). Paclitaxel-related CIPN is generally dose-dependent, and the symptoms often start in toes and fingers and then spread proximally in a “glove and stock” distribution (Ferrier et al., 2013). Paclitaxel-related CIPN is a predominantly sensory axonal neuropathy, represented by sensory alterations such as paresthesia, numbness, tingling, burning sensation, and peripheral neuropathic pain. Additionally, patients may experience motor weakness, and autonomic dysfunction due to CIPN. The symptoms of CIPN may ultimately lead to debilitating limitations in the routine daily living activities such as cooking, walking, driving, dressing, writing, and leisure activities (Bakitas, 2007; Reyes-Gibby et al., 2009; Tofthagen, 2010). With the progression of CIPN, patients may have problems with balance, concerns on repeated falls, experience limitations in mobility, household activities, familial and social roles, suffer from sleep disturbances and fatigue, and show low performance at work leading to gradual deterioration in health-related quality of life (QOL) (Bakitas, 2007; Shimozuma et al., 2012).

Considering the negative impact of CIPN on the QOL of breast cancer patients, prevention and/or alleviation of CIPN becomes essential. Unfortunately, there is presently no existing pharmacological approach that can completely prevent or cure CIPN. Once a patient suffers from CIPN, pharmacological agents such as tricyclic antidepressants, anticonvulsants, analgesics, and topical gels are prescribed to alleviate

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CIPN symptoms. However, the evidence of the efficacy of these agents is controversial, and treatment of CIPN is still largely symptomatic (Wolf et al., 2008). Therefore, breast cancer patients struggle with the management of CIPN, and 60% of the those receiving taxanes seek additional supportive and complementary strategies (Brami et al., 2016; Brunelli and Gorson, 2004). These strategies such as meditation, yoga, reiki, physical exercise, foot soak, acupuncture, aromatherapy, reflexology and massage therapy can relieve CIPN symptoms and may improve physical and emotional well-being when integrated into mainstream conventional therapies (Kurt and Can, 2018; Park and Park, 2015; Shiqianga et al., 2017; Speck et al., 2012).

Massage is one of the most commonly used touch-based therapy for holistic treatment of patients. While various forms of massage have been existing in the literature, classical massage (Swedish massage) is one of the most prominent among other massage therapies that affects regulation of muscles, joints, tendons and ligaments in the body by manipulation of soft tissues with effleurage, petrissage, friction and tapotement techniques (Collinge et al., 2012; Kashani and Kashani, 2014). Besides, classical massage is an easily applicable, cost-effective, safe and well-tolerated intervention in cancer patients. Hence, it is widely recommended by professionals for prevention and palliation of cancer symptoms including pain, fatigue, nausea, anxiety, depression, sleep quality and well-being (Alves et al., 2017; Collinge et al., 2012, National Comprehensive Cancer Network, 2019). Additionally, few reports indicated that classical massage has also promising effects on prevention and relief of CIPN (Coskun et al., 2014; Cunningham et al., 2011). A case report has highlighted that performing classical massage for six weeks in a patient suffering from CIPN associated with docetaxel and cisplatin reduced the severity of pain and the sensation of numbness and tingling (Cunningham et al., 2011). A recent experiment investigating the effects of classical massage on CIPN and QOL in patients with colorectal cancer receiving oxaliplatin also indicated that the rate of peripheral neuropathic pain was significantly lower, and QOL scores were significantly higher in the massage group (Coskun et al., 2014). However, no clinical study has investigated the effects of classical massage on CIPN and QOL in breast cancer patients receiving adjuvant paclitaxel. Moreover, both the aforementioned studies used only subjective measurements based on patient-reported scales for CIPN and did not employ an objective measure such as nerve conduction studies (NCS). Bearing this in mind, this randomized controlled trial aimed at examining the effect of classical massage in breast cancer patients receiving adjuvant paclitaxel using NCS combined with patient-reported outcomes, in order to assess CIPN. The study hypothesized that classical massage as a supportive therapy initiated with the first cycle of paclitaxel regimen would prevent chemotherapy-induced peripheral neuropathic pain and improve QOL in patients with breast cancer.

2. Material and methods

2.1. Study design and setting

This prospective, assessor-blinded, randomized controlled trial was conducted in the chemotherapy outpatient clinic of Health Sciences University Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital located in Turkey. All patients received adjuvant paclitaxel infusion in the oncology outpatient clinic once a week, totally 12 weeks between 10:00–11.00 a.m. All patients were scheduled to receive the first cycle of adjuvant paclitaxel regimen taught on side effects and food-drug interactions of this regimen only a single time by a specialized trained nurse as per usual care in the hospital. Participants in the intervention group were required to come to a special patient room with a thermostatically controlled temperature (20–22 °C) to receive classical massage sessions before paclitaxel infusion at 09.00–09.30 a.m. on the days of chemotherapy once a week. Participants in the intervention group continued to receive classical massage sessions once a week, totally 12 sessions concurrent with adjuvant paclitaxel regimen. The massage session was finalized on the last day of adjuvant paclitaxel infusion (at week 12). Participants in the control group did not receive any intervention except for usual care. No intervention was applied to neither the intervention nor the control group after the completion of adjuvant paclitaxel other than usual care (week 12) until the follow-up assessment (week 16). The follow-up assessment was performed only a single time at week 16 (four weeks after the last adjuvant paclitaxel infusion). The 2017 CONSORT Statement for Randomized Trials of Non-Pharmacological Treatments was used as a guide to report the study.

2.2. Sample size

Power analysis and sample size (NCSS-PASS, https://www.ncss.com/) software were used to calculate the required sample size for this study. Kutner et al. (2008) reported a change of 1.8 points in pain scores assessed by Brief Pain Inventory, and Smith et al. (2002) specified that a decrease in 2.2 points in pain score measured by Numerical Rating Scale in patients with cancer. Based on the mean difference as 2.2 points in the Self-Leeds Assessment of Neuropathic Symptoms and Sign (S-LANSS) between the study groups in this study, with two-sided α of 5%, statistical power of 80% and an anticipated dropout rate of 10%, at least 18 patients would be required for each group.

2.3. Randomization, allocation and blinding

Potential participants were listed every week by the patient consultant and reported to the researchers. The principal investigator (PI) assessed the patients in terms of eligibility criteria and explained the study protocol. A total of 63 patients were screened for eligibility from June 2017 to June 2018. A total of 23 participants were excluded due to not meeting inclusion criteria (n = 21), and declining to participate to the study (n = 2). After obtaining their informed consent, remaining 40 participants were divided randomly into two groups (Group A:19 and Group B:21) using a random number table generated by the software MS Excel (version 2013) by the 2nd co-author who not involved in intervention procedures (Fig. 1). The 2nd co-author coded study groups as Group A: classical massage, and Group B: control, informed the patients about the randomization results and asked them to not inform, the data collector (3rd co-author), the neurologist (5th co-author), and other patients in the study about their group allocation. All massage sessions were performed by the PI who was not blinded to the study groups due to the nature of classical massage application (Walton, 2010). Patient reported outcomes were collected by the 3rd co-author, NCS was performed and interpreted by the 5th co-author who were blinded to the study groups. Data were also analyzed by an independent statistician. Hence, the current study was performed as an assessor blinded randomized controlled trial.

2.4. Eligibility criteria and study sample

Eligible female patients with breast cancer included those who (a) were ≥18 years old; (b) had no documented history of CIPN; (c) had already received four cycle of Adriamycin and Cyclophosphamide (AC) regimen; (d) were scheduled to receive 80 mg/m^2 dose of adjuvant paclitaxel once a week for 12 weeks; (e) were receiving the first cycle of adjuvant paclitaxel. Exclusion criteria were (a) history of severe psychiatric disorder; (b) history of peripheral neuropathy due to previous neurotoxic chemotherapy; (c) had co-morbid conditions including diabetes mellitus, autoimmune disease, megaloblastic anemia, carpal tunnel syndrome, cervical/lumbar disc hernias; (d) had active lesions on hands or feet and so on; (e) had bleeding or coagulation disorders.

2.5. Classical massage procedure

1. The PI, who was qualified and experienced in massage therapy

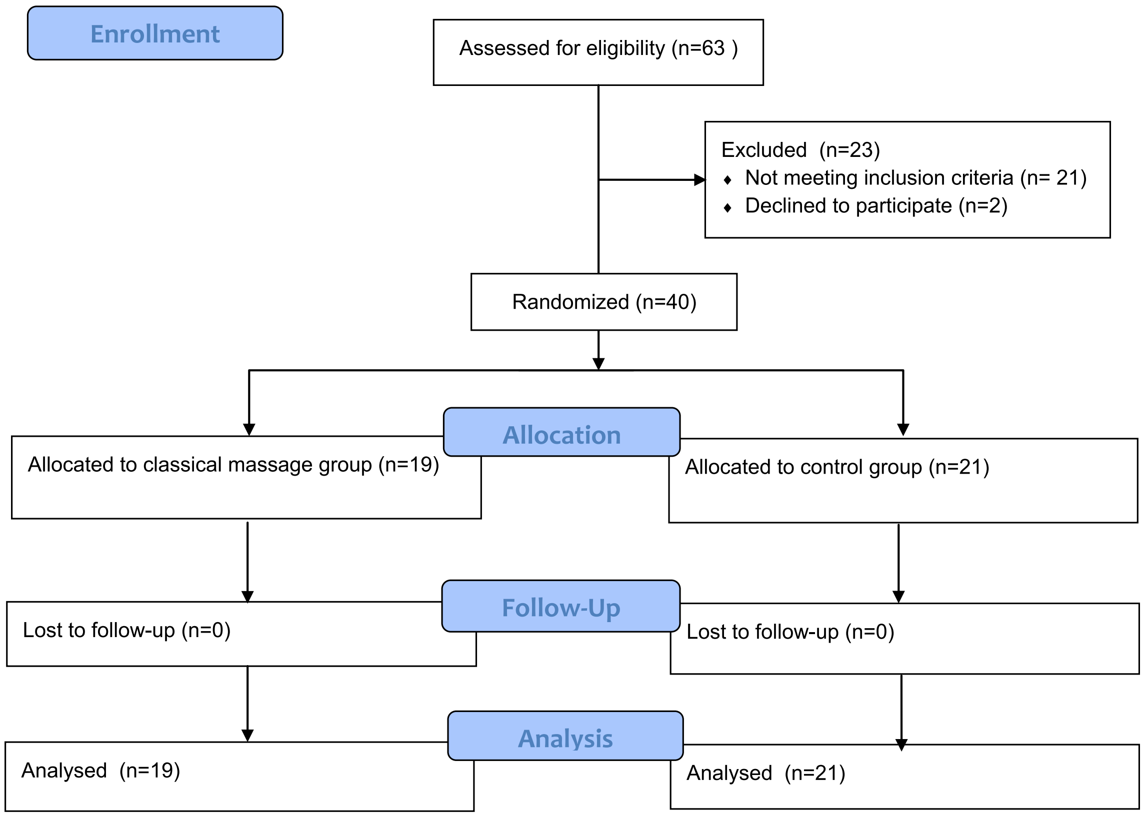

Fig. 1. Flow chart of study protocol.

performed all the massage sessions. Each participant received classical massage for 30 min in each session; 20 min for the feet, and 10 min for the hands on the days of chemotherapy cycles before paclitaxel infusion in the special patient room between 09.00 and 09.30 a.m. Liquid Vaseline was utilized as a massage lotion to lubricate the skin and facilitate the classical massage techniques.

2. The participants firstly lay on a bench, supine position, at the start of massage session. The PI sat on a chair facing the patients' feet, which were at the PI's chest level during foot massage. The foot massage session began by holding the right foot gently but firmly in both of the PI's hands. Effleurage was applied from toes to the ankle of foot, continued for all the fingers, and plantar muscles.
3. The PI used her thumb to make superficial friction over the entire sole and all fingers of the foot. The sole was spread by the PI's fingers.
4. Then superficial friction was utilized for all fingers. Following the dorsum and all fingers massage, effleurage, and superficial friction were performed for the sole.
5. Finally, the foot massage was finished with petrissage for the plantar muscles (10 min).
6. Immediately after that, all massage techniques were utilized in a same manner for the left foot (10 min).
7. After completion of foot massage, the patients were asked to sit on the bench. The PI held the patient's hand gently in one of her hands. The hand massage began with the right hand, and moving on to the left hand.
8. Effleurage was administered for the dorsum of the hand, and then moving on to all the fingers, and continued from the palm to the wrist.
9. And then, the PI used thumb and fingers to make superficial friction over the patient's entire palm, all fingers, and the outer surface of the hand, and finally petrissage for the thenar and hypothenar muscle groups. The palm was spread by the investigator's fingers. (5 min).
10. All massage techniques were used for the left hand (5 min) (Holey and Cook, 2011; Vickers et al., 2013).

2.6. *Outcome measures and study instruments*

The primary outcome of this study was the presence of peripheral neuropathic pain. The secondary outcomes were QOL and change in NCS findings. Patient-reported outcomes including the presence of neuropathic pain and CIPN-related QOL were assessed by the 'S-LANSS' and 'The European Organization for Research and Treatment of Cancer–Quality of Life Questionnaire for Chemotherapy-Induced Peripheral Neuropathy' (EORTC QLQ CIPN20), respectively. Additionally, NCS findings were recorded as a measure of objective outcome.

2.6.1. *Patient information form*

The patient information form was developed on the basis of the relevant literature (Park and Park, 2015; Shimozuma et al., 2012; Tanabe et al., 2013), and contained six questions on descriptive characteristics (age, educational level, marital status, body-mass index, duration after diagnosis, and previous chemotherapy history).

2.6.2. *Self-Leeds assessment of neuropathic symptoms and signs (S-LANSS)*

This scale was developed by Bennett et al. (2005) to distinguish neuropathic pain from nonspecific pain, and is commonly used to detect neuropathic pain. The S-LANSS is a self-reported questionnaire consisting of seven items. The first five items investigate the symptoms of pain, including tingling, color changes, mechanical hyperalgesia, electric shock-like sensation, and burning sensation in the painful area. The last two items examine allodynia and pinprick test based on the patient report. The maximum score on the scale is 24, and scores of 12 or higher represent neuropathic pain (Bennett et al., 2005). In the Turkish validity and reliability study, the Cronbach's alpha coefficient was 0.73, while the sensitivity and specificity of the diagnosis of neuropathic pain were 72.9% and 80.4%, respectively (Koc and Erdemoglu, 2010).

2.6.3. European Organization for the research and treatment of cancer – quality of Life Questionnaire for chemotherapy-induced peripheral neuropathy (EORTC QLQ CIPN20)

This scale was developed by Postma et al., 2005 to assess the symptoms and functional limitations resulting due to CIPN. The scale contains 20 items in a 4-point Likert format ranging from 0 (not at all) to 4 (very much). The EORTC QLQ CIPN20 consists of three sub-scales, including sensory (tingling, numbness, pain, imbalance while walking or standing, alteration in thermal sensibility, and impaired hearing), motor (cramps, difficulty in writing, grasping small objects and pedaling, and weakness) and autonomic (postural hypotension, visual disorder and erectile dysfunction). The ranges of sensory, motor and autonomic sub-scale scores are 1–36, 1–32, and 1–8, respectively, for females (excluding the erectile dysfunction item). All the sub-scale scores were converted to a 0–100 scale, with higher scores indicating more symptoms and functional limitations. Cronbach's alpha values for the sensory, motor, and autonomic subscales for the Turkish population were 0.78, 0.85 and −0.059, respectively. Additionally, the total item correlation for each item ranged between 0.32 and 0.78 for sensory, 0.32–0.83 for the motor, and 0.26–0.78 for autonomic subscales in the Turkish validity and reliability study (Onsuz, 2015).

2.6.4. Nerve conduction studies (NCS)

NCS was performed on all the patients by the same neurologist using an EMG device (Medelec Synergy, United Kingdom). The patients were asked to sit (for upper left limb), and then lie down in the supine position (for lower left limb) on an examination couch. Sensory nerve conduction studies (NCS) including sensory nerve action potential (SNAP) amplitude and conduction velocity were recorded for the median, ulnar, and sural nerves. For motor NCS, the latency, compound muscle action potential (CMAP) amplitude, and conduction velocity were recorded for the median, ulnar, peroneal, and tibial nerves.

The SNAP represents the sum of all the underlying sensory fiber action potentials. Similarly, the CMAP is the sum of the voltage responses from the individual motor muscle fiber action potentials. The decrease in SNAP and CMAP amplitudes indicate the presence of an axonal degeneration. The shortest latency of the CMAP and SNAP refers to the time from the stimulus artefact to the onset of response. Conduction velocity refers to the speed of propagation of an impulse through the motor or sensory muscle fibers. Prolonged latencies and slowed conduction velocities indicate a demyelinating process (Kiechl, 2003; Mallik and Weir, 2005).

2.7. Data collection procedure

The baseline data were collected using the patient information form, S-LANSS, EORTC QLQ-CIPN20 during the first interview with patients in the oncology outpatient clinic before the first massage session on the day of first adjuvant paclitaxel infusion. Just after the first interview, all patients were directed to the neurologist (5th co-author) for baseline NCS assessment. The S-LANSS and EORTC QLQ-CIPN20 scales were re-administered at weeks 4, 8, and 12 in the intervention group before the massage session in the oncology outpatient clinic. As for control group, the scales were re-administered at weeks 4, 8, and 12 before paclitaxel infusions at the same clinic. Re-assessment of NCS was performed for all patients after the completion of the paclitaxel regimen by the same neurologist at week 12. Patients were called for a single time by phone for follow-up assessment at week 16, and the S-LANSS and EORTC QLQ-CIPN20 were repeated.

2.8. Statistical analysis

All the statistical analyses were performed using IBM SPSS 23.0 (IBM Corp., Armonk, New York). The Shapiro-Wilk test, histogram, and normal Q-Q plot were used for tests of normality.

The baseline variables including age, S-LANSS and EORTC QOL CIPN20 scores with the two-sample *t*-test of the difference between groups, and time since diagnosis, body mass index, NCS findings were analyzed using Mann Whitney *U* test. We compared educational level, marital status, and stage of breast cancer between study groups with the Chi-square test at baseline. We compared the presence of peripheral neuropathic pain between groups at weeks 4, 8, 12, and 16 using the Chi-square test. The comparisons between groups in terms of S-LANSS, and EORTC QOL CIPN20 scores over time were made by one-way repeated measures ANOVA. Cochran's Q test was used to analyze intra-group differences in terms of presence of peripheral neuropathic pain over time. We deemed a p value less than 0.05 to be significant.

2.9. Ethical considerations

The study was approved by clinical trials ethics committee of the University of Health Sciences Ankara Oncology Training and Research Hospital (decision number: 2017–06/02) and performed in accordance with the Helsinki Declaration. After obtaining permission from the unit managers, the investigators approached eligible breast cancer patients at the chemotherapy outpatient unit. All the potential participants were requested to submit a written informed consent. The participants could withdraw from the study at any time without providing a reason, and they were not expected to pay for anything. Data were collected and recorded in a manner that protected the anonymity of the participants.

3. Results

3.1. Participant's adherence to classical massage

During the weekly adjuvant paclitaxel regimens, none of the participants dropped out due to unexpected adverse events of classical massage, indicating that classical massage was a safe and well-tolerated intervention for CIPN in breast cancer patients. All participants in the CMG received all massage sessions in line with the study protocol.

3.2. Characteristics of study participants

The mean ages of the patients in the CMG and CG were 44.5 ± 10.7 and 47.0 ± 9.6 years, respectively. Majority of the patients in both the groups were married (CMG = 89.5%; CG = 80.9%) and had completed primary education (CMG = 52.6%; CG = 52.4%). The median length of time since diagnosis were 4.0 (4.0–4.5) months in the CMG and 5.0 (4.0–6.0) months in the CG. More than half of the patients (52.6%) in the CMG and 28.5% in the CG had stage II breast cancer.

The study groups were homogeneous in terms of age, educational level, marital status, body mass index, previous history of chemotherapy, and breast cancer stage ($p > 0.05$) (Table 1).

3.3. Effects of classical massage on patient-reported outcomes

The mean score of S-LANSS tended to rise from baseline to week 12 and declined at week 16 in both the groups. The statistical analysis revealed a significant time effect on the mean score of S-LANSS within the study groups ($p < 0.001$). Considering the time × group interaction effect, S-LANSS scores were also statistically different, indicating that the increase of S-LANSS scores in the CG was higher than the CMG ($p < 0.05$) (Table 2).

A significant time effect was observed in the mean values of the motor and sensory sub-dimension scores of EORTC QLQ CIPN20 within the study groups ($p < 0.001$). However, this variation was not similar between the study groups. The increase in the CG was higher than that in the CMG ($p = 0.001$). In terms of the autonomic sub-dimension scores of EORTC QLQ CIPN20, the mean score of the CMG decreased throughout the study, while in the CG, it increased from baseline to

Table 1
Baseline characteristics of participants.

Characteristics	CMG (n = 19)		CG (n = 21)		p-value
Age	44.5 ± 10.7*		47.0 ± 9.6*		0.566[a]
	n	**%**	**n**	**%**	
Educational level					
Primary school	10	52.6	11	52.4	
High school	6	31.6	7	33.3	
Bachelor degree	3	15.8	3	14.3	
Marital status					
Married	17	89.5	17	80.9	0.661[b]
Single	2	10.5	4	19.1	
Body-mass index	28.8 (25.5, 32.8)#		26.7 (25.3, 30.6)#		0.694[c]
Time since diagnosis	4.0 (4.0, 4.5)#		5.0 (4.0, 6.0)#		0.126[c]
	n	**%**	**n**	**%**	
Stage of breast cancer					0.426[b]
Stage II	10	52.6	6	28.5	
Stage III	9	47.4	15	71.5	
Presence of peripheral neuropathic pain					
Present	2	10.5	0	0.0	0.219[b]
Not present	17	89.5	21	100.0	
S-LANSS	2.15 ± 5.12*	1.42 ± 3.09*	0.585[a]		
EORTC QOL CIPN 20					
Sensory	27.19 ± 3.76*	1.42 ± 3.09*	0.573[a]		
Motor	26.69 ± 2.48*	26.53 ± 2.89*	0.852[a]		
Autonomic	32.23 ± 10.47*	27.97 ± 8.75*	0.169[a]		

Abbreviations: CMG, classical massage group, CG, control group, S-LANSS, self-leeds assessment of neuropathic symptoms and sign; EORTC QOL-CIPN 20, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire for Chemotherapy-Induced Peripheral Neuropathy.
The mean ages of the patients in the intervention and control groups were 54.3 ± 8.8 and 57.2 ± 9.7 years, respectively.
The mean ages of the patients in the intervention and control groups were 54.3 ± 8.8 and 57.2 ± 9.7 years, respective.
Note.*Mean ± Standard deprivation.#Median (25th, 50th).
[a] Student's t-test.
[b] Chi-square test.
[c] Mann-Whitney *U* test.

Table 2
Comparison of patient reported outcome measures between in the study groups over time.

Study Groups	Measurement Time	S-LANSS	EORTC QOL-CIPN 20		
			Sensory	Motor	Autonomic
		X̄ ± SD	X̄ ± SD	X̄ ± SD	X̄ ± SD
CMG (n = 19)	Baseline	2.15 ± 5.12	27.19 ± 3.76	26.69 ± 2.48	32.23 ± 10.47
	Week 4	1.94 ± 3.87	28.51 ± 5.34	27.25 ± 3.80	31.57 ± 8.70
	Week 8	4.73 ± 4.44	31.42 ± 7.17	28.19 ± 4.10	30.26 ± 7.58
	Week 12	5.68 ± 6.41	30.99 ± 6.88	28.19 ± 3.34	29.60 ± 9.51
	Week 16	4.33 ± 4.61	29.16 ± 4.39	26.58 ± 4.28	25.69 ± 2.94
CG (n = 21)	Baseline	1.42 ± 3.09	26.45 ± 4.35	26.53 ± 2.89	27.97 ± 8.75
	Week 4	4.38 ± 5.25	29.75 ± 6.02	30.44 ± 7.01	31.45 ± 9.31
	Week 8	8.45 ± 5.77	36.39 ± 13.58	32.49 ± 7.90	29.37 ± 7.33
	Week 12	10.83 ± 7.51	41.97 ± 18.34	38.48 ± 18.14	33.33 ± 12.86
	Week 16	7.00 ± 6.65	37.03 ± 19.51	35.55 ± 12.67	30.83 ± 12.38
p-values*	Time	< **0.001**	< **0.001**	**0.002**	0.391
	Between Group	**0.007**	**0.037**	**0.010**	**0.006**
	TimexGroup	**0.041**	**0.001**	**0.004**	0.056

Notes: *One-way repeated measures ANOVA.
Abbreviations: X̄, mean; SD, standard deprivation; CMG, classical massage group; CG, control group; S-LANSS, self-leeds assessment of neuropathic symptoms and sign; EORTC QOL-CIPN 20, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire for Chemotherapy-Induced Peripheral Neuropathy.

Table 3
Comparison of the peripheral neuropathic pain occuring in the study groups.

Measurement time	Presence of peripheral neuropathic pain	CMG (n = 19)		CG (n = 21)		p-values*
		n	%	n	%	
Baseline	Present	2	10.5	0	0.0	0.219
	Not present	17	89.5	21	100.0	
Week 4	Present	1	5.5	2	10.5	0.999
	Not present	18	94.5	19	89.5	
Week 8	Present	2	10.5	6	28.6	0.241
	Not present	17	89.5	15	71.4	
Week 12	Present	2	10.5	12	57.1	**0.006**
	Not present	17	89.5	9	42.9	
Week 16	Present	2	10.5	8	38.1	0.069
	Not present	17	89.5	13	61.9	
	p-values#	0.955		< 0.001		

Notes: *Chi-square test; #Cochran's Q test.
Abbreviations: CMG, classical massage group; CG, control group.

week 12 and decreased at week 16. This difference between the study groups was statistically significant ($p < 0.05$).

The presence of peripheral neuropathic pain based on S-LANSS was 10.5% at baseline; 5.5% at week 4; and 10.5% at weeks 8, 12, and 16 in the CMG. In the CG, no patient exhibited peripheral neuropathic pain at baseline, 10.5% at week 4, 28.6% at week 8, 57.1% at week 12, and 38.1% at week 16. The presence of peripheral neuropathic pain in the CMG was statistically lower than that in the CG at week 12 ($p < 0.05$). Statistical analysis within the study groups showed that the presence of peripheral neuropathic pain in the CMG remained similar from baseline to week 16 ($p > 0.05$). However, the prevalence of peripheral neuropathic pain in the CG significantly increased from week 4 to week 12 ($p < 0.05$) (Table 3).

3.4. Nerve conduction studies (NCS) findings

At baseline, the CMG and the CG were similar in terms of motor and sensory NCS ($p > 0.05$). The SNAP amplitude of the median nerve in the CMG was statistically higher at week 12, compared to the CG. Tibial nerve latency was significantly shorter in the CMG compared to the CG at week 12. CMAP amplitudes and conduction velocities of both the groups were statistically similar at week 12 (Table 4).

4. Discussion

Classical massage is one of the mostly used nursing interventions to prevent chemotherapy related toxicities. In the present study, we hypothesized that classical massage applied concurrent with adjuvant paclitaxel regimen in breast cancer patients would prevent chemotherapy-induced peripheral neuropathic pain and improve QOL. Till date, there have been two reports including one case study and one randomized controlled clinical trial exploring the effects of classical massage on CIPN based on patient reported outcomes, and these studies have highlighted that classical massage reduced CIPN and its related symptoms (Coskun et al., 2014; Cunningham et al., 2011). To the best of our knowledge, this is the first assessor-blinded, randomized controlled study on the use of classical massage to prevent CIPN and improve QOL in patients with breast cancer by utilizing NCS as an objective measurement as well as patient reported outcomes.

In our study, after 12 sessions of classical massage, patients suffering from peripheral neuropathic pain in the CG increased starting from baseline, while there were no changes in the CMG. In line with our finding, Coskun et al. (2014) reported that classical massage applied in patients with colorectal cancer receiving oxaliplatin significantly prevented CIPN in their randomized controlled study. Previous literature indicates that classical massage techniques stimulate vasomotor nerves resulting in improved systemic venous and lymphatic blood flow, and cause to local hyperemia, which contributes to an increase in the local blood microcirculation (Cunningham et al., 2011; Jamsek, 2013). Accordingly, a possible explanation for clinical benefits of classical massage on CIPN could be that improved circulation may prevent the accumulation of neurotoxic compounds of chemotherapy, while increased blood flow to the vasa nervorum that supplies blood to the neurons may contribute to the removal of neurotoxic compounds from the peripheral nervous system (Jamsek, 2013). Thus, classical massage applied concurrently with adjuvant paclitaxel regimen may be preventive for peripheral neuropathic pain due to its circulation-boosting effects.

CIPN causes not only severe neuropathic pain, but also significant sensory and motor symptoms such as numbness, tingling, and motor weakness, that deteriorate the functional activities and QOL (Kim et al., 2013; Shimozuma et al., 2012). At the end of monitoring period, we detected significant improvements in all sub-dimension scores of QOL in the CMG. Coskun et al. (2014) emphasized that classical massage applied in patients with colorectal cancer receiving oxaliplatin significantly improved QOL. Shiqianga et al. (2017) used acupuncture in cancer patients diagnosed with breast, lung, gastrointestinal, or ovarian cancer, and also specified that significant increase in QOL. Similarly, Kurt and Can (2018) reported that reflexology applied in patients with CIPN significantly improved sensory sub-dimension of QOL. Supporting previous outcomes, we can associate the improvements in QOL with the reduction in CIPN-related symptoms and prevention of peripheral neuropathic pain following classical massage.

In addition to patient reported outcomes, NCS was also utilized as an objective measurement technique to reveal the effects of classical massage on prevention of CIPN and its related symptoms in this study. The studies have emphasized that paclitaxel infusion produces a symmetric, length-dependent and axonal distal neuropathy (Argyriou et al., 2014; Mallik and Weir, 2005). Previous reports investigating the electrophysiological changes in paclitaxel-related CIPN have revealed that the amplitudes of the peripheral nerves were often decreased. However, with the increase in loss of motor axons, some of the largest conducting fibers may be lost. Therefore, distal motor latencies may be slightly prolonged in the patients suffering from paclitaxel-related CIPN (Argyriou et al., 2014; Mallik and Weir, 2005). When comparing the study groups in terms of NCS results, we detected a significant difference in the SNAP amplitude of the median nerve. The median nerve, which runs along the palm-side of the wrist and supplies sensory innervation to the thenar muscles and the two lateral lumbricals in the hand, is one of the major long-peripheral nerves of the upper limb (Murphy and Morrisonponce, 2018). During the massage sessions, we applied classical massage techniques from the fingers to the wrist and manipulated the thenar and hypothenar muscles. The higher SNAP amplitude of the median nerve in the CMG may result from the improved blood circulation of these muscles during the massage. Another striking NCS finding in our study was the shorter tibial nerve latency in the CMG. The tibial nerve is one of the longest nerves of the flexor compartment of the leg and its plantar branches supply the muscles of the sole (Elbarrany and Altaf, 2017). Manipulation of the foot muscles of the sole during the massage sessions may contribute to this finding. Due to lack of any study that using NCS for showing the prevention effect of classical massage on CIPN in the literature, we could not make direct comparisons. However, a pilot study investigating the effects of acupuncture on CIPN specified improvements in NCS findings of patients (Schroeder et al., 2012). Consequently, based on our study findings, the NCS outcomes supported our hypothesis that classical massage has positive effects on the prevention of CIPN by maintaining the functions of the median and tibial nerves.

Table 4
Findings of nerve conduction studies before and after the intervention.

	CMG (n = 19)	CG (n = 21)	p-values*	CMG (n = 19)	CG (n = 21)	p-values*
	Baseline			Week 12		
	Median (25th,75th)	**Median** (25th,75th)		**Median** (25th,75th)	**Median** (25th,75th)	
Sensory nerve conduction studies						
Sensory nerve action potential (SNAP) amplitudes						
Median nerve	110.9 (42.0, 153.6)	98.3 (33.9, 138.7)	0.478	80.6 (68.3, 122.9)	35.2 (9.1, 108.0)	**0.015**
Sural nerve	13.5 (9.4, 23.3)	15.9 (13.1, 29.1)	0.193	17.6 (13.4, 26.7)	13.9 (3.6, 19.8)	0.075
Conduction velocity						
Median nerve	60.4 (50.7,70.3)	66.7 (58.6, 70.9)	0.279	62.6 (51.2, 97.6)	59.3 (44.4, 72.3)	0.361
Ulnar nerve	55.0 (48.9, 58.7)	54.1 (47.1, 63.0)	0.963	52.4 (48.9, 58.4)	53.1 (44.5, 59.9)	0.910
Sural nerve	49.1 (35.8, 55.8)	57.1 (39.4, 66.7)	0.236	50.0 (30.5, 61.5)	51.9 (24.6, 68.3)	0.842
Motor nerve conduction studies						
Latency						
Median nerve	3.1 (2.8, 3.4)	3.1 (2.7, 3.6)	0.965	3.1 (2.7, 3.4)	3.1 (2.7, 3.5)	0.751
Ulnar nerve	2.4 (2.1, 2.8)	2.5 (2.3, 2.7)	0.217	5.6 (5.4, 5.9)	5.3 (4.8, 6.1)	0.563
Peroneal nerve	4.2 (3.6, 4.7)	3.7 (3.3, 4.2)	0.684	4.3 (3.5, 4.9)	3.8 (3.5, 4.9)	0.641
Tibial nerve	4.5 (4.0, 5.0)	4.2 (3.5, 5.1)	0.863	4.2 (3.8, 4.6)	4.6 (4.2, 4.9)	**0.045**
Compound Muscle Action Potential (CMAP) Amplitudes						
Median nerve	4.8 (3.0, 7.8)	6.0 (2.9, 10.1)	0.409	4.4 (2.9, 6.2)	5.1 (2.6, 6.5)	0.624
Ulnar nerve	6.3 (4.0, 7.4)	5.6 (3.6, 7.3)	0.496	5.3 (4.7, 6.6)	4.6 (3.5,5.4)	0.134
Peroneal nerve	2.9 (2.1, 3.9)	2.7 (2.2., 3.3)	0.594	2.2 (1.5, 3.5)	2.2 (1.2, 3.9)	0.954
Tibial nerve	6.1 (4.3, 8.6)	5.7 (3.2, 7.9)	0.300	5.0 (3.9, 8.9)	3.7 (2.3, 7.4)	0.065
Conduction velocity						
Median nerve	65.5 (60.7, 68.2)	61.0 (55.0, 64.0)	0.685	65.0 (59.0, 68.0)	63.0 (56.0, 67.0)	0.461
Peroneal nerve	60.0 (58.2, 62.4)	67.0 (60.0, 73.0)	0.414	61.0 (55.0, 66.0)	54.0 (48.0,61.7)	0.277

Notes: *Mann-Whitney *U* test.

4.1. Limitations

The current study has some limitations worth consideration. Firstly, the classical massage intervention was applied to female breast cancer patients receiving adjuvant paclitaxel and the study conducted at only one clinical setting. Therefore, the study results cannot be generalized to other patients receiving neurotoxic chemotherapy. Secondly, we only had a short-term follow-up period after the completion of the massage sessions. Thus, the long-term effects of the intervention were not investigated. Thirdly, NCS was performed only at baseline and at the end of week 12. Hence, we cannot interpret whether classical massage has any effect on the NCS findings at week 8, when the CIPN symptoms tend to exacerbate. The data collector and neurologist were also the co-authors of this study, this could be considered as other limitation.

4.2. Recommendations

In view of all the study findings, classical massage seems to have an effect on CIPN. Nurses have key roles in informing breast cancer patients on complementary approaches and encouraging them to receive classical massage to cope with peripheral neuropathic pain well. Classical massage is a well-tolerated, safe and cost-effective intervention. No severe side effects have been reported. An examination couch, a lubricant such as Vaseline and a certified massage therapist are the only requirements. Therefore, nurses may integrate this intervention into the clinical setting after participating in specific training programs on classical massage. Before initiating the paclitaxel regimen, healthcare providers can discuss the benefits of classical massage on CIPN with the patients and provide the volunteering patients with this opportunity concurrent with the chemotherapy regimens.

5. Conclusion

In summary, the results of our study have revealed that performing classical massage concurrent with chemotherapy, starting from the first cycle of adjuvant paclitaxel to the last cycle, largely prevents chemotherapy-induced peripheral neuropathic pain and improves QOL. NCS findings also supported the beneficial effects of classical massage on CIPN. Thus, classical massage can be safely applied to breast cancer patients receiving adjuvant paclitaxel by the nurses certified in classical massage therapy.

Conflicts of interest

None of the authors declare any conflicts of interest.

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