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The Effect of Peppermint (*Mentha piperita*) Extract on the Severity of Nausea, Vomiting and Anorexia in Patients with Breast Cancer Undergoing Chemotherapy: A Randomized Controlled Trial

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Abstract

Background and Objective: Nausea, vomiting, and anorexia are the most common side effects reported in cancer patients undergoing chemotherapy. The present study aimed to determine the effect of peppermint extract on the severity of nausea, vomiting, and anorexia in patients with breast cancer undergoing chemotherapy. **Methods and Materials:** In this randomized controlled trial, we selected 84 patients with breast cancer undergoing chemotherapy. They were then assigned to 2 groups of experimental and control (n = 42, each) using block randomization. Patients in the experimental group received 40 drops of peppermint extract mixed in 20 cc of tap water every 8 hours, while patients in the control group received 40 drops of distilled water mixed in 20 cc of tap water every 8 hours. The severity of nausea, vomiting, and anorexia was measured and recorded before the intervention, and immediately, 24 and 48 hours after the chemotherapy using the Visual Analogue Scale. Statistical analysis of the data was conducted using SPSS software version 21. **Results:** The results of the present study revealed that there was a significant difference between the 2 groups at 24 and 48 hours after the chemotherapy ($P < .05$), so that the mean score of the severity of nausea, vomiting, and anorexia in the experimental group was lower than in the control group ($P < .05$). **Conclusion:** The use of peppermint as a method in complementary medicine may improve nausea, vomiting, and anorexia in patients with breast cancer undergoing chemotherapy. Further studies with greater sample size and longer follow-up period are needed to confirm the current findings.

Keywords

peppermint, nausea, vomiting, anorexia, breast cancer, chemotherapy

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Introduction

The prevalence of cancer as a life-threatening disease is currently on the rise, so that cancer mortality is projected to rise by about 45% in developed countries by 2035.[1] Breast cancer is the most frequent cancer among females, impacting 2.1 million women each year.[2] Patients with breast cancer receive various treatments including radiotherapy, chemotherapy, and surgery. Among these, chemotherapy is a long-term and repetitive treatment that causes many side effects by damaging both normal and cancer cells.[3,4] Nausea, vomiting, and anorexia are common side effects of chemotherapy and frequently encountered by cancer

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patients.[5] Nausea and vomiting are associated with side effects such as dehydration, fluid and electrolyte imbalance, malnutrition, chemotherapy intolerance, and treatment refusal in patients. Uncontrollable nausea and vomiting can delay the chemotherapy schedule and decrease patients' quality of life.[6] Moreover, anorexia and weight loss occur in cancer patients due to reduced dietary intake and abnormal metabolism.[7] These conditions are life-threatening as they increase mortality, reduce the treatment success rate, and cause severe psychological distress in patients and their families.[8] Despite many advances in breast cancer treatment, patients still suffer from the physical and psychological symptoms of the disease. Therefore, efforts to alleviate the complications and side effects of cancer treatment are of great importance. Regarding the adverse effects and low efficacy of antiemetics used for chemotherapy-induced nausea and vomiting, 1 of the basic and low-risk measures to use is the complementary and alternative medicine (CAM).[9] Based on the results of recent research, complementary medicine causes fewer side effects and cuts the treatment costs. It is also more effective, less invasive, and more accessible compared to other treatments. Recent studies have also indicated the increasing use of CAM in cancer treatment.[10-12] *Mentha piperita* is a well-known herb in the food and pharmaceutical industries and is mostly used in the form of oily products or essential oils. The active ingredient in peppermint essential oil is called menthol and about 70% of peppermint essential oil is free menthol and menthol esters.[13] *Mentha piperita* is utilized as a remedy for spasm, cramp, headache, migraine, indigestion, nausea, and flatulence. It also has antibacterial activity.[14]

Considering the fact that a large number of breast cancer patients undergoing chemotherapy suffer from nausea, vomiting, and anorexia, the present study aimed to determine the effect of peppermint extract on the severity of nausea, vomiting and anorexia in these patients.

Methodology and Materials

Design

This study was a triple-blinded randomized placebo-controlled trial conducted from November 2018 to July 2019 in one of the educational hospitals in Arak, Iran.

Ethical Considerations

Full ethical approval was obtained from the Ethics Committee of Arak University of Medical Sciences (with approval No. IR.ARAKMU.REC.1396.314). The study was also registered in the Iranian Registry of Clinical Trials (with registry No. IRCT20130731014229N7). Prior to the beginning of the study, all participants were provided with clear explanations of the study objectives and methodology, and the possibility of withdrawal from the study. They were then assured of the confidentiality of the data and the anonymity of the questionnaires. Subsequently, written informed consent was obtained from all participants. The study protocol was written in accordance with the principles of the Declaration of Helsinki.

Participants

We recruited a total of 84 patients with breast cancer undergoing chemotherapy who met clinical inclusion criteria. We determined the study sample size using the formula of compare means *t*-test and G*Power tool,[15] and in accordance with the results of a study by Haddadi et al[9] in which the nausea mean scores ± standard deviation (SD) were 2.9 ± 1.78 and 1.96 ± 1.24 in the control and the experimental group, respectively. The minimum sample size for each group was calculated to be 34 with 95% confidence interval and 80% power. Regarding the probability of sample attrition, the final sample size for each group was considered as 42. Inclusion criteria consisted of the followings: (a) patient with definite diagnosis of breast cancer by an oncologist, (b) having a history of receiving at least 1 cycle of chemotherapy, (c) having a history of nausea following chemotherapy sessions, (d) having no comorbidity causing nausea such as high blood pressure, hepatic and renal failure, and gastrointestinal disorders, (e) receiving no total-dose/upper abdominal radiotherapy concomitant with chemotherapy, and (f) having no sensitivity to peppermint. Exclusion criteria consisted of the followings: (a) forgetting to take peppermint oral drop 3 or more times in a row, (b) using medications or other treatments to reduce nausea severity other than the antiemetics prescribed for chemotherapy, (c) patient with refractory nausea and vomiting, (d) being affected by severe gastrointestinal side effects during the study period, and (e) premature withdrawal from the study. Eligible patients were enrolled in the study using convenience sampling. The participants were then randomly assigned to 4 homogeneous subgroups (blocks) of intervention (n = 2) and control (n = 2) using block randomization by statistical staff. Two blocks named "A" and 2 blocks named "B" were allocated the intervention (A, A) and the control group (B, B), respectively. Then, the group of each patient was determined by telephone consultation the statistical staff.

Intervention

The intervention was performed during 1 cycle of chemotherapy. Before the intervention, the severity of nausea and anorexia and the frequency of vomiting episodes in the 2 groups were measured using the Visual Analogue Scale (VAS) and the frequency table, respectively. Patients in both groups performed the intervention from 12 hours

before[16] up to 48 hours after chemotherapy so that, in addition to routine antiemetics, patients in the experimental group received 40 drops of peppermint extract (Supermint oral drop produced by Barij Essence Pharmaceutical Co., Kashan, Iran) mixed in 20 cc of tap water every 8 hours, and patients in the control group received 40 drops of distilled water mixed in 20 cc of tap water every 8 hours.[17] For blinding, the peppermint oil and distilled water were dispensed in identical bottles with equal volume. The measurements were conducted again using the same tools immediately, 24 and 48 hours after the chemotherapy. Confounding variables, especially the antiemetics and other medications administered, were controlled using random assignment.

Data Collection

Data collection tools included a standard demographic survey, patients' medical records, frequency table (for measuring the frequency of vomiting episodes), and the VAS (for assessing the severity of nausea and anorexia).

The VAS for appetite measurement consists of a 10-cm line in which the extremities were anchored by 0 being "not at all hungry" to 10 being "very hungry," and the VAS for nausea severity measurement is also made up of a 10-cm line anchored with extreme nausea perceptions on the both ends from "0 = no feeling of nausea" to "10 = severe feeling of nausea." The reliability and validity of this scale have been established in previous studies.[18-20] Moreover, the reliability of this tool was approved by Shahinfar et al[21] with a Cronbach's alpha of 0.88. So, patients were able to assess and self-report the severity of their nausea and anorexia using this scale. We used this scale to assess the severity of nausea and anorexia in patients at 4 time-points of before the intervention, and immediately, 24 and 48 hours after the chemotherapy.

Statistical Analysis

Statistical analysis of the data was conducted using SPSS software version 21 (IBM Corp., Armonk, NY, USA). Data were described using descriptive statistics including mean, standard deviation, and frequency distribution. Moreover, analytical statistics including χ^2 test, independent *t*-test, paired *t*-test, and repeated measures *Analysis of Variance (ANOVA) were* used to analyze the differences between and within the 2 groups.

Results

Of the 105 eligible patients, 14 did not meet the inclusion criteria and 7 refused to participate. Of the remaining 84 patients, all adhered to the study protocol and were included in the final analysis and none of the patients had any specific side effects due to the intervention performed during the study (Figure 1).

The mean age of the patients in the intervention group was 11.78 ± 49.60 years and in the control group was 9.52 ± 51.90 years. The mean number of chemotherapy cycles prior to the study in the intervention group was 5 ± 2.69 and in the control group was 5.40 ± 2.97 ($P = .515$). The educational level of 59% of the patients was less than high school diploma. Moreover, 88% of the participants were married and 85% were housewives. The mean duration of the illness in the experimental and the control group was 24.24 and 20.71 months, respectively. Both groups were homogeneous in terms of disease and demographic characteristics $P > .05$ (Table 1).

There was no significant difference in the mean score of nausea severity between the two groups before the intervention ($P > .05$). However, the difference was statistically significant at 24 and 48 hours after the chemotherapy ($P < .05$) so that the mean score of nausea severity in the experimental group was lower than in the control group ($P = .001$). In this regard, the results of repeated measures ANOVA with a Greenhouse-Geisser correction (1959) also showed that the Time effect, Group effect, and the Time × Group interaction were significant ($P = .001$) (Table 2; Figure 2).

The difference in the mean score of anorexia severity between the 2 groups was not statistically significant before the intervention ($P > .05$). However, the difference was statistically significant at immediately, 24 and 48 hours after the chemotherapy ($P < .05$) so that the mean score of anorexia in the experimental group was lower in than the control group ($P = .001$). Based on the results of repeated measures ANOVA with a Greenhouse-Geisser correction, it was revealed that the Time effect, Group effect and the Time × Group interaction were significant ($P < .05$) (Table 3; Figure 3).

There was no significant difference in the mean frequency of vomiting episodes between the 2 groups before the intervention ($P > .05$). However, the results showed a significant difference between the 2 groups at 24 and 48 hours after the chemotherapy ($P < .05$) as the mean frequency of vomiting episodes was lower in the experimental group compared to the control group ($P = .001$). Moreover, the results of repeated measures ANOVA with a Greenhouse-Geisser correction indicated that the Time effect, Group effect and the Time × Group interaction were significant ($P < .05$) (Table 4; Figure 4).

Discussion

In this study, we aimed to determine the effect of peppermint extract on the severity of nausea, vomiting and anorexia in patients with breast cancer undergoing chemotherapy. Based on the results of this study, no significant

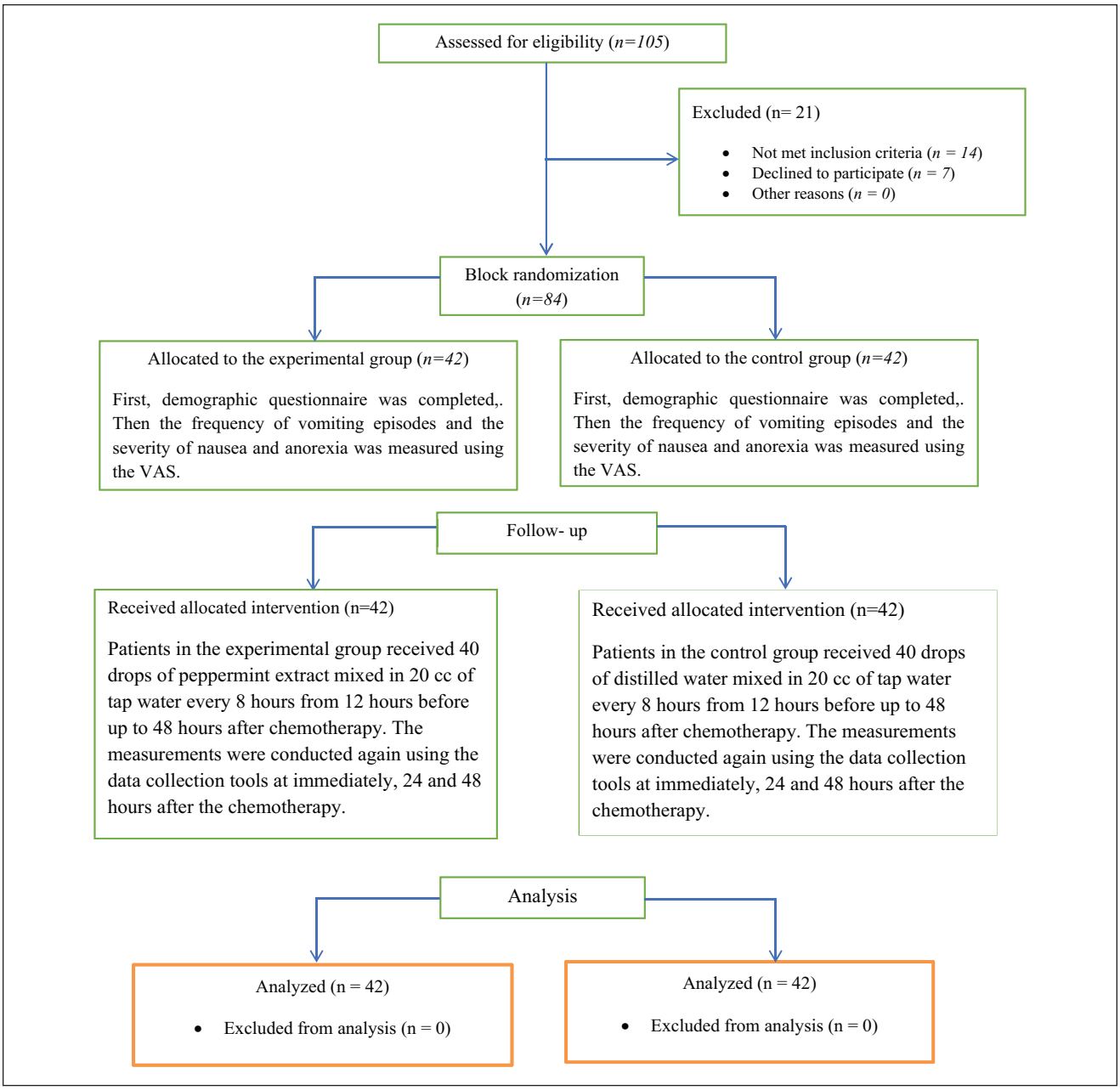

Figure 1. The CONSORT flow diagram of the patients' recruitment.

difference in the demographic variables was found between the 2 groups. It was also found that there was no statistically significant difference in the severity of nausea and anorexia, and the frequency of vomiting episodes between the 2 groups before the intervention. This was indicative of the similarity between the study groups. The results of this study showed a significant difference in the severity of nausea between the 2 groups at 24 and 48 hours after the chemotherapy as the severity of nausea in the experimental group was lower than in the control group. The results of repeated measures ANOVA also indicated that the severity of nausea decreased over the study period as there was a further significant reduction in the severity of nausea in the experimental group compared to the control group.

The results of a study by Haddadi et al[9] showed that sucking ice bits containing mint extract during chemotherapy significantly decreased the severity of nausea. Eghbali et al[22] revealed that aromatherapy with peppermint essential oil has led to a significant reduction in the severity of nausea during the acute phase of chemotherapy in patients with breast cancer. Based on the results of a study by Zorba and Ozdemir,[23] it was found that the severity of nausea was significantly

Table 1. Demographic Characteristics in the Experimental and Control Groups.

Group		Experimental group		Control group		
		Frequency	%	Frequency	%	*P*-value*
Demographic characteristics						
Marital status	Single	6	14.3	4	9.5	.369
	Married	36	85.7	38	90.5	
Educational level	Illiterate	5	11.9	3	7.1	.539
	Less than diploma	18	42.9	24	57.1	
	Diploma	15	35.7	13	31	
	Collegiate	4	9.5	2	4.8	
Occupation	House wife	34	81	38	90.5	.361
	Employee	7	16.7	4	9.5	
	Self-employed	1	2.4	0	0	
Medication regimens used for nausea	Granisetron, metoclopramide, dexamethasone	37	88.1	40	95.2	.216
	Ondansetron, granisetron, dexamethasone	5	11.9	2	4.8	
Chemotherapy drugs	Trastuzumab	5	11.9	4	9.5	.104
	Doxorubicin, cyclophosphamide	32	76.2	25	59.5	
	Doxorubicin, cyclophosphamide, docetaxel	5	11.9	13	31	

*Obtained from independent *t*-test or K2 test, where appropriate.

Table 2. The Mean Scores of Nausea Severity in the Experimental and Control Groups.

		Group		
		Experimental group (n = 42)	Control group (n = 42)	*P*-value (repeated measures ANOVA)
Intervention time	Before the intervention	2.33 ± 1.73	1.83 ± 2.17	.247
	Immediately after the chemotherapy	4.12 ± 1.72	4.12 ± 2.47	1.000
	24 h after the chemotherapy	4.26 ± 2.06	6.10 ± 2.30	<.001
	48 h after the chemotherapy	3.17 ± 1.97	5.76 ± 2.91	<.001
Group effect		*F* = 6.231542		<.001
Time effect		*F* = 69.629765		<.001
Time × Group interaction		*F* = 21.364054		<.001

lower among patients in the inhalation aromatherapy group compared to the control group. In a study on the effect of aromatherapy with 3 types of essential oils including peppermint, ginger, and a combination of both on postoperative nausea and vomiting, Firington et al[24] indicated that aromatherapy with the 3 types (each alone or in combination) could reduce the severity of postoperative nausea and there was no significant difference between the 3 types of inhalers used. The results of the above studies are consistent with the results of our study. However, in the above studies, mint aromatic inhalers were used to decrease the severity of nausea. Moreover, various studies have been conducted on the effect of mint on the severity of nausea in other patients.

In a study by Shahinfar et al,[21] 25 drops of 2% mint extract mixed in 30 cc of water were given to the patients in the experimental group. The results showed that the incidence and mean severity of nausea during cesarean section in the experimental group was significantly lower than in the control group. However, there was no statistically significant relationship between the 2 groups regarding the incidence and mean severity of nausea and vomiting at 2 and 4 hours after the surgery.[25] Briggs et al[26] found that peppermint oil inhalation is a viable treatment for postoperative nausea in patients undergoing cardiac surgery. The above studies confirm the positive effect of mint extract on nausea severity. Ferruggiari et al[27] stated that inhalation aromatherapy with peppermint oil is not effective in decreasing the frequency and severity of postoperative nausea and vomiting. Najafi et al[28] concluded that inhalation aromatherapy with peppermint essential oil does not affect postoperative nausea and vomiting in patients undergoing abdominal surgeries. In a study by Joulaeerad et al,[29] it was found that aromatherapy with peppermint oil has no effect on the severity of nausea in pregnant women. The results of the

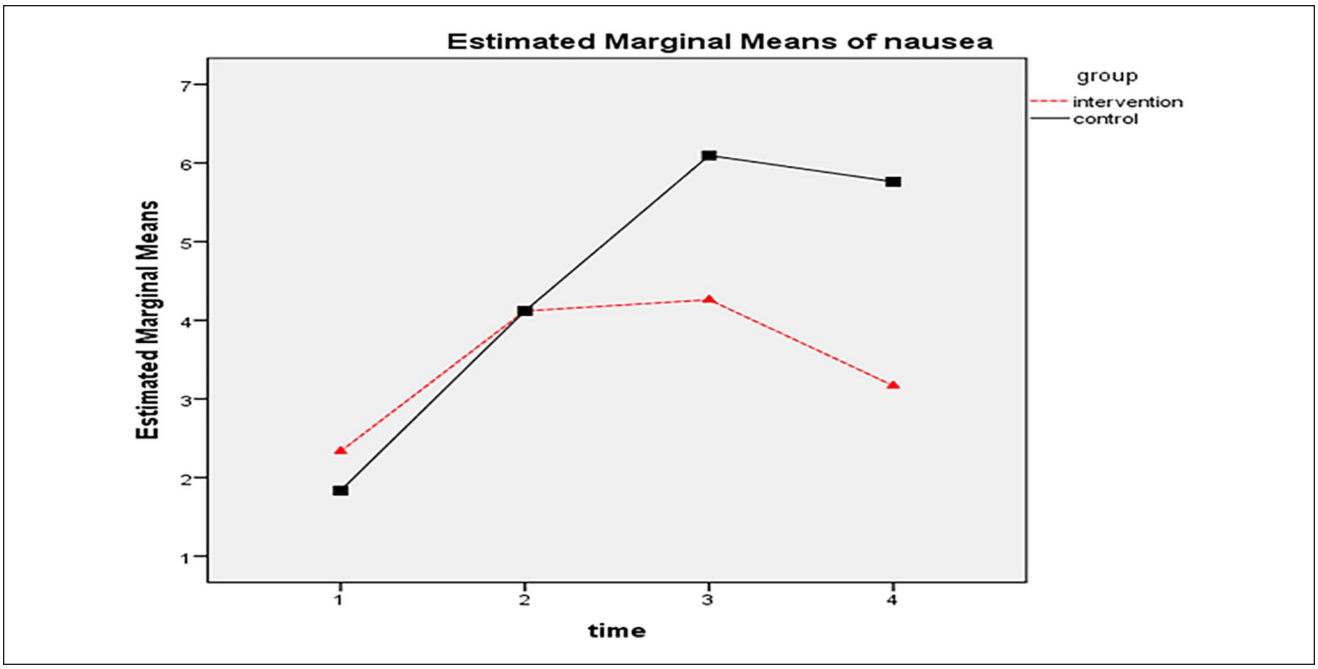

Figure 2. The mean scores of nausea severity at 4 time-points (before the intervention, and immediately, 24 and 48 hours after the chemotherapy) in the experimental and control groups.

Table 3. The Mean Scores of Anorexia Severity in the Experimental and Control Groups.

		Group		
		Experimental group (n = 42)	Control group (n = 42)	*P*-value (repeated measures ANOVA)
Intervention time	Before the intervention	1.24 ± 1.69	0.9 ± 1.16	.296
	Immediately after the chemotherapy	2.57 ± 1.97	3.50 ± 1.89	.031
	24 h after the chemotherapy	3.26 ± 2.03	4.48 ± 2.02	.008
	48 h after the chemotherapy	2.24 ± 1.75	3.38 ± 2.02	.007
Group effect		*F* = 6.539992		.012
Time effect		*F* = 53.013599		.003
Time × Group interaction		*F* = 21.364054		.001

above studies are not in line with our findings. These discrepancies are due to the diversity of the study populations, research settings, and methods of intervention. In our study, the patients received 40 drops of 2% peppermint extract mixed in 20 cc of tap water every 8 hours. Regarding the greater efficacy of gastrointestinal absorption, it seems that the oral administration of peppermint extract is more effective than inhalation.

The results of our study showed a statistically significant difference in the frequency of vomiting episodes between the 2 groups at 24 and 48 hours after the chemotherapy, so that the frequency of vomiting episodes significantly reduced in the experimental group compared to the control group. The results of repeated measures ANOVA also showed that the frequency of vomiting episodes decreased over the study period. In line with our findings, Ghani and Ibrahim[30] showed that inhalation aromatherapy with lavender and peppermint oils resulted in a significant reduction in the frequency of vomiting episodes. Shahinfar et al[21] indicated that the incidence and mean severity of vomiting episodes during cesarean section was significantly lower in the experimental group compared to the control group. In a study by Eghbali et al,[22] it was also found that the frequency of vomiting episodes during the acute phase of chemotherapy was lower in the experimental group compared to the control group. However, this reduction was not statistically significant cancer.[22] Haddadi et al[9] stated that sucking ice bits containing mint extract has no effect on the frequency of chemotherapy-induced vomiting episodes. Pasha et al[31] found that peppermint essential oil does not affect nausea and vomiting during pregnancy. In a study by

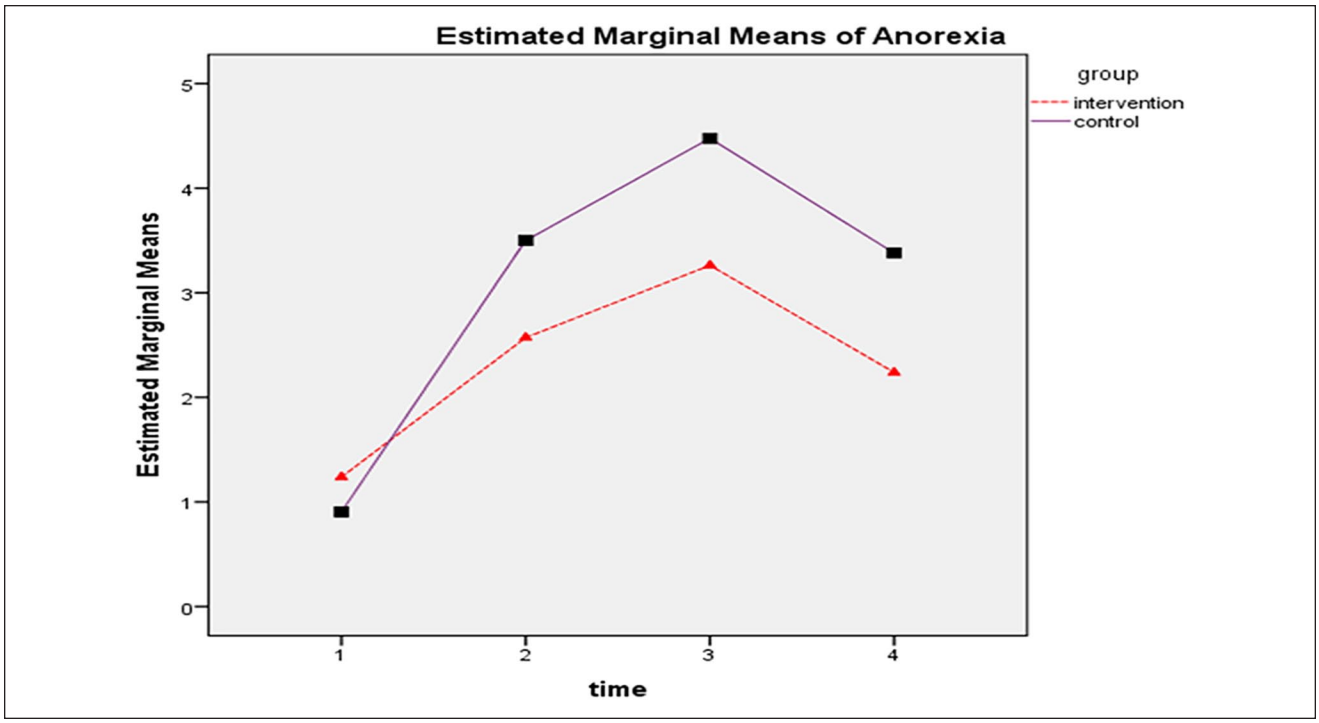

Figure 3. The mean scores of anorexia severity at 4 time-points (before the intervention, and immediately, 24 and 48 hours after the chemotherapy) in the experimental and control groups.

Table 4. Comparison of the Mean Frequencies of Vomiting Episodes in the Experimental and Control Groups.

		Group		
		Experimental group (n = 42)	Control group (n = 42)	*P*-value (repeated measures ANOVA)
Intervention time	Before the intervention	0.0 ± 0.0	0.0 ± 0.0	
	Immediately after the chemotherapy	0.0 ± 0.0	0.05 ± 0.216	.156
	24 h after the chemotherapy	0.17 ± 0.537	0.48 ± 0.707	.026
	48 h after the chemotherapy	0.12 ± 0.395	0.36 ± 0.557	.030
Group effect		$F = 6.857105$		.011
Time effect		$F = 16.242982$		<.001
Time × Group interaction		$F = 3.559584$		.035

Najafi et al,[28] the findings showed that inhalation of peppermint essential oil has no effect on postoperative vomiting in patients undergoing abdominal surgeries. Joulaeerad et al[29] revealed that aromatherapy with peppermint oil has no effect on the severity of vomiting in pregnant women. The results of the above studies are not in line with the results of our study. The reason for this discrepancy can be attributed to the study populations, types of intervention, and the mint dosage. In the present study, a high dose of peppermint was used, which can be more effective in reducing the severity of nausea and vomiting.

There are limited studies about the effect of CAM on anorexia in cancer patients. The results of the present study showed that the difference in the mean score of anorexia severity between the 2 groups was statistically significant after the chemotherapy so that the mean severity of anorexia in the experimental group was lower than in the control group. Furthermore, based on the results of repeated measures ANOVA, it was revealed that the severity of anorexia decreased over the study period so that there was a further significant reduction in the severity of anorexia in the experimental group. The results of a study by Jung and Lee[32] demonstrated that aromatherapy with mint extract was effective in reducing the intensity of anorexia in cancer patients undergoing chemotherapy. Delavar et al[33] found that peppermint oil capsules are effective in alleviating gastrointestinal complaints caused by

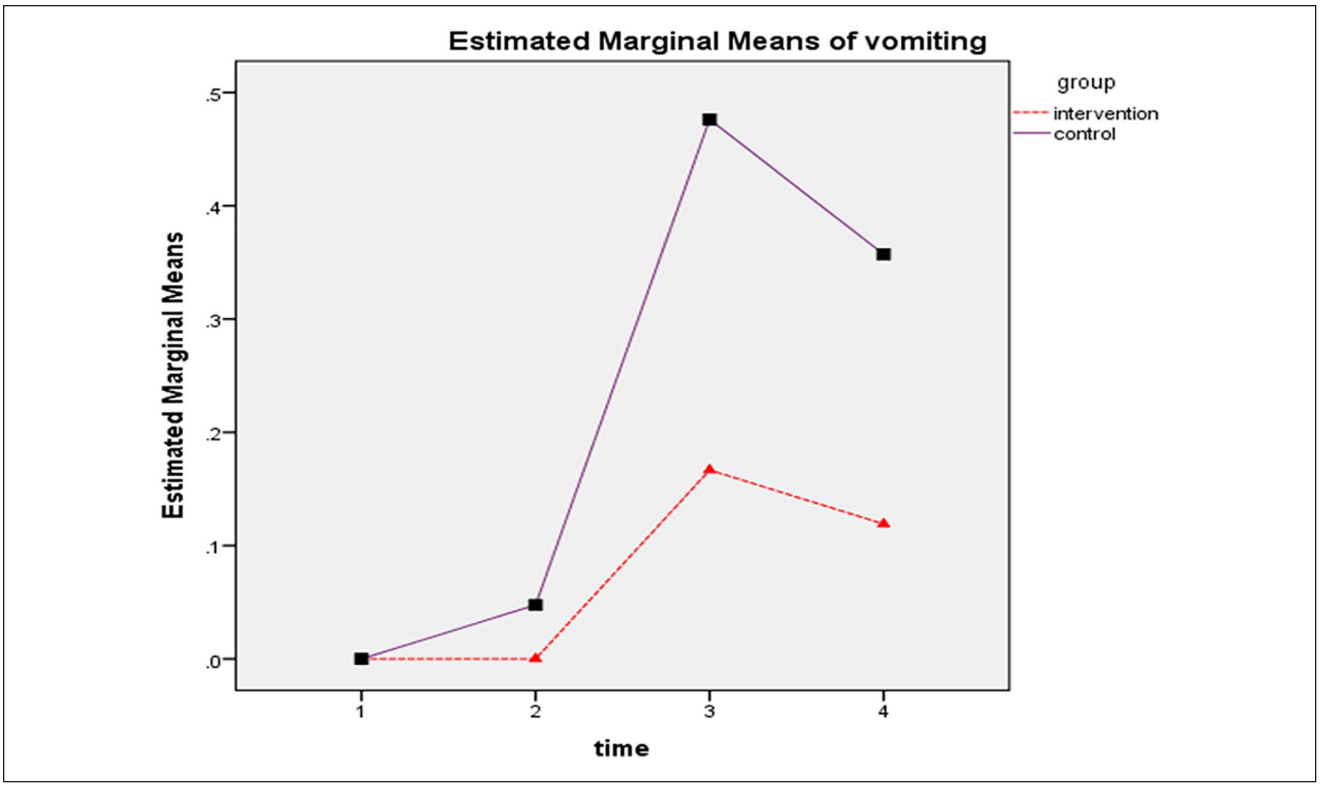

Figure 4. The mean frequencies of vomiting episodes at 4 time-points (before the intervention, and immediately, 24 and 48 hours after the chemotherapy) in the experimental and control groups.

premenstrual syndrome. Various studies have investigated the positive effects of peppermint on the gastrointestinal tract.[34-36] The results of a study by Mizuno et al[37] revealed that oral administration of peppermint oil decreases spasm at the esophagus, lower stomach, and duodenal bulb. Considering that the participants and the mechanism causing anorexia in the above studies are different from the ones in the present study, it is difficult to draw a comparison between the studies. Anorexia in patients undergoing chemotherapy can be caused by activation of the hypothalamic inflammatory pathways secondary to intestinal inflammation (inflammation triggers anorexia) or to dehydration from diarrhea.[38]

Based on the results of our study, it seems that a standard dose of peppermint extract (oral drop) causes no side effects and can be used as a treatment along with other medication treatments to reduce chemotherapy-induced nausea and vomiting. Since this study was conducted on patients with breast cancer, further studies are recommended to be conducted on patients with different types of cancer to clarify more points about the use of this approach.

Study Limitations

One of the limitations of this study is the effect of confounders on the results. To eliminate the confounding factors, random sampling was used to select identical samples. Moreover, the mean score of the severity of nausea, vomiting and anorexia was measured before the intervention and after the chemotherapy, and the mean scores were then compared. The second limitation is that this study was conducted on women with breast cancer undergoing chemotherapy. Therefore, it is not possible to generalize the study results to other patients undergoing chemotherapy. The third limitation is the small number of samples. Further studies with greater sample size are needed to confirm the current findings. A fourth limitation was the potential that patients guessed the type of intervention performed because of the smell of peppermint essential oil, a factor for which there is no control in this study.

Conclusion

We concluded that peppermint extract has the effect of reducing the severity of nausea and vomiting and improving the appetite in patients with breast cancer undergoing chemotherapy. Peppermint extract thus has the potential to be used as a non-invasive and low-cost nursing intervention along with other treatments to reduce the severity of nausea and vomiting and improve the appetite in cancer patients undergoing chemotherapy. Further studies with greater sample size and longer follow-up period are needed to confirm the current findings.

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Authors' Contribution

HJM, MA, MZ and MH: Study conception and design, data collection, data interpretation, and critical revision of the paper; MH, HJM and RH(clinical supervision): study conception and design; HJM and MH: study conception and design, and critical revision of the paper; MH and HJM: study conception and design, data analysis and interpretation, manuscript preparation, and critical revision of the paper. All the authors read and approved the final manuscript for submission.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical confirmation

The Ethics Committee of Arak University of Medical Sciences, Arak, Iran, approved this study (IR.ARAKMU.REC.1396.314).

Trial registration

This trial was registered in the Iranian Registry of Clinical Trials (**IRCT20130731014229N7**).

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