Review

A Systematic Review Of Non-Pharmacological/Complementary Methods Of Chemotherapy-Induced Nausea And Vomiting Prevention In Breast Cancer Patients

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Abstract:

Background: Nausea and vomiting caused by chemotherapy are one of the treatment problems in patients with different types of cancer.

Methods: In this systematic review, we systematically searched for different types of non-pharmacological treatments for nausea and vomiting in breast cancer patients. Based on Prisma guidelines, in MEDLINE databases, Cochrane, Central Register of Controlled Trials, EMBASE, Scopus, Web of Science, and SID, and with the help of the Google scholar search engine, clinical trials reporting the effect of non-pharmacological interventions on nausea and vomiting in women undergoing chemotherapy for breast cancer were sought. Collected data were used qualitatively for evidence synthesis and chance of bias was assessed based on the Cochrane scale.

Result: Finally, 15 studies were selected. Five studies investigated methods based on herbal medicine. Acupressure in different forms was investigated in 6 reports. Three studies with psychophysical exercises and yoga were included in the present review. A total of 952 participants were analyzed in all the reviewed studies in this review. It seems that there is not enough evidence to use different types of oral or inhaled medicinal forms of herbs like ginger or mint to reduce nausea and vomiting in breast cancer patients undergoing chemotherapy. Sumac and black cumin can be used as the subject of future research in this regard.

Conclusion : The variety of available methods in acupressure limits the decision for clinical use of these methods. The number of articles about each of the ear acupressure methods, wristbands-aided acupressure, massage, yoga, and psychophysical methods is not enough to check the superiority of each of these methods.

Keywords: Nausea and Vomiting, Chemotherapy, Breast Cancer, Complementary Medicine

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Introduction

Nausea and vomiting caused by chemotherapy are one of the treatment problems in patients with different types of cancer (1). However, chemotherapy can save the lives of many patients, especially those with breast cancer, and the continuation of chemotherapy treatment and the patient's compliance with the treatment necessitate the reduction of nausea and vomiting caused by chemotherapy drugs (2). Drugs commonly used to control chemotherapy-induced nausea/vomiting include serotonin, neurokinin 1 (NK-1) receptor antagonists, corticosteroids, and metoclopramide (3). There is evidence that shows that after prevention with these antiemetic drugs, the effects of acute and delayed nausea and vomiting can be prevented in up to 50% of cases (4, 5). However, the high cost of these agents and their side effects, such as extrapyramidal disorders, hypotension, headache, constipation, fatigue, dry mouth, dizziness, diarrhea, and irritability, have limited the use of these drugs (6). The limitations of pharmacological treatment have led to an increase in the use of complementary medications or alternative methods to manage nausea and vomiting. The non-pharmacological medical cares that are mostly used to control nausea and vomiting in people with cancer undergoing chemotherapy are diverse and this article aims to systematically review the non-pharmacological and complementary methods in preventing nausea and vomiting caused by chemotherapy.

Method

This systematic review study was structured based on PRISMA guidelines and conducted from November to December 2022. We searched several databases including MEDLINE, Cochrane Central Register of Controlled Trials, EMBASE, Scopus, Web of Science, and SID to identify relevant trials for this systematic review with no time restriction. Keywords of "complementary medicine", "traditional medicine", "herbal", "non-medicinal" were mixed with keywords of "breast cancer", "chemotherapy", "nausea", "vomiting" with AND function along with (AND) "clinical trial" and "randomized" in both Persian and English languages. The Google scholar search engine was also used along with the SID database for Persian keywords.

Eligibility

We included all studies of patients older than 18 years who were diagnosed with breast cancer and were receiving active chemotherapy. Studies with complementary medicine interventions in the form of clinical trials were included in the study. Pre-test and post-test studies were excluded. Studies on dietary supplements or lifestyle education were not included in this study.

Eligibility of each study was assessed independently by two authors using a standardized form. If there was a disagreement between the authors, the third author, who is a senior researcher was consulted. To be included in this review article, the study had to be a fully randomized trial. The study could have had a parallel control study design or a crossover. We excluded studies that included patients receiving palliative care.

Data extraction

Two authors independently performed data extraction. Information including study characteristics: study design, country where the trial was conducted, inclusion and exclusion criteria for each trial, number of samples, age, clinical characteristics, including cancer stage, intervention details including types of interventions, frequency , duration, number and details of the control group were recorded.

The main outcomes including objective data, time interval between the end of intervention

and outcome measurement, and reported side effects were recorded for qualitative inference. To check the quality of the studies and the chance of bias, Cochran's checklist was used, which includes checking the random sequence generation method, allocation concealment method, degree of blinding, any sample loss after randomization, loss of patients in follow-up, and the selected report of results.

Results

After the initial search, 1001 article titles were obtained. After removing 149 duplicate items, among the remaining 852 titles, 451 items were removed due to lack of relevance. Among the remaining 401 titles, abstracts were read and 244 cases were excluded due to lack of relevance or observational study design. Among the remaining 157 studies whose full text was read, 12 cases were due to nutritional intervention, 57 cases were due to intervention before and after the study, and 73 cases were due to the use of new medicinal compounds as intervention. The main ones were excluded from the study, and finally, 15 studies were selected (Figure 1).

Figure 1. Studies' selection process bssed on the PRISMA flowchart

Finally, 5 studies investigated methods based on herbal medicine. Acupressure in different forms was investigated in 6 cases. Three studies with psychophysical exercises and yoga were examined in the present review. A total of 952 participants were analyzed in all the studies reviewed in this review. The basic characteristics of the included studies are given in Table 1.

In the study of Thamlikitkul et al. (7), ginger was used as an anti-nausea drug, which was not more effective than the standard treatment with ondansetron and dexamethasone. More studies have been done on this herb. In a well-designed clinical trial, Ebrahimi et al. showed that ginger has a good effect in reducing nausea/vomiting caused by chemotherapy in breast cancer (8); But another similar study, which was controlled, three-group and three-blinded, showed that this effect of ginger was not on the severity of nausea and it only reduced the frequency of nausea and vomiting (9). Another study prescribed this herb for aromatherapy. In 5 days of using ginger essential oil aromatherapy after chemotherapy, the VAS score of nausea after inhalation of ginger essential oil in the acute phase was significantly lower than the placebo group ($P = 0.040$), but it was not stable for the overall treatment effect (10). Peppermint essential oil aromatherapy has also been used in this case. In a clinical trial with a relatively high probability of bias conducted by Iqbali et al., the parameters of nausea in the intervention group were lower than in the control group, but there was no significant difference in terms of vomiting (11). Another study measured the effect of traditional Iranian herbal supplements on this issue. This combination, which contained Sicilian sumac and black cumin, had a good effect in reducing nausea and vomiting caused by chemotherapy (12).

Pressure-based methods are also suggested in complementary medicine; Based on the available evidence, compared to the standard treatment of nausea/vomiting, auricular acupressure has been more effective in reducing the frequency of vomiting and the severity of nausea, and there are no specific side effects; But the quality of this evidence is low (13). But another study that used pressure wristbands to control nausea/vomiting in patients undergoing chemotherapy with doxorubicin showed that this method does not work (14). In other studies, this method has been named P6-specific acupressure, which in the study of Molassiotis et al. (15) had better results than the control group, showing statistical significance. In Shen et al.'s study (16), assisted electroacupuncture was more effective in controlling vomiting than acupuncture or antiemetic drug therapy alone,

although the observed effect was of limited duration. Shen et al.'s study had high quality in design and sample size.

Massage therapy is also a similar method that was discussed in the study of Vanaki et al. (17) and its high efficiency was seen, but the mentioned study has many limitations and a high chance of bias. In the study of Billhult et al. (18), massage therapy, along with standard treatment, caused a significant reduction in nausea in patients, but the sample size of patients in this study was very limited.

Raghavendra et al. (19) showed that a yoga program can prevent nausea and vomiting in patients undergoing chemotherapy. But the patients under their study were also undergoing radiotherapy and surgery, which raises the heterogeneity between studies for quantitative and qualitative conclusions. But another high-quality study showed that the yoga program is not useful in managing nausea and vomiting symptoms caused by chemotherapy in women with breast cancer (20). Molassiotis et al. (21), addressed the intervention of progressive muscle relaxation training. According to their study, progressive muscle relaxation is a useful adjunctive technique to supplement antiemetics for chemotherapy-induced nausea and vomiting. But other studies that have used similar methods were not clinical trials.

Qualitative analysis

It seems that there is not enough evidence to use different types of oral or inhaled medicinal forms of ginger or mint to reduce nausea and vomiting in breast cancer patients undergoing chemotherapy. More recent options investigated in the background of traditional medicine research, such as sumac and black cumin, can be used as the subject of future research in this regard. In the case of acupressure and massage, there is better evidence for reducing nausea and vomiting, but the variety of available methods limits decision-making for evidence synthesis. The number of articles about each of the ear acupressure methods, acupressure with the help of wristbands, massage, yoga, and psycho-physical methods is not enough to check the superiority of each of these methods.

Risk of bias

Most of the studies included in this review had little bias, but the studies that were published in Persian had a high chance of bias. The risk of bias for these studies is shown in Table 2.

Discussion

In reviewing the literature of research on the pharmaceutical methods of controlling nausea/vomiting caused by chemotherapy, a study reviewed more than 30 clinical trial studies, combining drug treatments of the drug groups of NK1 and 5-HT receptor inhibitors. These are considered the main basis of the therapeutic approach to control nausea and vomiting caused by chemotherapy (22), which based on the aggregated analyzes of studies, among these drugs, aprepitant + granisetron regimens, fosnetupitant + palonosterone have been the best in completely controlling nausea and vomiting. However, the dominant calculations of meta-analysis studies are based on different types of malignancies, and there is no study on breast cancer alone. In the present study, this goal was also addressed, but the focus was on non-pharmacological methods. Only one review study in Persian language has had this goal, which has included 5 studies (23), and in this study, a larger number of studies were reviewed. Our study showed that there are different methods that can be used as a supplement to standard treatments to prevent nausea and vomiting in breast cancer patients. According to the guidelines of the American Society of Clinical Oncology to prevent nausea/vomiting caused by chemotherapy in various types of malignancies, cisplatin, anthracycline, cyclophosphamide and dacarbazine have been classified as highly

nauseating drugs. A four-drug regimen that is a combination of an NK1 receptor antagonist, a serotonin (5-HT3) receptor antagonist, dexamethasone, and olanzapine has been proposed to prevent nausea in this class of chemotherapy drugs (24). In real-world studies specific to breast cancer, applying the guidelines of the American Society of Clinical Oncology was associated with reducing the rate of nausea/vomiting by half (25). Although the treatment regimens for the prevention and treatment of nausea and vomiting play an important role in the occurrence of nausea after chemotherapy, but some factors such as the experience of pain and insomnia, the history of nausea and vomiting in previous chemotherapy, chemotherapy with Highly emetogenic drugs (26), age less than 40 years, and not eating before treatment (2) increase the chance of this complication. These variations in nausea severity differ in sections of chemotherapy or in different chemo-medications. For example, patients treated with cyclophosphamide experience more prolonged nausea (27). Very diverse patterns of nausea experience in women undergoing chemotherapy show that an individual-based therapeutic approach is needed for a better response to anti-nausea treatment (28). These were all things that we were not able to address in our study because the heterogeneity between studies in the field of these factors was extremely high.

Limitations of the study

Although we tried to conduct a comprehensive search, it is possible that some studies were not found in our search. Also, search engines for Persian articles do not provide proper performance for accurate search of sources, which increases the chance of not finding published studies. There is a possibility that some studies may not be published for various reasons. Despite extensive research on this issue, it seems that measuring the complication of nausea and vomiting based on the patient's report or the therapist's interview faces challenges (1).

Conclusion

According to the present review, there are various complementary and non-pharmacological methods to prevent nausea and vomiting. But in the meantime, acupressure seems to prevent the occurrence of severe nausea and vomiting in patients undergoing chemotherapy due to breast cancer using various methods that have been used in research. Therefore, it is suggested that future research be done to standardize the methodology of acupressure interventions.

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Tables

Table 1: Studies included in the systematic review

Characteristics of the study	Mean age	intervention	n	Control	n	Chemotherapy regimen	Breast cancer grade	Nausea measurement method	Study design
Thamli kitkul	49	Ginger capsule500 mg twice + normal andanstero) ne + dexamethas (one	34	Placebo	-	Adriamycin + cyclophosphamide	More II		clinical trialstudy - crossover
Eghbali	46.02 ± 7.23	Ear acupressure	24	Standard treatment	24	cisplatin and anthracycline	mild to severe	Morrow standard questionnaire (1984)	clinical trialstudy - crossover
Roscoe	49.5	Compression wristband	32	Control without wristband and sham group wristband) in an inappropriate place outside (the wrist	64	doxorubicin	not mentioned	Likert scale	Clinical trial
Vanaki	49.7	therapeutic touch	36	Placebo and control	72	not mentioned	not mentioned	massage therapy touch) (therapy	Clinical trial
Billhult	51.8	massage	19	Control	20	epirubucin , fluorouracil, cyclophosphamide	I(5); II A (21); II B (12); III (1)	VAS	Clinical trial
Raghavendra	not mentioned	yoga	28	) Control supportive counseling and coping preparation (	34	5-fluorouracil, adriamycin , cyclophosphamide, methotrexate ,	II and III	MANE	Clinical trial
Molassiotis a	49.5	Compression wristband	17	Control	19	Doxorubicin + Cyclophosphamide/ FEC/ Epirubicin + CMF	I-III	INVR	Clinical trial

Shen	46	Electric acupressure	37	Acupuncture with low intensity and control group	Low intensity acupuncture (٣٣), control (٣٤)	Doxorubicin and Cyclophosphamide or equivalent Epirubicin	not mentioned	Number of vomiting during days ٥ after chemotherapy	Clinical trial
Molassiotis b	45.03	Progressive muscle relaxation exercise	38	Control	33	Adriamycin + cyclophosphamide	I-III, mostly in II	MANE	Clinical trial
Nazari	47.4	Black cumin and sumac and then placebo	35	Crossover group starting with placebo treatment	34	not mentioned	II and III	VAS	clinical) trial crossover study (
Lua	47.3	Ginger aromatherapy	30	Placebo control with aromatic oil	30	5-Flouracil + epirubicin + cyclophosphamide (FEC)/ Docetaxel + doxorubicin and cyclophosphamide (TAC)/ Docetaxel	I-IV	VAS	Clinical trial
Anestin	50.4	yoga	52	Control	30	AC, CMF/ FEC, AC-T, TAC	I (26); II (53); III (3)	MANE	Clinical trial
Ebrahimi	41.8 against 40.1	Ginger capsule one gram/day	40	Control	40	not mentioned	not mentioned	VAS	Clinical trial
Najafi	40.33	Ginger capsule one gram/day	10	Control	20	not mentioned	not mentioned	VAS	Clinical trial
Eghbali	47.8 against 45.7	Peppermint essential oil aromatherapy	50	Control	50	not mentioned	not mentioned	Rhodes questionnaire	Clinical trial

Morrow Assessment of Nausea and Emesis, MAN; Rhodes Index of nausea, vomiting and retching, INVR

Table 2. Risk of bias of clinical trial studies based on Cochran's checklist

study	Random sequence generation	Allocation concealment method	Degree of blinding	Sample drop	Non-selective reporting of results	Chance of bias
Thamlikitkul	*	**	**	**	**	Low
Eghbali	*	*	*	*	**	Top
Roscoe	*	*	*	*	**	Top
Vanaki	**	**	*	*	**	Low
Billhult	**	-	-	**	**	Some sources of bias
Raghavendra	**	**	-	**	**	Low
Molassiotis a	**	**	-	**	**	Low
Shen	**	**	**	**	**	Low
Molassiotis b	**	*	-	**	**	Some sources of bias
Nazari	**	**	**	**	**	Low
Lua	**	**	**	**	**	Low
Anestin	**	**	**	**	**	Low
Ebrahimi	*	*	*	*	**	High
Najafi	*	*	*	*	*	High
Eghbali	*	*	*	*	**	High

*Reported (Some sources of bias). ** Reported in full (low chance of bias). - Not reported (high chance of bias).