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The effect of omega-3 capsules on vasomotor disturbances induced by tamoxifen in breast cancer patients: A double-blind controlled clinical trial

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Abstract

Background and objectives: Vasomotor disturbances are among the most important side effects of tamoxifen. It is the most widely used anti-cancer drug in the world which may affect the quality of life. This study aimed to investigate the effect of omega 3 on vasomotor disturbances in women taking tamoxifen for breast cancer.

Materials and methods: The present study was a randomized double-blind controlled clinical trial carried out on 140 women with breast cancer who were suffering from side effects of tamoxifen. They were randomly assigned into two omega-3 and placebo groups. Then 1000 mg omega-3 capsules or placebo were administered to both groups per day for 12 weeks. Every week, a part of Green questionnaire was used to measure hot flashes and night sweats. T-test, Chi square, Whitney test and Friedman test were used to analyze the data.

Results: After 12 weeks of intervention, there was a significant difference between the two groups in terms of hot flashes ($p<0.001$). Moreover, a statistical significant difference was observed between the two groups in terms of night sweats ($p<0.001$).

Conclusion: It seems that omega-3 supplementation would be beneficial to reduce the amount of hot flashes and night sweats in women taking tamoxifen for breast cancer.

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Introduction

Breast cancer is the most common cancer and the second cause of cancer-related mortalities among women [1]. In the past decade, the percentage of women with stage I and stageII cancer, reached 65-80% from 41% [2]. Clinical experience indicated that women with breast cancer not only suffered from cancer but also experienced drug side effects such as vasomotor disturbances, nausea and vomiting, hot flashes, fatigue, and mood disorders [3-6]. Tamoxifen is one of the most common treatments for breast cancer [7]. Tamoxifen is a nonsteroidal antiestrogen medicine with poor estrogenic effects that controls Estradiol receptors. It is used for systemic treatment of breast cancer after mastectomy as a preventive agent for breast cancer in patients who have no history of cancer but are at high risk [8]. Hot flashes are the most important common side effects of tamoxifen [9]. Although hormone therapy is very effective in relieving hot flashes, it has little control over hot flashes in breast cancer patients [10,11]. Over the last decade, the use of alternative therapies such as nutrition, exercise, aromatherapy, homeopathy, herbal medicine, relaxation and herbal medications is increased dramatically that are useful to relieve hot flashes [12,13].

People prefer those treatments that can reduce symptoms and have fewer side effects. During the past decade, the role of polyunsaturated fatty acids such as omega-3 in reducing vasomotor disturbances has been investigated. Omega 3 is a food supplement that plays an important role in human health, especially cardiovascular health, brain, inflammatory diseases and depression [14,15].

There are some studies conducted, mostly on postmenopausal women, about the successful application of omega-3 on vasomotor symptoms [15]. The present study aimed to investigate the effect of omega-3 supplements on vasomotor disturbances in women with breast cancer who were taking tamoxifen.

Materials and methods

This study was a randomized double-blind controlled trial on women who were in stage I and stage II breast cancer treated with tamoxifen and were suffering from its side effects such as hot flashes and night sweats ,referring to Motahhari breast cancer clinic, Shiraz, Iran.

The protocol of the study is shown in figure 1.

The sample size was determined based on Lucas et al's study [16]based on this formula

$$n= (e^* p1(1-p1)+p2(1-p2)) / (p1-p2)^2$$

with the Alpha value of 0.05, capability assessment of 80% ,114-subject sample size (57 in each group) was estimated. According to the longitudinal design of the study and loss rate of 20% , finaly 140 patients were determined for the study. The inclusion criteria included patients who were in stage I and stage II breast cancer treated with tamoxifen and were suffering from its side effects such as hot flashes and night sweats (the selection of patients in these stages was not due to using tamoxifen in higher stages of breast cancer, patient's bad conditions and discontinuation of treatment during the study), premenopausal and postmenopausal due to the absence of using medications or surgery, completion of secondary therapies such as chemotherapy, the absence of mental and physical diseases such as diabetes, cardiovascular disease, depression, hypertension, high cholesterol, thyroid disease, liver disease and kidney disease, no use of psychiatric medications , no use of other medications and supplements to reduce side effects and no sensitivity to omega-3. The exclusion criteria included unwillingness to continue participation in the study, using medications or placebo incorrectly, disease relapse, and change in cancer's stages. Patients were selected based on available sampling in compliance with the inclusion criteria and through convenience sampling .Randomized permutation block design was used for randomization and samples were equally assigned to omega-3 and placebo groups, respectively. This was a double-blind study.Both patients and investigator were blinded to omega3 and placebo capsules and medications were coded by the pharmacist as group A and B. Data collection forms contained demographic characteristics such as personal information, history of disease and patient's complaints. One part of Green questionnaire was used to measure hot flashes and night sweats.

Individual scores obtained from the questionnaire ranged from 0 to 3. In this questionnaire, zero indicates the absence of symptoms; 1, 2 and 3 indicated symptoms of mild , moderate and severe intensity, respectively. 0 represented the lowest amount of suffering while 3 represented the highest suffering [17]. The questionnaire was frequently used by various researchers, the reliability for Vasomotor Scale has been reported 0.83 [18].

After the collection of personal information and completing the initial questionnaire, patients received proper trainings of correct documentation of symptoms, referrals and forms of recording symptoms. Omega-3 capsules (1000 mg) approved by the Ministry of Health prepared for experimental group and placebo capsules containing 1000 mg of oral non-absorbable paraffin similar to omega-3 capsules in terms of color, shape and size were prepared for the control group. Next, one capsule in coded packages was administered per day for 12 weeks. Moreover, each week both groups received a form to record information related to the severity of hot flashes and night sweats at the end of each week to submit them to the researcher. During the course of treatment and in the case of patients' non-referral to the clinic, the researcher called patients once a week or visited them at their homes to control and ensure the accurate use of supplements and completion of related forms. Data were collected during 12 weeks and demographic data between the two groups were compared by independent t-test and Chi-square test. Friedman and Mann-Whitney tests were used for intragroup and intergroup comparisons , respectively. All the tests were calculated as significant at the 5%level and analyzed using SPSS software, version 16.

Ethical considerations: After obtaining the approval of the Research Vice-chancellor of Shiraz University of Medical Sciences and receiving the ethics code from the Ethics Committee (CT-90-5786) and Iranian Registry of Clinical Trials (code: IRCT201104052515N3), written informed consents were signed by the participants. Also, omega3 capsules were given to the control group after the end of the study.

Results

This study was carried out on 140 women at stage I and stage II breast cancer treated with tamoxifen who experienced side effects such as hot flashes and night sweats. 101 patients among 140 individuals (51 patients in experimental group and 50 patients in control group) completed the study. 39 patients were excluded (19 patients in omega-3 group and 20 patients in placebo group) because of severe hot flashes and poor response to Omega-3treatment or for not properly using capsules

in 2 and 3 weeks, respectively.

Results indicated that there was no significant difference in terms of demographic characteristics while there was a significant difference in menarche age between the two groups (P = 0.012) (Table 1) . The mean scores of hot flashes between the two groups were compared every week (from the 1st to the 12th week). Hot flash scores, before and after the study, significantly decreased in both groups (P <0.001 .) Median hot flash scores in the experimental and control groups were 3 (2-3) before the intervention but after the 5th week, there was a significant difference between the two groups (p< 0.001) .This significant difference was also observed at the end of the study (after the 12th week) between the two groups ((1-2) vs. 2(1-2) (p<0.001) (Table 2). Moreover, the median scores of night sweats in both groups were compared weekly (from the 1st to the 12th week). There was a significant difference in night sweat scores before and after the study in both groups (p<0.001). The median scores of night sweats in the experimental and control groups were equal to 3(2-3) before intervention. But after the 4th week, there was a significant difference between the two groups (p< 0. 001). Moreover, this significant difference was also observed at the end of the study (after the 12th week). (1(0-2) vs 1 (2-1) 2 (p<0.001) (Table 2). The median scores decreased to 1 after the 4th week. Moreover, night sweat scores in 25% of individuals in omega-3 group decreased from 2 to 1 after four weeks and it was reduced to 0 after 8 weeks. Whereas the median in the control group was remained to be 2 until the last week (the 12th week). There was no significant difference in night sweats between scores of the two groups from the 1st to the 5th weeks. However, there was a statistically significant difference after 5 weeks (p<0.001) (Table 2).

Table 1: Comparison of the mean of demographic characteristics in two groups

Variable	Omega3 Mean± SD	Control Mean± SD	P-Value
Age	40.2±4.1	38.8±5.1	0.133
Marriage age	22.4±4.1	23.8±4	0.096
Age at menarche	13±1.3	12.4±1.2	0.012
Age at first pregnancy	23.6±4.5	25±3.8	0.127
Number of children	1.9±1	1.94±.9	0.846
BMI (Body Mass Index)	26.4±3.7	26.2±3.4	0.795

Table 2: Comparison of the mean of hot flashes and night sweats in two groups

Group Variable name	Omega 3 M (Q1-Q3)	Control M (Q1-Q3)	P-Value
Hot flashes (before intervention)	3 (2-3)	3 (3-2)	0.368
Hot flashes (after intervention)	1 (1-2)	2 (2-1)	0.001
(p-value) Within groups	0.001	0.001	
Night sweats before intervention	3 (2-3)	3 (3-2)	0.1
Night sweats after intervention	1 (0-2)	2 (2-1)	<0.001
(p-value) within groups	0.001	0.001	

Discussion

Hot flashes had a large impact on woman's quality of life. A close relationship between hot flashes and quality of life in women with breast cancer was observed. These women experienced a higher level of fatigue, sleep disorders, and lower levels of physical health than women who had not hot flashes [19]. Neurotransmitters are directly involved in hypothalamic heat-regulating center that seems to be a major factor of hot flashes and night sweats [20]. Different drugs are used for alleviating vasomotor disturbances in patients with breast cancer including progestins. However, some physicians and patients are concerned about using any hormone for hot flashes and night sweats in patients. Moreover, non-hormonal treatments have limited applications and some side effects [21].

Our study results indicated that there was a significant difference in the amount of hot flashes between omega-3 group and control group after 12 weeks. There was a significant declining trend in hot flash rates over time within groups. Although a declining trend was observed in both groups, this trend was faster in the experimental group. The same result was observed in night sweats as well.

It seems that the most important mechanism of omega-3 fatty acids to alleviate vasomotor symptoms was balancing the production of neurotransmitters by polyunsaturated fatty acids [22]. Omega-3 fatty acids affect the nervous system through influencing phospholipids of nerve cell walls and proper functioning and secretion of neurotransmitters. This will reduce vasomotor symptoms [23].

A study which aimed to investigating the effect of omega-3 supplementation in postmenopausal women with depression and vasomotor disturbances,it was reported a significant decrease in hot flashes [24].

A comparative study investigated the effect of Isoflavones in combination with and without Omega-3 on hot flashes in menopause women. In this study, the mean reduction of hot flashes after treatment using Isoflavones with and without Omega 3, was 38.5% and 20% ,respectively. Moreover, this reduction was significant between the two groups that is consistent with our study results [25]. However, this difference was not significant between groups in another study which compared the effects of omega-3 and yoga and aerobic exercise on reducing vasomotor disturbances in women with preeclampsia after 12 weeks of daily administration of 1.8 g of omega-3 supplementation [19]. In this regard, these results are not consistent with the results of the present study.

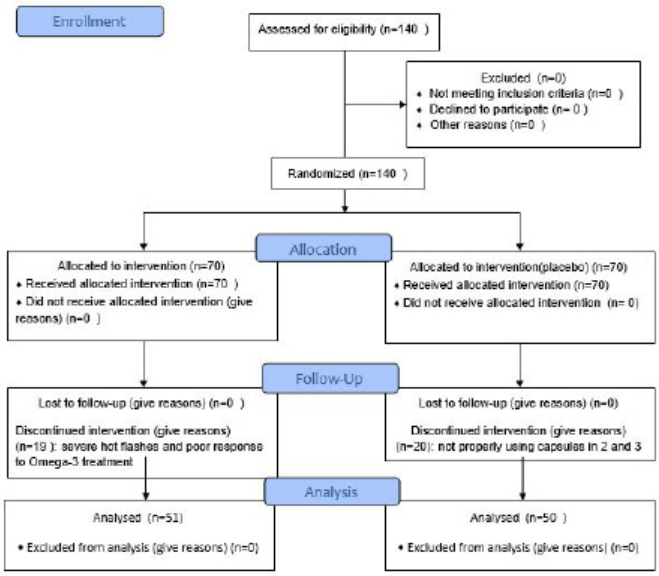
Another study was investigated the effects of omega-3 supplementation on hot flashes in middle-aged women. It was concluded that there was a significant difference between mean scores of hot flashes between groups after 8 weeks. According to that study, the average reduction of daily hot flashes after 8 weeks, in Omega 3 and placebo groups, was 55% and 25%, respectively [16]. Meanwhile, in the present study the average decrease in hot flashes in intervention and placebo groups was 66% and 33%, respectively. This difference may be related to women's general health in these two studies. Although the study participants were diagnosed with breast cancer, women's general health status was good. However, in Lucas et al's (2009) study, mild to moderate depression was observed among women. The duration of Omega-3 supplementation consumption was different in these two studies.

According to one study which aimed to investigate the effects of omega-3 on pre-menopausal depression and hot flashes, positive effects were observed after 8 weeks of omega-3 consumption [26]. In other studies, the beneficial effects of omega-3 within 12 weeks were compared with exercise and yoga in reducing vasomotor symptoms which is consistent with the results of the present study [27].

In other studies which examined the effect of linseed on vasomotor symptoms, the decrease in the frequency of hot flashes and night sweats was observed which is in agreement with our results [28, 15]. Linseed is a main source of Isoflavones and fatty acid of Linolenic type in Omega - 3 groups [29].

The limitations of this study were related to problems such as patients'rejection to use daily supplementation due to the prolonged treatment course, no weekly referral to clinic due to home-clinic distance, cost , fatigue, big capsules and difficulty in swallowing capsules or change in cancer's stage, which forced us to exclude some patients from the study.

CONSORT 2010 Flow Diagram



Conclusion

According to results of this study, it seems that omega-3 supplements will reduce hot flashes and night sweats in women taking tamoxifen for breast cancer. Despite vasomotor disturbances caused by tamoxifen, it seems appropriate to use omega-3 as supplement which has no side effects. It is suggested to carry out studies with more sample size and longer duration.

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