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Compare the effect of flaxseed, evening primrose oil and Vitamin E on duration of periodic breast pain

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Abstract:

BACKGROUND: Breast periodic pain is the most common disorder of the breast which leads to consultation with knowledgeable people like a midwife. The aim of this study was to compare the therapeutic effect of flaxseed, evening primrose oil, and Vitamin E on the duration of the period of breast pain.

MATERIALS AND METHODS: This study is a quasi-randomized clinical trial conducted in 2015 on ninety patients complaining of breast periodic pain referring to Gynecologic Clinics of Ghaem Hospital or residents living in dormitories of Mashhad University of Medical Sciences. Randomization was conducted based on the study environment. The first group received 30 g of powdered flaxseed, the second group received two 1000 mg capsules of evening primrose, and the third group received 1 capsule of 400 IU Vitamin E, daily and for two menstrual cycles. Cyclical breast pain was measured at the beginning and end of both intervention periods by daily subscription form of pain duration. Data analysis was performed by SPSS 16 software and Kolmogorov-Smirnov, Chi-square, Friedman, Fisher's, and one-sided ANOVA tests. The level of significance was set at $P < 0.05$.

RESULTS: The mean duration of breast pain in flaxseed group within 2 months of intervention decreased significantly (confidence interval [CI] = 95%, $P = 0.006$), but despite reducing the duration of pain in evening primrose oil group (CI = 95%, $P = 0.058$) and Vitamin E (CI = 95%, $P = 0.306$), this reduction was not significant. In overall, the average duration of breast pain in all three flaxseed, evening primrose oil, and Vitamin E groups was not significantly different before the intervention (CI = 95%, $P = 0.286$), 1 month after the intervention (CI = 95%, $P = 0.195$), and 2 months after the intervention (CI = 95%, $P = 0.667$).

CONCLUSION: The use of flaxseed, evening primrose oil, or Vitamin E may reduce breast pain, and this is a significant reduction in flaxseed.

Keywords:

Breast pain, evening primrose oil, flaxseed, Vitamin E

Introduction

Periodic pain of the breast is referred to moderate-to-severe pain in one or both breasts lasting more than five consecutive days and is overcome after menopause.^[1] Breast periodic pain is related to intensification of symptoms before the menstrual period which is started in the luteal phase of the period and is

accompanied by congestion, pain, burning, heaviness, and two-sided sensitivity of the breast.^[2] Pain is the most common type of breast pain and makes up about 67% of the total breast tenderness and takes more than 7 days in 11% of cases.^[1,3,4] This pain interferes with sexual activity in 48%, in 37% of cases with physical function, and with social functioning in 12% of cases.^[5]

Three main causes of periodic pain of breast are estrogen increase, decrease of

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progesterone, and increase of prolactin.^[5] Reduction in the proportion of unsaturated fatty acids to saturated ones as well as the role of inflammatory mechanisms including increased levels of inflammatory biomarkers such as 6 and 1-alpha interleukins and tumor necrosis factor-alpha have also been proposed.^[3,6] Drugs used for the treatment of breast periodic pain such as danazol, tamoxifen, and bromocriptine are often hormonal and leave serious side effects.^[1]

Gynecologic symptoms such as breast periodic pain which are often chronic in nature can be treated by herbs and supplements which are natural and have few side effects and have more fans compared to prescription and nonprescription drugs. Midwives should be aware of evidences on treatments with fewer side effects and fewer interactions with other drugs.^[7,8] Of alternative treatments used as first-line treatment of breast periodic pain are flaxseed, evening primrose oil, and Vitamin E.^[4,9,10]

Flaxseed with the scientific name *Linum usitatissimum* includes some unsaturated essential fatty acids which cause synthesis of omega-3 fatty acid and through it, the production of some arachidonate metabolites are reduced, and eicosanoids with less pro-inflammatory effect are produced. Eicosanoids, derived from omega-3 found in flaxseed, have less inflammatory and even anti-inflammatory properties compared to omega-6 available in evening primrose. In addition, flaxseed contains large amounts of phytoestrogen lignan which is an antioxidant, inhibits the activity of the aromatase enzyme, resulting in decreased production of estrogen, thereby, plays a role in preventing cancers related to estrogen such as breast cancer.^[4,11-13] The chemical structure of lignans is similar to estrogen receptor selective modulators such as tamoxifen which is of hormonal drug treatments of periodic breast pain.^[14,15] According to the study of Mirghafourvand *et al.*, the average time period of breast pain significantly decreased in all three groups.^[1] Due to the fact that in women with periodic pain of breast, plasma levels of essential fatty acids such as gamma linolenic acid and precursors of class prostanoïd prostaglandin E₁ are low, so supplements containing gamma linolenic acid such as evening primrose oil can be used in the treatment of period pain of the breast.^[8,9] The study of Alvandipour *et al.* showed that evening primrose oil and Vitamin E have similar therapeutic effects in reducing breast pains.^[16]

The mechanism of Vitamin E in reducing the periodic pain of the breast due to its antioxidant benefits is the ability to prevent the lipoxygenase and cyclooxygenase and prevent the oxidation of unsaturated fatty acids and hence prevent the formation of prostaglandins,

and with increasing internal opioids of the body, enhance the individual's tolerance to pain and reduce it.^[17] In the study of Jafarnejad *et al.*, Vitamin E has been effective in reducing periodic breast pain duration.^[12]

Due to the fact that people prefer the use of herbal supplements such as flaxseed in the treatment of chronic diseases such as cyclical breast pain^[7] and due to the fact that all three drugs of flaxseed, evening primrose, and Vitamin E have been introduced as the first line of treatment of breast periodic pain and a study is not available to compare the impact of these three first-line drugs on periodic pain of breast, the present study was conducted to compare the three drugs for periodic pain breast.

Materials and Methods

This study is a quasi-randomized clinical trial performed in 2015 on ninety women with periodic breast pain, which was repeated for at least five consecutive days in two previous menstrual cycles, and they referred to Ghaem Educational, Research and Treatment Center or were resident in the dorms of Mashhad University of Medical Sciences.

Patients having the following criteria were studied: informed consent, age of 18–45 years, having a cyclical breast pain for at least 5 consecutive days in two previous menstrual cycles, regular 21–35 day menstrual cycles, lack of any abnormal case in breast clinical examination, no history of breast cancer or any breast masses in themselves or first-degree relatives such as mother and sister, absence of tumors and cancers in other organs, no history of breast surgery and gel injections in the breast, and lack of having constipation and were excluded from the study in case of the following conditions: pregnancy, taking hormonal drugs such as oral contraceptives, sensitivity or intolerance to supplements and medication side effects during the study, lack of medication for three consecutive days or five periodic days, and withdraw from the study.

The sample size according to other studies^[4,8,18] with a power of 80% and 95% confidence level was 27 persons in each group and a total of 81. Due to the nature of the study which was a quasi-randomized clinical trial and lasted for two menstrual cycles, the rate of loss was considered 10% according to other studies, resulting in a total sample size of ninety patients and thirty persons per group.

After getting permission from the Ethics Committee, sampling began through coordination with the

centers selected for sampling, which were residences of Mashhad University of Medical Sciences and Gynecology Clinic of Ghaem Medical Center of Mashhad. Given that this study was a quasi-clinical trial and six centers were selected for sampling, and due to the fact that there was no possibility of blinding the drugs used, and people within each center were linked together, to control the dissemination of information, centers were divided into three groups randomly and based on the table of random numbers, and both centers were laid in one treatment groups. Then, people who had the profile of the study center were chosen based on easy way and objective. First, the basic form of demographic characteristics and duration of pain in people who complained of breast periodic pain was completed. The diagnosis criterion was breast periodic pain for at least five consecutive days provided that this case is repeated in their two previous menstrual cycles. Then, breast of people was examined in terms of mass, secretion, symmetry, and unnatural cases. Then, people were asked until the start the next menstrual period to use proper bra which were as supporters and minimizing movements of the breasts, and with the support of mammary tissue, prevent aggravating of the pain,^[2] and intervention began with next menstrual cycle start. They were divided into three groups as follows: the flaxseed group received 30 g of milled flaxseed into two 15 g packages, each package must be solved in a glass of water, juice, doogh, milk, soup, yogurt, or salads. Group of evening primrose oil capsules received two 1000 mg capsules daily and group of Vitamin E received a 400 IU capsule daily. All three drugs were taken orally with a glass of water for two menstrual cycles.

Flaxseed used in this study was milled and weighed after preparation, and because of the possibility of oxidation, the packaging lid was vacuumed and was delivered to the research units on a weekly basis. Capsules of evening primrose oil (manufactured by Barij oil pharmaceutical company) have thirty number packages and capsules of Vitamin E (manufacturing of Co. Zahravi) in ten number sheets and were provided from drug store and were delivered to research units on a monthly basis. The research centers were called every week to remind taking medications and to answer questions of the individuals. Checklist of daily use of medication for daily record throughout the week, with the weekly checklist and duration of breast pain based on daily recording form of pain were given to the research units by the researcher. At the end of each month of treatment, criteria for the withdrawal during the study including a delay in medication for 3 consecutive days or 5 continuous days, use of any other treatments for breast pain, and pregnancy were

evaluated and based on which those who have not observed the study circumstances were excluded from the study.

The validity of all forms made by the researcher including personal information form, examination form, form of elimination criteria during the study, and form of daily record of pain and medication checklists were determined by content validity method. Reliability of form of daily record of pain duration was determined by inter-rater reliability method, and the correlation between the responses was confirmed by 0.91 Cronbach's alpha coefficient. Other research tools included clear questions and were frequently asked research units, so no need to determine the reliability.

Finally, the data were analyzed by statistical software SPSS (IBM – Company, Armonk, NY-USA, version 16). Kolmogorov-Smirnov test was used to evaluate the normality of variables, Chi-square and Fisher's exact test and one-sided ANOVA statistical tests were used to verify the homogeneity of variables, Friedman test was used to determine the drug's effect on individual groups, and Kruskal-Wallis test was used to compare the effects of drugs among the three groups. $P < 0.05$ was considered statistically significant.

Independent variables in this study were flaxseed, evening primrose oil, and Vitamin E and the dependent variable was periodic breast pain duration. Furthermore, the confounding variables were controlled by eliminating, taking under consideration, and assimilating.

This quasi-randomized clinical trial has been recorded with number IR.MUMS.REC.1394.503 in Ethics Committee of Mashhad University of Medical Sciences and with code IRCT2015072123281N1 in Clinical Trial Center of Iran.

Results

Mean and standard deviation of age group was 30 ± 7.09 years in flaxseed, 27.90 ± 5.61 years in evening primrose oil, and 27.50 ± 6.65 years in Vitamin E, which the difference was not significant (confidence interval [CI] = 95%, $P = 0.222$). The average age was reported generally 28.4 ± 6.5 years and the mean duration of periodic breast pain as 6.9 ± 5.5 years.

The people under study were homogeneous in terms of the primary variables [Table 1]. The average number of pregnancies, age at first birth, age at menarche, number of children given milk, height, weight, and BMI showed no statistically significant difference between the groups. The mean duration and standard deviation of periodic

pain of breast in the flaxseed group were 5.61 ± 4.60 days, 7 ± 5.16 days in evening primrose oil group, and 8.26 ± 6.61 days in Vitamin E; there was no statistically significant difference between the three groups.

The mean duration of pain before and 1 and 2 months after treatment was compared to the three flaxseed, evening primrose oil, and Vitamin E groups [Table 2]. Kruskal-Wallis test results showed that the mean duration of breast pain in all groups of flaxseed, evening primrose oil, and Vitamin E before the intervention (CI = 95%, $P = 0.286$), 1 month after the intervention (CI = 95%, $P = 0.195$), and 2 months after the intervention (CI = 95%,

$P = 0.667$) were not significantly different from each other.

Based on inter-group comparisons within in each group, Friedman test showed that the average duration of breast pain before the intervention, 1 and 2 months after the intervention was significant only in flaxseed (CI = 95%, $P = 0.006$) and was not significantly different in the groups of evening primrose oil (CI = 95%, $P = 0.058$) and Vitamin E (CI = 95%, $P = 0.306$) [Table 2].

The mean duration of breast pain in the flaxseed, evening primrose oil, and Vitamin E groups before the

Table 1: Frequency distribution of women with periodic breast pain in three groups

Variable	Group			Total, <i>n</i> (%)	Test result
	Flaxseed, <i>n</i> (%)	Evening primrose oil, <i>n</i> (%)	Vitamin E, <i>n</i> (%)		
Age group					
≤25	8 (26.7)	12 (40)	16 (53.3)	36 (40)	$P1^a=0.222$,
26-35	15 (50)	14 (46.7)	12 (40)	41 (45.6)	$P2^b=0.053$
>35	7 (23.7)	4 (13.3)	2 (6.7)	13 (14.4)	
Marital status					
Single	18 (60)	18 (60)	15 (50)	51 (56.7)	$\chi^2^c=0.814$, $df^d=2$,
Married	12 (40)	12 (40)	15 (50)	39 (43.3)	$P3^e=0.665$
Level of education					
Diploma	4 (13.3)	4 (13.3)	7 (23.3)	15 (16.7)	$\chi^2=1.44$, $df=2$,
BSc or higher	26 (86.7)	26 (86.7)	23 (76.7)	75 (83.3)	$P3=0.487$
Job					
Housekeeper	4 (13.3)	6 (20)	10 (33.3)	20 (22.2)	$\chi^2=3.6$, $df=2$,
Occupied	26 (86.7)	24 (80)	20 (66.7)	70 (77.8)	$P3=0.165$
Regular exercise					
Yes	10 (33.3)	5 (16.7)	3 (10)	18 (20)	$\chi^2=5.4$, $df=2$,
No	20 (66.7)	25 (83.3)	27 (90)	72 (80)	$P3=0.067$
Contraception method					
Condom	5 (50)	5 (45.5)	5 (38.5)	15 (44.1)	$\chi^2=1.798$,
Natural	4 (40)	6 (54.5)	7 (53.8)	17 (50)	$P1=0.916$
IUD (TCU380A)	1 (10)	0	1 (7.7)	2 (5.9)	
History of periodic breast pain					
Yes	15 (50)	15 (50)	16 (53.3)	46 (51.1)	$\chi^2=1.18$, $df=4$,
No	5 (16.7)	5 (16.7)	7 (23.3)	17 (18.9)	$P3=0.881$
Don't know	10 (33.3)	10 (33.3)	7 (23.3)	27 (30)	
History of using other cyclical breast pain relief methods					
Yes	1 (3.3)	2 (6.7)	1 (3.3)	4 (4.4)	$\chi^2=0.69$,
No	29 (96.7)	28 (93.3)	29 (96.7)	86 (95.6)	$P1=1.00$

^aAccording to Fisher's exact test, ^bRegression analysis, ^cChi-square test, ^dDegrees of freedom, ^eBased on the Chi-square test. IUD=TCU380A

Table 2: The mean and standard deviation of duration of breast pain before, 1 and 2 months after the intervention in women with periodic breast pain in separation of the three groups

Variable	Group						Kruskal-Wallis test results (<i>P</i>)
	Flaxseed		Evening primrose oil		Vitamin E		
	<i>n</i>	Criterion±SD	<i>n</i>	Criterion±SD	<i>n</i>	Criterion±SD	
Duration of breast pain before intervention (days)	30	8.33±2.99	30	8.20±2.85	30	7.20±2.28	0.286
Duration of breast pain 1 month after intervention (days)	28	8.46±2.70	28	7.42±3.75	30	7.16±2.81	0.195
Duration of breast pain 2 months after intervention (days)	28	7.17±2.90	28	6.50±3.89	30	6.5±3.14	0.667
Friedman test results (<i>P</i>)		0.006		0.058		0.306	

SD=Standard deviation

intervention with 1 month after the intervention, before the intervention with 2 months after the intervention, and also 1 month after intervention with 2 months after the intervention had not statistically significant difference.

All research units during the two interventions based on Fisher's exact test were similar in use of pain, diuretic and sedative medications, as well as the use of soy and its derivatives. Within 2 months of intervention, 83 patients (92.2%) in the 1st week, 85 patients (98.8%) in the 2nd week, 84 patients (97.7%) in the 3rd week, 85 patients (98.8%) in the 4th week, and 100% of patients in the 5th, 6th, 7th, and 8th weeks had no medical complications. In the whole intervention period, five patients in flaxseed group and five ones in evening primrose oil group reported medication complications, which these complications in flaxseed group included diarrhea, flatulence and nausea in mild and nausea, drowsiness and mild headache in evening primrose oil group and no complication was not reported in Vitamin E group as well. In general, three groups had not statistically significant difference in terms of side effects. During the study, four patients were excluded, two of which in flaxseed group, one due to lack of access to powder and one due to forgetfulness in taking powder for 4 consecutive days, and two people from evening primrose oil group, one due to flavor of capsules and unwillingness to continue the study, and the other due to forgetfulness in taking the capsules for 5 consecutive days in month.

Discussion

In the present study, the effect of flaxseed on the duration of breast periodic pain was more than evening primrose oil and Vitamin E. Three groups have not statistically significant differences at the beginning of the study in the duration of breast pain.

According to the present study, duration of breast pain into three groups of flaxseed, evening primrose oil, and Vitamin E per month of treatment was not significantly different in the total population. Blommers *et al.* reported that 120 patients with severe breast pain treated with evening primrose oil or fish oil; the days of pain in the entire study population were significantly reduced.^[19] The results of the present study do not match with the research mentioned. In the present study, pain duration did not significantly reduce in the evening primrose oil group. The reason for this difference might be that in Blommers *et al.*'s study, both cyclical and noncyclical breast pains were investigated, which in the noncyclic pain because of they exist in the whole menstrual cycle, pain duration is more than that of cyclic. Another possible reason is the difference in the dosage of evening primrose oil used in the study of Blommers *et al.* as

3 g daily, while in the present study, it was 2 g daily. Furthermore, the duration of treatment in the study of Blommers *et al.* was longer as 6 months.

The results of Mirghafourvand *et al.* showed that the average duration of pain was significantly decreased in the three groups studied using flaxseed, Vitex agnus, or placebo.^[1] In the present study, reduction of the duration of pain was significant only in flaxseed group as well. The reason of this similarity probably was almost the same dosage of flaxseed used and the same duration of the intervention. Study of Alvandipour *et al.* showed that evening primrose oil and Vitamin E have the same treatment effects in reducing breast pain,^[16] the results of which are consistent with this study because in this study, both evening primrose oil and Vitamin E drugs reduced duration of periodic pain but no significant difference was observed between them. The reason for the similarity of the results of this study and the present study may be the used similar doses of evening primrose oil and Vitamin E. In the study of Momeni *et al.*, the number of days without pain 2 months after the intervention, had a significant decrease only in evening primrose and Vitex agnus, and not a significant difference found in Vitamin E. The results of this study on evening primrose are different from results of the present study and is similar regarding Vitamin E. In our study, despite the pain reduction in each of the three groups, this reduction was significant only in flaxseed group. The reason for this difference may be different doses of evening primrose and similar doses of Vitamin E as well as a higher number of individuals in each group.^[18] In the study of Jafarnejad *et al.*, Vitamin E and fish oil both led to a significant reduction in periodic breast pain. In the present study, despite the reduction in the duration of pain in Vitamin E, this reduction was not statistically significant, the reason for this difference may be due to the higher number of research units in the study of Jafarnejad, *et al.*^[12]

Of the strengths of this study were to compare flaxseed with the most common treatments for periodic breast pain, which due to the ethical limitations, the examination and identification of periodic breast pain were conducted as retrospective and the correctness of the remarks of research units were applied as selection criterion and it was not possible to blind the study because of various medication forms and nonacceptance of research units of concomitant use of two different medication forms and high cost of providing the placebo.

Conclusion

This study found that all three drugs of flaxseed, evening primrose oil, and Vitamin E reduce breast pain duration, but this reduction is impressive in flaxseed group. Since

the reduction in the duration of breast pain in flaxseed group was more than the other two groups. Therefore, it is suggested to use this herbal medicine which is the richest source of omega-3 essential fatty acids, contains phytoestrogens, lignans, and antioxidant, and has few side effects, and rejuvenating properties, including the reduction of breast cancer, to reduce the periodic pain;^[4] and its impact in the treatment of noncyclic pains that are usually longer, be also measured.

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Conflicts of interest

There are no conflicts of interest.

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