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Vitamin E versus Evening Primrose Oil versus Placebo for the Treatment of Cyclic Mastalgia: A Double-Blind Randomized Controlled Trial

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ABSTRACT

Background: Reassurance is important because it influences lifestyle choices or fears of breast cancer in 70% of women of reproductive age who have breast discomfort and seek medical attention. Either cyclic or noncyclic mastalgia exists. Breast discomfort needs to be carefully evaluated and should be looked into the same way as any other breast symptom. Natural remedies like evening primrose oil and vitamin E are now being used as therapeutic options because of the undesirable side effects of other treatment approaches.

Objective: In order to treat cyclic mastalgia, we compared the efficacy and adverse effects of vitamin E and evening primrose oil. **Patients and Methods:** We conducted a double-blind randomized controlled trial between February 2018 and February 2019 at Al-Jedaani Hospitals, KSA. A total of 160 women of reproductive age with a chief complaint of cyclic mastalgia were enrolled into this study. They were randomly assigned into 3 groups: group A of 55 patients (34.4%) received vitamin E, group B of 45 patients (28.1%) received evening primrose oil and group C of 60 patients (37.5%) received placebo. Overall pain severity and the effect of pain on patients' lifestyle were assessed at 1-month and 3-month follow-up visits.

Results The mean age of the patients was 31.23 ± 6.82 years. Highest respondents were aged between 30 and 38 years (34.5%). The median pain score and the effect of pain on patients' lifestyle were significantly decreased on successive follow-up visits. Although this decrease was significant in each individual group, it was not statistically significant compared to one another (P value = 0.619 and 0.621 respectively).

Conclusion Vitamin E and evening primrose oil have a good impact on cyclic breast pain but their effect is not much different than placebo effect

Keywords: Cyclic Mastalgia, Evening primrose oil, Vitamin E.

INTRODUCTION

Mastalgia may affect up to 70% of females during their reproductive age. It ranges from tension or discomfort to real pain. It is typically classified as cyclic, non-cyclic and extra-mammary pain [1]. Although benign factors are more frequently to blame for this disease, breast cancer should be ruled out since it is the most common source of concern for patients. It is important to rule out extra-mammary sources of pain such Tietze syndrome or transferred pain. Severe mastalgia has a major impact on women's daily activities [2]. Numerous illnesses, including stress, anxiety, depression, irritable bowel syndrome, and various mental disorders, have been linked to mastalgia, which may indicate a psychosomatic basis or multifactorial aetiology [3].

Increased serum prolactin levels, oestrogen sensitivity, reduced serum progesterone, an antioxidant or gamma linoleic acid deficit, or a systemic condition of salt and water retention are only a few of the causes of cyclic mastalgia that have been suggested [4]. The most crucial management move once cancer has been ruled out is reassurance [5]. Various treatment modalities have been used like Tamoxifen, Danazol, Bromocriptine but their side effects preclude their use except for resistant cases only. This makes the use of natural supplements like Oenothera biennis (Evening primrose oil) and vitamin E an attractive treatment option [1].

Evening primrose oil (EPO) is native plant of North America. The seed contains a variety of amino acids as lysine, tyrosine, phenylalanine, etc., while the seeds' oil contains the omega 6 fatty acid gamma-linolenic acid (GLA), which is thought to be deficient in patients with mastalgia [6]. Lack of GLA renders the epithelium of breast cells more susceptible to circulating hormones. In addition, GLA plays a critical role in the production of anti-inflammatory eicosanoids via the lipoxygenase and cyclooxygenase pathways [6].

Vitamin E is an antioxidant that acts by preventing the formation of and scavenging reactive oxygen species (ROS), eventually stabilizing the epithelium of breast cells while lowering the amount of oxidative stress indicators and shielding them from harmful free radicals [7]. In order to treat cyclic mastalgia, we compared the efficacy and adverse effects of vitamin E and evening primrose oil.

MATERIALS & METHODS

Population

We included one hundred sixty eligible women who were presented to the Breast Clinic at AL-Jedaani Hospitals between February 2018 and February 2019, complaining of cyclic mastalgia for at least 3 months.

We excluded women with suspected breast lesion, diagnosed breast cancer, pregnant, lactating, non-cyclic

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mastalgia, severe mastalgia (VAS≥7), previous breast surgery, any contraindications, or interactions to used medications, use of oral contraceptive pills, diabetics and patients with hormonal abnormality.

All patients had a comprehensive medical history recorded, and a regular breast exam was done. All patients under the age of 35 years received ultrasonography, while those over 35 had mammography in addition to ultrasonography. For certain individuals, a breast MRI was sought in the event of an ambiguous diagnosis. For individuals who had any clinical symptoms or evidence of a hormonal imbalance, the hormonal profile was examined.

All of the involved women were given the full assurance that they did not have breast cancer and were given advice on changing their lifestyles, such as wearing a supportive bra, exercising to lose weight, reducing mental stress with relaxation techniques, and changing their diets to consume less fat and caffeine while consuming more dietary fiber.

At each follow-up appointment, every patient was asked if they would still like to participate in the study. Patients were instructed not to use any analgesics during the research period and to let doctors know if their pain level increased.

Intervention: Management of cyclic mastalgia
Comparators: Population was divided into three groups: Group A received vitamin E 200 mg capsules once daily, group B received evening primrose oil 500 mg capsules twice daily, and group C received placebo capsules twice daily. A placebo capsule was a sugar pill, and it was almost identical to the active capsules in size, appearance and taste.

Outcomes: Visual Analogue Scale, side effects of used medications and the effect of pain on patients' lifestyle were determined at 1-month and 3-months follow-up visits. Therapeutic success was evidenced by diminished assessed pain score. The enrolled patients were asked to record their breast pain using a daily chart of Visual Analogue Scale (VAS) (0 = no pain; 10 = worst pain) as shown in figure (1). The sum of the daily VAS within a menstrual cycle was considered as the breast pain chart as shown in figure (2).

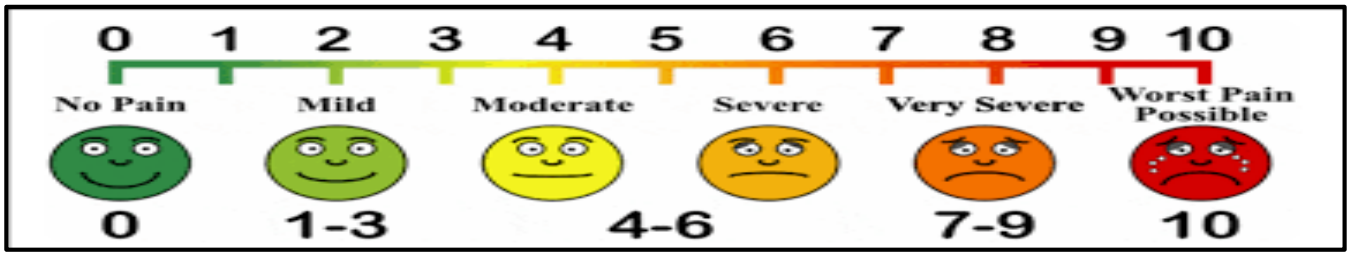

Figure (1): Visual Analogue Scale (VAS) [3].

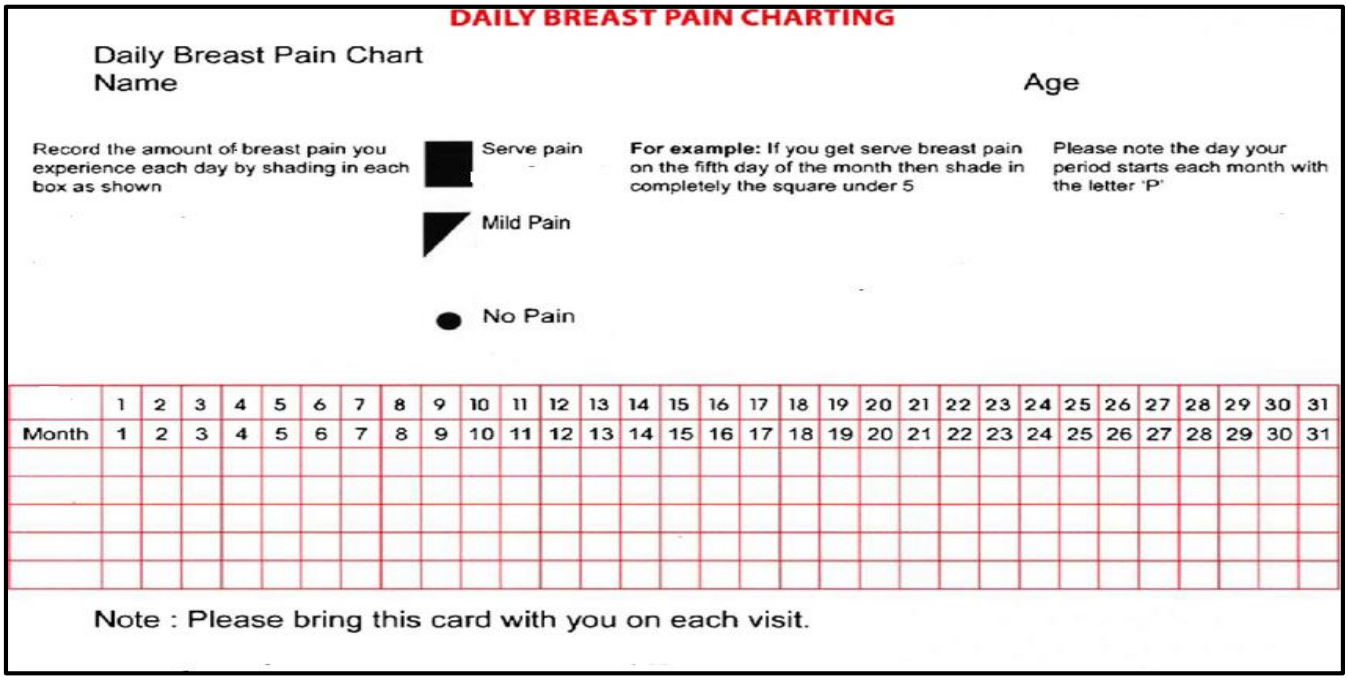

Figure (2): Breast pain chart. [3]

In addition, the influence of pain on patients' lifestyle (work, sexual activity, and sleep) was subjectively assessed using a number scale ranging from 1 to 10.

The Ethical Institutional Review Board in our hospital approved the study. After explaining our research objectives. This study was conducted in compliance with the code of ethics of the world medical association (Declaration of Helsinki) for human subjects.

Statistical analysis

The information was examined using SPSS 25 (IBM: USA). Randomized controlled experiment with double blinding. The pharmacists administered the pills before therapy so that neither the physician nor the patient knew which substance had been dispensed. Enrolled patients were randomly assigned to one of three groups, with each patient drawing a chit and being assigned to the matching group. Throughout the trial, patients were uninformed of their group type. The investigators did not have access to the randomization code. Only when the volunteers decreased did the investigators gain access to the codes. All participants signed an informed consent form. The frequency, mean, and standard deviation. The correlation is calculated using the chi-square and ANOVA tests, with a p value ≤ 0.05 deemed significant.

RESULTS

Thirty-eight patients (23.8%) withdrew from the study during the follow-up visits. Among those who withdrew, 15 (39.5%) were receiving vitamin E, 11 (28.9%) were receiving primrose and 12 (31.6%) were receiving placebo. All withdrawn patients were included in the analysis until the point of withdrawal. Finally, 122 patients (76.3%) completed the study as shown in figure (3).

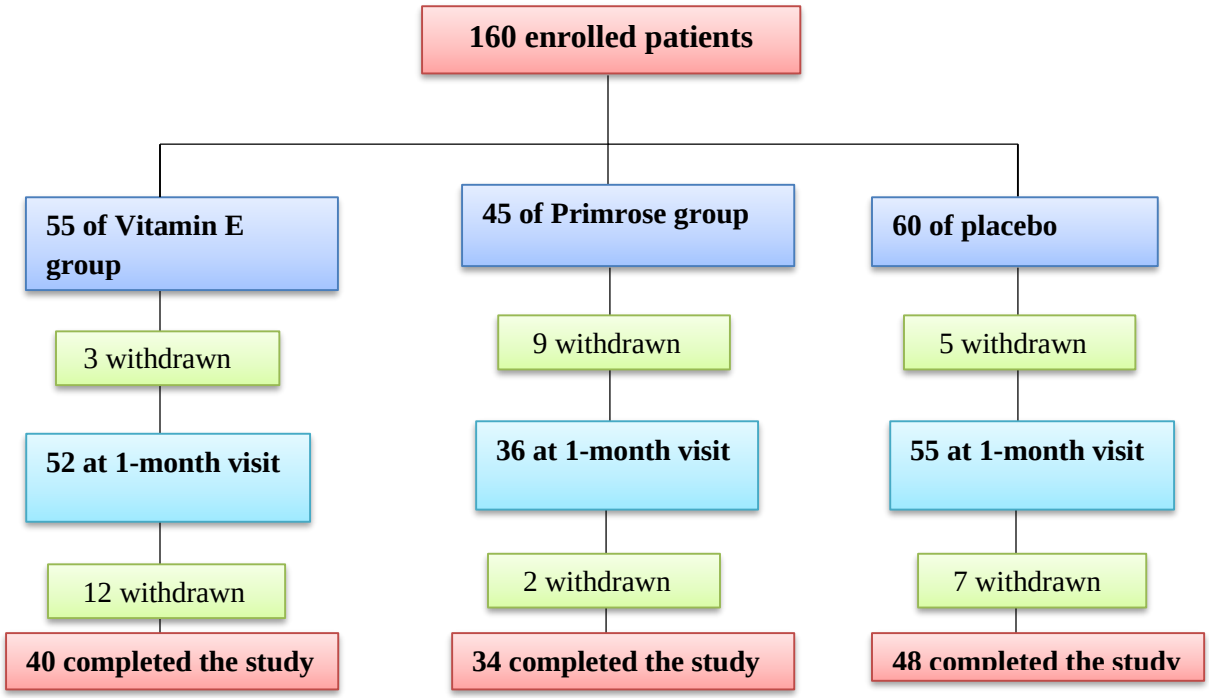

Figure (3): Enrolled and withdrawn patients.

In our study, the mean age of the patients was 31.23 ±6.82 years. Highest respondents were aged between 30 and 38 years (34.5%).

Pain distribution: The pain was mostly felt bilaterally (74.4%) and diffuse (90%) as shown in table (1).

Table (1): Pain distribution

Pain	Group A: Vitamin E (n=55)	Group B: Primrose (n=45)	Group C: Placebo (n=60)
Diffuse localized	50 (90.9%) 5 (9.1%)	41 (91.1%) 4 (8.9%)	53 (88.3%) 7 (11.7%)
Laterality Right sided Left sided bilateral	 11 (20%) 4 (7.3%) 40 (72.7%)	 5 (11.1%) 7 (15.6%) 33 (73.3%)	 9 (15%) 5 (8.3%) 46 (76.7%)

Drug side effects:
No unforeseen side effects were detected in any treatment group. Common side effects were shown in table (2).

Table (2): Side effects of used drugs

Side effect	Drug	1 month follow-up visit Number of patients	3-month follow-up visit Number of patients
	Primrose		
Bloating/ cramps		3 (8.3%)	2 (5.9%)
Headache		2 (5.5%)	1 (2.9%)
Diarrhea		0%	1 (2.9%)
	Vitamin E		
Bloating/ cramps		1 (1.9%)	2 (5%)
Headache		0%	1 (2.5%)
Diarrhea		1 (1.9%)	1 (2.5%)
	Placebo		
Bloating/ cramps		0%	1 (2.1%)
Headache		0%.	0%
Diarrhea		1 (1.8%)	1 (2.1%)

Pain score: The mean scores of ‘‘overall pain severity’’ at the beginning of the study was 5.25, 5.47, and 5.39 in vitamin E, primrose and placebo groups respectively. The severity of pain was decreased significantly by the end of the 3 months follow-up in the three groups (3.72, 3.91 and 4.14 respectively). Although this decrease was significant in each individual group, it was not statistically significant compared with one another (P value= 0.619) as shown in table (3) and figure (4).

Table (3): Overall pain severity

		Group	Number	Mean	P value
Pain severity	Initial assessment 0-month	Vitamin E	55	5.25±2.41	0.917
		Primrose	45	5.47±1.89	
		Placebo	60	5.39±2.1	
	1-month Follow-up	Vitamin E	52	4.91±2.09	0.851
		Primrose	36	4.61±1.94	
		Placebo	55	5.12±1.67	
	3-month Follow-up	Vitamin E	40	3.72±2.2	0.619
		Primrose	34	3.91±1.79	
		Placebo	48	4.14±2.04	

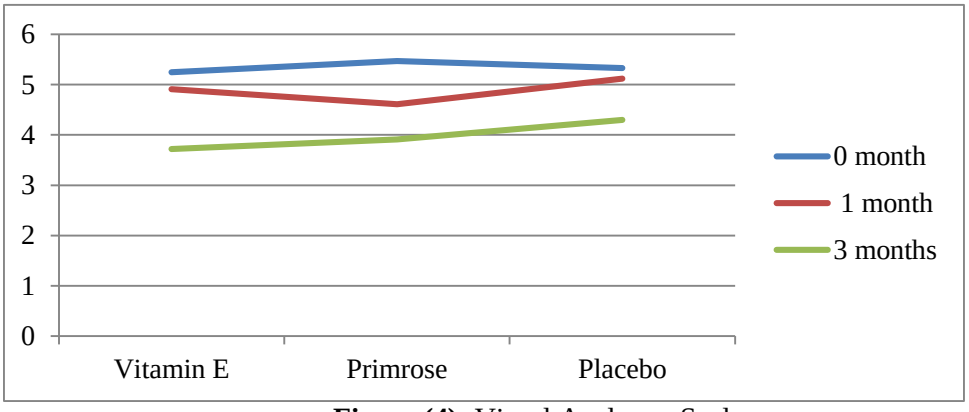

Figure (4): Visual Analogue Scale.

Effect of pain on patients’ quality of life

Although the mean score of ‘‘effect of pain on patients’ lifestyle has decreased in each group on serial follow-up visits, no significant differences was found among the three groups (P value=0.621) as shown in table (4) and figure (5). This can indicate that vitamin E and primrose have a good impact on the patient’s lifestyle, but their effect is not much different than placebo effect.

Table (4): Effect of pain on patients' quality of life

		Group	Number	Mean	P value
Effect of pain on patients' lifestyle	Initial assessment 0-month	Vitamin E	55	4.12±1.41	0.947
		Primrose	45	4.38±2.1	
		Placebo	60	3.98±1.89	
	1 month Follow-up	Vitamin E	52	3.86±2.09	0.804
		Primrose	36	4.31±1.94	
		Placebo	55	3.72±1.67	
	3-months Follow-up	Vitamin E	40	3.73±2.2	0.621
		Primrose	34	4.12±1.79	
		Placebo	48	3.81±2.04	

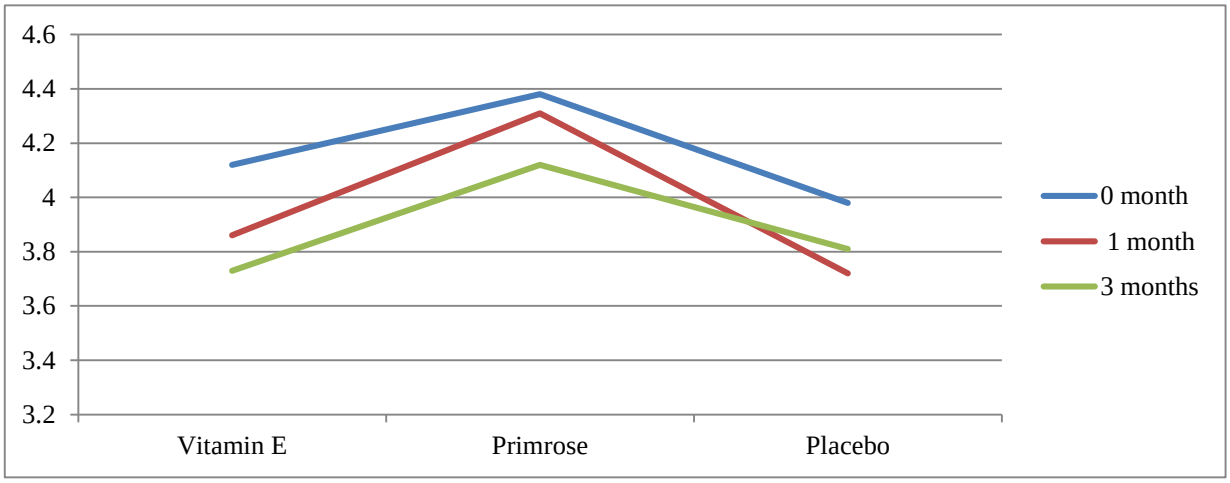

Figure (5): Effect of pain on patients' **quality of life**

DISCUSSION

Though the majority of patients have mild to moderate mastalgia, 5 to 15% of individuals have severe pain that is distressing [8]. Mastalgia is frequently interpreted by women as an indication of breast cancer. However, only 8% to 10% of all breast cancer cases are said to be accompanied by discomfort [2]. Mastalgia patients may avoid physical exertion, personal interaction, or sexual activity due to breast discomfort. Additionally, sadness, anxiety, and somatization have all been linked to treatment-resistant mastalgia [9]. About 67% of instances of mastalgia are cyclic, and they often manifest in the third decade of life as dull, burning, or **agonizing** discomfort in both breasts. This kind of breast discomfort often gets greater during the luteal phase and goes away when menstruation starts [10].

In our study, the mean age of the patients was 31.23 ± 6.82 years and the maximum respondents were aged between 30 and 38 years (34.5%). Similar observations were found in studies done by **Scurr *et al.*** [10], **Godazandeh *et al.*** [11] and **Ghazanfor *et al.*** [12] who reported a mean age of 29.35 ± 6.76 years.

In our study, both breasts were involved in 74.4%, left breast in 10 % and right breast in 15.6 %. This differs from a study done by **Sangma *et al.*** [13] who observed that 48% were right breast involvement, 40% were left breast involvement, while both breasts were affected only in 12%.

The relatively high dropout rate in our study (23.8%) is expected given that many mastalgia patients are extremely concerned about their risk of developing breast cancer. For the majority of them (85%), reassurance from a professional may help to lessen their anxiety and the pain it causes in their breasts. This might be viewed as the cause of the significant number of withdrawals throughout this research and all other comparable studies. This is in keeping with **Mohammed's** [5] conclusion that reassurance should be used as the first line of care since it is successful in reducing breast discomfort. Additionally, **Kaviani *et al.*** [8] noted that reassurance can greatly reduce the complicated sensation of breast discomfort.

In the current study, lifestyle modification advice played a very important role in patients' response, and it also might be responsible for the dropout rates. In some patients, the discomfort may go away on its own without any medical intervention [14]. A low-fat diet, regular exercise, weight reduction and daytime well-fitting bra to prevent active breast movements helped to decrease the

breast pain and should be considered as the first line of the treatment [15].

One of the most effective scales of the numerous created to gauge the degree of pain is the VAS [16]. In the current study, regarding pain severity, we reported significant decrease of the mean VAS by the end of the 3-months follow-up visits in each individual group but on the other hand, this decrease was not statistically significant when comparing one group to another**.** This agrees with **Ghazanfor *et al.*** [12] who reported a positive change of VAS from 5.76 ± 0.96 to 3.74 ± 1.6 in vitamin E group and from 5.60 ± 0.82 to 4.86 ± 1.44 in Primrose group. Also **Fathizadeh *et al.*** [17] found an initial mean VAS score of 5.69 ± 0.04 and 5.66 ± 0.8 in vitamin E group and primrose group respectively. After 6 months, it became 3.70 ± 1.5 and 4.78 ± 1.47.

In the present study, vitamin E and primrose had a good impact on the patient's lifestyle but their effect is not much different than placebo effect. Also, **Fathizadeh *et al.*** [17] observed the same mood and emotional improvement in all patients whatever they received vitamin E or primrose treatment.

In this study, most of the side effects were reported with primrose; bloating (7.1%), headache (4.2%) and diarrhea (1.5%). Whereas only 3.5% had bloating, 2.2 % had diarrhea and 1.3 % had headache due to vitamin E use. In this case, a single patient occasionally complained of several adverse symptoms. In several earlier research by **Rajswaroob *et al.*** [18]**, Neogi *et al.*** [19] and **Nirhale *et al.*** [20]**,** a nearly same observation is made. In our study, the reported side effects due to Primrose use were comparable to **Mostary *et al.*** [21] who reported bloating in 6.7% and headache in 2.2% of patients treated with primrose. On the other hand, the reported side effects due to vitamin E use in the current study were mild and uncommon as we used safe low doses of vitamin E (200 mg/day). Coagulation disorders are reported with higher doses of vitamin E (1000 mg/day) [12].

This study emphasizes that both vitamin E and primrose had a good influence on cyclic mastalgia, but their effect is not much different than placebo effect. No available sufficient evidence about the effectiveness of evening primrose oil treatment in most of the patients with mastalgia. Also, vitamin E preparations are of low value in most patients but may be of value in women with cyclic mastalgia and are taking hormonal therapy [22].

In order to treat cyclic mastalgia, **Pruthi *et al.*** [6] examined the outcomes of both supplements whether administered separately or together. No medicine was discovered to be better, however all treatment modalities showed a general tendency of benefit. Both supplements were equally beneficial, according to **Alvandipour *et al.*** [7]. Although both medications alleviated pain, primrose was actually superior to vitamin E when taken regularly in substantial dosages for a few months, according to **Fathizadeh *et al.*** [17].

CONCLUSION

Evening primrose oil and vitamin E have a positive impact on reducing cyclic breast pain with no superiority over placebo.

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