



Effect of vitamin E on severity and duration of cyclic mastalgia: A systematic review and meta-analysis



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ABSTRACT

Objectives: A systematic review was conducted to assess the effect of vitamin E on the severity and duration of Cyclic Mastalgia compared to vitamin B6, fish oil, herbal medicines and placebo.

Design: A systematic review and meta-analysis of clinical trials.

Methods: A search was carried out in PubMed, Cochrane Library, Embase, Scopus and Google Scholar and Persian databases for articles published from 1980 to 2018. The data obtained were analyzed in RevMan and reported in forest plots. The Odds Ratio (OR) was used to find the effect for the dichotomous data and the Standardized Mean Difference (SMD) for the continuous data. The heterogeneity of the studies was assessed using I^2 and the Random Effects Model was used instead of the Fixed Effects Model if $I^2 > 25\%$.

Results: A total of 1051 titles and abstracts were extracted. Fourteen articles ultimately remained, and 11 of them were entered into the meta-analysis. The meta-analysis showed significant differences between vitamin E and placebo in the severity (SMD = -0.51 ; 95% CI = -0.21 to -0.82) and duration (MD = -1.47 ; 95% CI = -0.91 to -2.57) of cyclic mastalgia, although herbal medicines had a greater effect on the severity of mastalgia than vitamin E (SMD = 0.51 , 95% CI = 0.06 to 0.96).

Conclusion: Although herbal medicines are more effective than vitamin E, vitamin E reduces both the severity and duration of the disorder compared to placebos, which only reduce its severity, and can therefore be considered a treatment with minimum side-effects. Due to the high heterogeneity of the studies, the researchers recommend further research on the subject using a standard tool based on the CONSORT statement.

1. Introduction

Most women (41–79%) feel pain and heaviness in their breasts before their menstrual cycle up to seven days after its start; this condition is referred to as cyclic mastalgia.¹ The three main causes of breast pain include increased estrogen, reduced progesterone and increased prolactin.² A reduced ratio of unsaturated to saturated fatty acids and inflammatory mechanisms such as interleukin (IL-6 and IL-1 α) and Tissue Necrosis Factor (TNF- α) are also considered possible causes of breast pain.^{3,4} A relationship has recently been found between stress and cyclic mastalgia.⁵ Mastalgia is one of the main reasons for which women visit primary care clinics and is a condition that may lead to unnecessary mammography as well as sexual (48%), physical (37%), social (12%), employment or educational (8%) dysfunction.^{6,7}

Due to its multifactorial nature, several methods have been used for

the treatment of mastalgia, including pharmaceutical (Bromocriptine, Danazol, Tamoxifen) and non-pharmaceutical techniques (supplements, oils, herbal medicines) with fewer side-effects. Several herbal medicines (evening primrose oil, vitagnus, flaxseed, etc.) have been shown to reduce the severity and duration of mastalgia compared to placebo.^{8,9} Herbal medicines have also been compared to drugs such as NSAIDs,¹⁰ Danazol¹¹ or Mefenamic acid¹² and supplements such as vitamin B6,¹³ vitamin E¹⁴ and fish oil.¹⁵

Vitamin E is the most common supplement used for the treatment of cyclic mastalgia that owes its effectiveness to antioxidant properties that protect the cell membranes against the harmful effects of free radicals produced during the process of normal body metabolism, such as the synthesis of steroidal hormones. This vitamin also reduces the ratio of saturated to unsaturated fatty acids by preventing the oxidation of unsaturated fatty acids. The effects of vitamin E have also been

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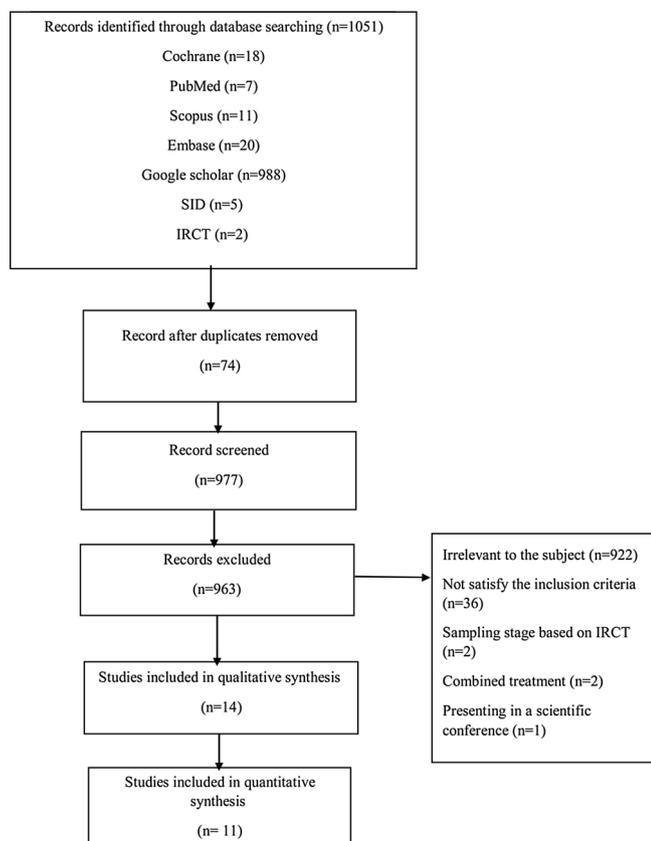


Fig. 1. PRISMA flow diagram of article selection progress.

attributed to the reduced degree of change in the metabolism of prostaglandins.^{7,16} Alpha-Tocopherol is the more active form of vitamin E that is widely spread in nature with various biological activities. It is a fat-soluble antioxidant that is responsible for protecting the membranes against lipid peroxidation and can slow down the process of aging in humans and animals. With its multiple roles, including antioxidant properties, prostaglandin metabolism and cell membrane protection, vitamin E can be effective in reducing mastalgia.^{17,18}

Several clinical trials have been conducted on the effect of vitamin E alone or in comparison to other supplements on cyclic mastalgia, but no comprehensive systematic reviews have yet been conducted on this subject. The present systematic review thus seeks to determine the effect of vitamin E compared to vitamin B6, fish oil, herbal medicines and placebo on cyclic mastalgia.

2. Material and methods

2.1. Search strategy

First, a search was carried out in Cochrane using the keywords Mastodynia OR Mammalgia OR Breast Pain OR Mastalgia OR Premenstrual Syndromes OR PMS AND Vitamin E AND Randomized Controlled Trial. The search yielded no review studies of clinical trials conducted to examine the effect of vitamin E on the severity and duration of cyclic mastalgia. English databases, including PubMed, Google Scholar, Embase, Cochrane Library and Scopus, and Persian databases, including the Scientific Information Database (SID) and the Iranian Registry of Clinical Trials (IRCT), were then searched for Persian and English human clinical trials published from January 1980 to June 2018.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Alvandipour 2010	?	?	+	+	+	+
Delfan 2015	-	+	-	-	+	+
Fathizadeh 2008	?	?	+	-	+	+
Jaafarinejad 2013-A	+	+	+	+	+	+
Jaafarinejad 2013-B	-	+	+	+	+	+
Jaafarinejad 2016	-	-	-	-	+	+
Jaafarinejad 2017	+	?	-	-	?	+
Maasumi 2017	+	?	+	+	?	+
Olfati 2006	+	?	+	+	+	+
Parsay 2009	+	-	+	+	+	+
Pruthi 2010	+	+	+	+	-	+
Salehi 2013	?	?	+	+	+	+
Shobeiri 2018	?	?	+	+	+	+
Thakur 2016	-	?	-	-	+	+

Fig. 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

2.2. Eligibility criteria

The present study was conducted on women of reproductive age who had been diagnosed with cyclic mastalgia as the participants. Trial studies (RCT, quasi-experimental) that had investigated the effect of vitamin E (i.e. the intervention) on the severity and duration of mastalgia (i.e. the outcomes) compared to placebo, herbal medicines, oils and supplements (i.e. as the controls) between 1980 and 2018 were included in the study. Articles presented in conferences, articles on PMS that did not separately assess mastalgia, case reports, case series and

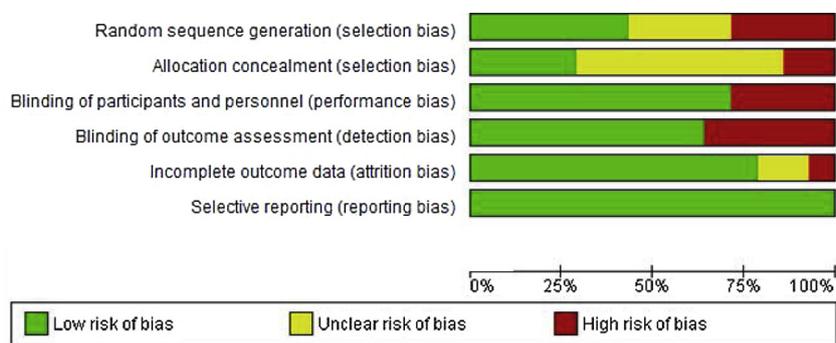


Fig. 3. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

articles that had assessed vitamin E in conjunction with other therapies were excluded. In the studies that had assessed the severity and duration of pain on different occasions, the mean values from the last post-treatment assessment were examined.

2.3. Study selection

A total of 1051 titles and abstracts were extracted, but 74 repeated articles were eliminated in endnote. Of the 977 articles retrieved, 826 titles, 98 abstracts and 53 full texts were reviewed. The titles and abstracts of all these articles were then independently assessed by two authors, and those that did not meet the inclusion criteria were excluded from the study.

A total of 959 articles were excluded for the following reasons: 922 were irrelevant to the subject, 32 did not satisfy the inclusion criteria, two had investigated vitamin E in conjunction with other treatments, two were recorded on the IRCT website and were in their sampling stage, and one was related to a science conference. Ultimately, 14 articles remained, and 11 of them entered the meta-analysis (Fig. 1).

Out of 14 articles, 11 articles had been conducted in Iran. Eight of these articles had been indexed in PubMed or Scopus and three had been indexed in Google Scholar. Four articles had been published in English and seven other articles had been published in Persian and all of them had English abstracts.

2.4. Quality assessment and data extraction

All the data for this systematic review were extracted according to the Cochrane Handbook for Systematic Reviews and included the following: Authors' name, year of publication, country of publication, study design and features, patients' characteristics, sample size after randomization, treatment duration, type of blinding, intervention details, type of controls, method of diagnosis, side-effects and results.

Two authors (K. H. & R. H.) independently reviewed the titles and abstracts of the retrieved articles. The articles that did not meet the criteria were excluded. If the abstract lacked sufficient information for making a decision, the entire article was reviewed. Differences of opinion between the two authors with respect to the eligibility of the articles were resolved through discussion. If they did not reach an agreement, a third author was consulted (M. M. & S. M. A.).

Two authors (K. H. & R. H.) independently assessed the risk of bias in each study based on the criteria specified in the Cochrane Handbook for Systematic Reviews of Interventions Version 5.2.0 (updated June 2017). Any disagreements were resolved through discussion and, if necessary, through consultation with a third person (M. M. & S. M. A.). The Review Manager (RevMan) software Version 5.3 was used for the risk of bias graph.

2.5. Synthesis of results

All the studies that had investigated the effect of vitamin E on cyclic

mastalgia were analyzed in RevMan, and the results were reported in forest plots. The OR was used to find the effect for the dichotomous data and the Standard Mean Difference for the continuous data (due to the different assessment tools used). The heterogeneity of the studies was assessed using I-squared (I^2).

3. Results

3.1. Risk of bias of included studies

The quality of the articles reporting the results of the randomized clinical trials was assessed using the Cochrane Collaboration's Tool for Assessing Risk of Bias in Randomized Trials. Figs. 2 and 3 present the results of the risk of bias assessment of the reviewed studies. Only one study had a low-risk bias in terms of all the criteria.¹⁹ Two other studies also had a low bias in terms of all the criteria, except for random allocation²⁰ and sample attrition.¹⁴ Almost 50% of the reviewed studies in this meta-analysis were low-risk in terms of random allocation and 75% of the studies in terms of blinding and sample attrition; meanwhile, only 25% were low-risk in terms of allocation concealment.

Table 1 presents the features of all the studies that entered this meta-analysis of the effect of vitamin E on mastalgia. The effect of vitamin E on mastalgia was analyzed with respect to two outcomes, including the severity and duration of mastalgia, and five comparisons were made.

3.2. Vitamin E compared with other treatments (fish oil, vitamin B6, herbal medicines), severity of mastalgia, continuous data

Jafarinejad et al. (2013b) investigated the effect of vitamin E compared to fish oil on the severity of mastalgia in 70 women aged 15–49 years, and the results showed no significant differences between the two groups.²⁰ Shobeiri et al. (2018) investigated the effect of vitamin E compared to vitamin B6 on the severity of mastalgia, and their results showed no significant differences between the two groups.¹ Regarding the effect of vitamin E compared to other herbal medicines on the severity of breast pain, five comparisons were carried out in four of the studies. Alvandipour et al. (2010) investigated the effect of vitamin E compared to Evening Primrose Oil (EPO) on the severity of mastalgia in 100 women with mastalgia, and the results showed no significant differences between the two groups.²¹ Masumi et al. (2017) also investigated the effect of vitamin E compared to EPO on the severity of mastalgia in 70 women, and found that EPO had a significantly greater effect.²² Pruthi et al. (2010) compared the effect of vitamin E and EPO and did not find any significant differences between the two.¹⁴ Salehi et al. (2013) compared the effect of vitamin E and Vitagnus and observed that Vitagnus had a significantly greater effect on the severity of mastalgia, but no significant differences were observed between the effects of vitamin E and EPO.²³

The final meta-analysis of the effect of vitamin E (210 participants) and the other treatments (211 participants) on the severity of mastalgia

Table 1
Characteristics of included studies.

Author (s) Locality/(year)	Study design	Age of patients	Treatment group	Type of blinding	Intervention	Comparison	Number of patient in both group	Method of diagnosis	results
Alvandipour Iran / (2010) ²¹	RCT [*]	Reproductive age	Group 1: EPO [†] Group 2: Vitamin E Group 3: EPO [†] and vitamin E Group 4: Placebo	Double- blind	Vitamin E	EPO [†] Placebo	Group 1: (n = 25) Group 2: (n = 25) Group 3: (n = 25) Group 4: (n = 25)	MCGILL	The mean McGill pain score reduced in all the three groups compared to the placebo group (P = 0.000).
Fathizade Iran / (2008) ²⁷	Semi experimental study	18-40	Group 1: Placebo Group 2: EPO [†]	Single- blind	Vitamin E	EPO	EPO [†] (n = 33) Vitamin E (n = 33)	Cardiff chart	The severity of mastalgia reduced significantly in both groups after the treatment. (P < 0.05).
Masoumi Iran / (2017) ²²	RCT [*]	> 18	Group 1: vitamin E Group 2: EPO [†]	Double- blind	Vitamin E	EPO [†]	(n = 35) Vitamin E (n = 35)	Daily status of premenstrual syndrome (DSR)	The mean score reduced significantly in the Evening Primrose Oil group after the intervention (P = 0.025)
Salehi Iran / (2013) ²³	RCT [*]	Reproductive age	Group 1: Vitagnus Group 2: EPO [†] Group 3: Vitamin E	Triple -blind	Vitamin E	Vitagnus EPO [†]	Vitagnus (n = 70) EPO [†] (n = 70) Vitamin E (n = 70)	Cardiff chart	"The mean pain score in the three groups decreased after intervention, and the mean painless days increased in three groups, and the mean daily pain with moderate pain decreased in three groups, and the mean of days with severe pain decreased in three groups (Cardiff chart) (p < 0.0001). Statistical tests showed that the effect of Vgnus was higher than other material (p < 0.0001)."
Pruthi United state / (2010) ¹⁴	RCT [*]	≥18	Group 1: vitamin E Group 2: EPO Group 3: Vitamin E and EPO [†] Group 4: Two placebo capsule Group 1: EPO [†] Group 2: Vitamin E	Double- blind	Vitamin E	Placebo EPO [†]	Vitamin E + placebo (n = 21) EPO [†] + placebo (n = 21) Vitamin E + EPO [†] (n = 21) Placebo + placebo (n = 21)	Modified McGill pain question	"Analysis showed a difference in worst-pain improvement with treatments vitamin E (P = 0.04) and EPO plus vitamin E (P = 0.05), but no difference with placebo (p = 0.93)."
Thakur India / (2016) ²⁶	Prospective experimental study	20-42	Group 1: EPO [†] Group 2: Vitamin E	Single blind	Vitamin E	EPO [†]	EPO [†] (n = 33) Vitamin E (n = 34)	Cardiff breast pain score	The rate of response to treatment was 60.6% for EPO vs. 47.07 for vitamin E.
Shobeiri Iran / (2018) ¹	RCT [*]	Reproductive age	Group 1: Vitamin E Group 2: Vitamin B6	Double- blinded	Vitamin E	Vitamin B6	Vitamin E (n = 40) Vitamin B (n = 40)	Cardiff breast pain score	There was a substantial difference between the duration of mastalgia in the first and second cycles after the intervention in both groups.
Jafarnejad Iran / (2017) ²⁴	Quasi-Randomized Clinical Trial	Reproductive age	Group 1: Flaxseed Group 2: EPO [†] Group 3: Vitamin E	Single blind	Vitamin E	Flaxseed EPO [†]	Flaxseed (n = 30) EPO (n = 30) Vitamin E (n = 30)	Daily subscription form of pain duration	The duration of breast pain reduced significantly in the flaxseed group (P = 0.006), but the reductions in the EPO and vitamin E groups were not significant (P = 0.085)
Jafarnejad Iran / (2013) ²⁰	RCT [*]	15-49	Group 1: Vitamin E Group2: Fish oil	Double- blinded	Vitamin E	Fish oil	Vitamin E (n = 35) Fish oil (n = 35)	McGill	"Overallly the mean scores of breast pain intensity decreased before and after the intervention in both groups (P < 0.001)."
Olfati Iran / (2006) ²⁵	RCT [*]	Reproductive age	Group 1: Vitamin E Group 2: Placebo	Double- blinded	Vitamin E	Placebo	Vitamin E (n = 75) Placebo (n = 75)	Breast pain chart and Visual analog scale	The administration of vitamin E for two and four months reduces the severity and duration of mastaigia.
Jafarnejad Iran / (2013) ¹⁹	RCT [*]	15-49	Group 1: Vitamin E Group2: Fish oil	Triple blinded	Vitamin E	Fish oil	Vitamin E (n = 35) Fish oil (n = 35)	Registration table of breast pain	"Overallly the mean scores of breast pain duration decreased before and after the intervention in both groups (P < 0.001)."

* Randomized Controlled Trial.
† Evening Primrose Oil.

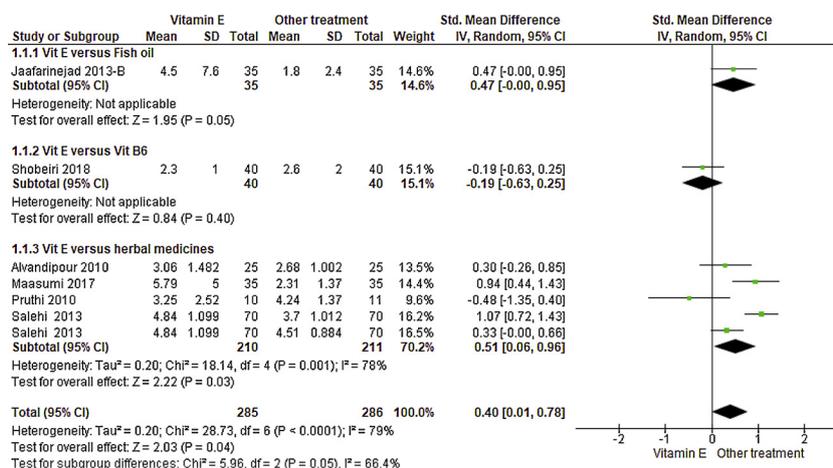


Fig. 4. Forest plot of included study- Effect of vitamin E compared with other treatment on severity of mastalgia.

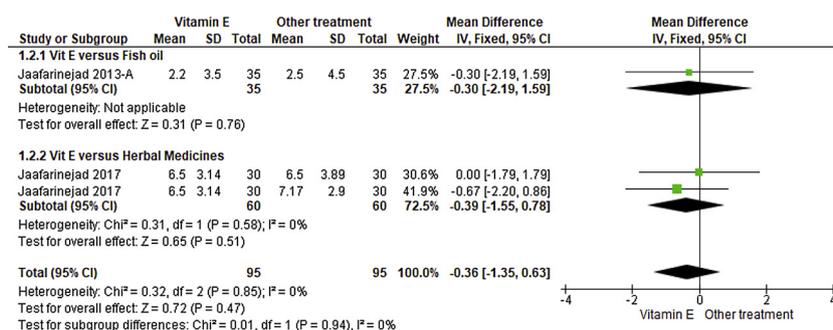


Fig. 5. Forest plot of included study- Effect of vitamin E compared with other treatment on duration of mastalgia.

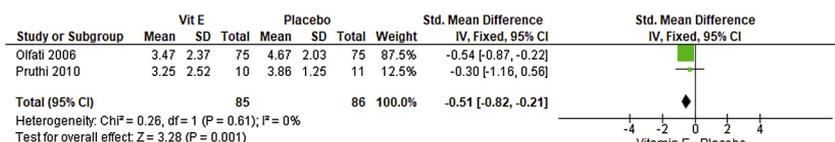


Fig. 6. Forest plot of included study- Effect of vitamin E compared with placebo on severity of mastalgia.

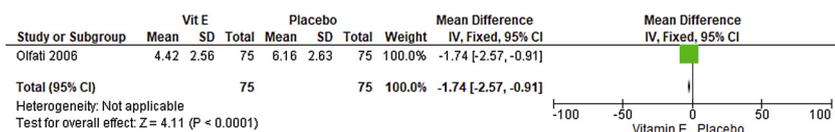


Fig. 7. Forest plot of included study- Effect of vitamin E compared with placebo on duration of mastalgia.

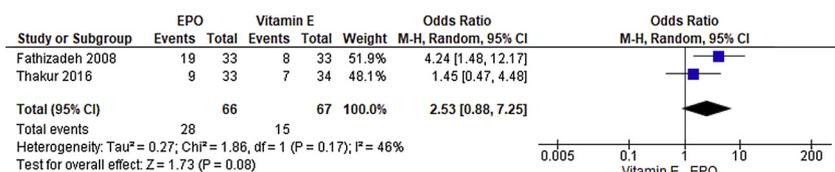


Fig. 8. Forest plot of included study- Effect of vitamin E compared with EPO on severity of mastalgia.

in this study showed that herbal medicines are significantly more effective (SMD = 0.51, 95% CI = 0.06 to 0.96, P = 0.03); (Fig. 4)

3.3. Vitamin E compared with other treatment (fish oil, herbal medicine), duration of mastalgia, continuous data

Jafarnejad et al. (2013a) investigated the effect of vitamin E compared to fish oil on the duration of mastalgia in 70 women and found no significant differences between the two groups.¹⁹ One study made two comparisons regarding the effect of vitamin E and other herbal medicines on the duration of breast pain. Jafarnejad et al. (2017) investigated the effect of vitamin E compared to EPO and

Vitagnus on the duration of mastalgia in 60 women and reported no significant differences between vitamin E and herbal medicines.²⁴ The final meta-analysis of the effect of vitamin E (95 participants) and the other herbal medicines and fish oil (95 participants) on the duration of mastalgia in the present study showed no significant differences between the two group (MD = -0.36, 95% CI = -1.35 to 0.63, P = 0.94); (Fig. 5).

3.4. Vitamin E compared with placebo, severity of mastalgia, continuous data

Pruthi et al. (2010) investigated the effect of vitamin E compared to

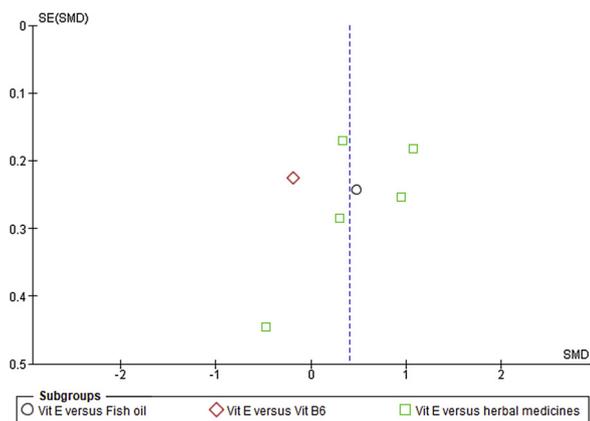


Fig. 9. Funnel plot of the studies regarding the effect of vitamin E compared with other treatment on severity of mastalgia.

placebo on the severity of mastalgia and showed that vitamin E has a greater effect than placebos, although not by a statistically significant amount.¹⁴ Olfati et al. (2006) investigated the effect of vitamin E compared to placebo on the severity of mastalgia in 150 women and found that vitamin E is significantly more effective.²⁵ The final meta-analysis of the effect of vitamin E (85 participants) and placebo (86 participants) on the severity of mastalgia showed that vitamin E is significantly more effective (SMD = -0.51, 95% CI = -0.82 to -0.21, P = 0.001); (Fig. 6).

3.5. Vitamin E compared with placebo, duration of mastalgia, continuous data

Olfati et al. (2006) investigated the effect of vitamin E compared to placebo on the duration of mastalgia in 150 women and found that vitamin E is significantly more effective.²⁵ The final meta-analysis of

the effect of vitamin E (85 participants) and placebo (86 participants) on the severity of mastalgia in the present study showed that vitamin E is significantly more effective (MD = -1.47, 95% CI = -2.57 to -0.91, P < 0.0001); (Fig. 7).

3.6. Vitamin E compared with EPO, severity of mastalgia, dichotomous data

In the final meta-analysis of the present study, which compared the data from the two studies dichotomously,^{26,27} no significant differences were observed between vitamin E and EPO (OR = 2.53, 95% CI = 0.88–7.25, P = 0.08); (Fig. 8).

The following studies were reviewed but not included in the meta-analysis due to the lack of access to their mean and standard deviation or frequency and percentage and also their lack of a control group.

Parsay et al. (2009) investigated the effect of a twice-daily administration of vitamin E over four months and compared it to the administration of placebos on the severity of mastalgia in 150 women and found a significant reduction in the severity of mastalgia in the intervention group in the second month. This study was excluded from the present meta-analysis for not reporting a mean and standard deviation or frequency and percentage.¹⁶

In another study, Delfan et al. (2014) divided 88 women with cyclic mastalgia into two groups. The first group (n = 44) was given 400 units of vitamin E per day, and the second group (n = 44) received the same dose of vitamin E plus 1200 mg of Omega-3, 6 and 9 per day over three months. The results showed a greater reduction in the severity of mastalgia with the administration of vitamin E plus Omega-3, 6 and 9 compared to vitamin E alone. This study was excluded from the present meta-analysis for not reporting a mean and standard deviation or frequency and percentage.²⁸

Jafarinejad et al. (2016) investigated the effect of vitamin E compared to flaxseed and EPO on the severity of mastalgia in 90 women and found a reduction in the median of the severity of mastalgia in all the three groups compared to before the intervention. This study was

Table 2
Quality assessment of randomized trials on mastalgia.

Quality assessment								Certainty
1. Vitamin E versus placebo or other treatments (Severity of mastalgia)								
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	MD (95% CI) [*]	Certainty
Vitamin E versus fish oil								
1	Randomized Controlled Trials	Low risk	No serious	No serious	Serious	Undetected	0.47 [-0.00 to 0.95]	Moderate ⊕⊕⊕○
Vitamin E versus vitamin B6								
1	Randomized Controlled Trials	Serious	No serious	No serious	Serious	Undetected	-0.19 [-0.63 to 0.25]	Low ⊕⊕○○
Vitamin E versus herbal medicines								
5	Randomized Controlled Trials	Serious	Serious	Serious	No serious	Undetected	0.51 [0.06 to 0.96]	Very low ⊕○○○
Vitamin E versus placebo								
2	Randomized Controlled Trials	Low risk	No serious	Serious	Serious	Undetected	-0.51 [-0.82 to -0.21]	Low ⊕⊕○○
2. Vitamin E versus placebo or other treatments (Duration of mastalgia)								
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	MD (95% CI) [*]	Certainty
Vitamin E versus fish oil								
1	Randomized Controlled Trials	Low risk	No serious	No serious	Very serious	Undetected	-0.30 [-2.19 to 1.59]	Low ⊕⊕○○
Vitamin E versus herbal medicine								
2	Randomized Controlled Trials	Serious	No serious	No serious	Very serious	Undetected	-0.39 [-1.55 to 0.78]	Very low ⊕○○○
Vitamin E versus placebo								
1	Randomized Controlled Trials	Low risk	No serious	No serious	Serious	Undetected	-1.74 [-2.57 to -0.91]	Moderate ⊕⊕⊕○
3. Vitamin E versus Evening Primrose Oil (Severity of mastalgia)								
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	OD (95% CI) [†]	Certainty
2	Randomized Controlled Trials	Serious	Serious	Serious	Serious	Undetected	2.53 [0.88 to 7.25]	Very low ⊕○○○

* Mean Difference (95% Confidence Interval).

† Odds Ratio (95% Confidence Interval).

excluded from the present meta-analysis for not reporting a mean and standard deviation or frequency and percentage.²⁹

The severity was assessed using the Cardiff Breast Pain Chart,^{1,23,26,27} the McGill Pain Index,^{14,20,21} and the Visual Analog Scale¹⁶ and duration was assessed using daily pain diaries.^{19,24,25}

The funnel plot showed no publication bias in terms of the effect of vitamin E compared to the other treatments. A funnel plot is a scatter plot of the effect estimates from individual studies against some measure of each study's size or precision. It can show publication bias³⁰ (Fig. 9). According to the GRADE approach, the evidence available for the comparison of the effect of vitamin E and other treatments and placebos on the duration and severity of cyclic mastalgia was poor in terms of quality and the results are only close to real with little confidence. Table 2 presents the results of the quality assessment of the evidence.

4. Discussion

The present systematic review investigated the effect of vitamin E on the severity and duration of cyclic mastalgia compared to vitamin B6, fish oil, placebo and herbal medicines. Most studies on the subject were RCTs and had been performed with blinding. No review studies or meta-analyses were found that had assessed the effect of vitamin E compared to other treatments.

The meta-analysis of the data of the reviewed studies showed a significant difference between the vitamin E group and the placebo group in terms of mastalgia; however, the meta-analysis of the continuous and dichotomous data showed that herbal medicines had a significantly greater effect than vitamin E in reducing the severity of cyclic mastalgia.

The authors couldn't find a systematic review that explored the effect of herbal medicines compared to other supplements or vitamins on mastalgia. In two studies, however, two herbal remedies were systematically reviewed separately. One of these two studies had investigated EPO by the inclusion of ten studies and had proposed the substance for the treatment of mild mastalgia.³¹ The other study had investigated the effect of Vitagnus by the inclusion of five studies and had shown it to be a safe and effective remedy for mastalgia.³²

In a study by Murshid (2011) on fibrocystic changes of the breast and the treatments used, only three studies had used vitamin E as a method of treatment and had reported the positive effects of vitamin E in reducing the severity of cyclic mastalgia with minimal side-effects compared to other hormonal and chemical medications. In this review study, vitamin E had a 41% rate of response to treatment and presented minimal side-effects while Danazol had a 70% rate of response and presented side-effects in one-third of the patients.³³ In a clinical study conducted by Bundred et al. (2007), GRADE was used to assess the quality of the evidence available on the interventions conducted on mastalgia and no systematic reviews or clinical trials were found that met the necessary qualifications for assessing the effects of vitamin E on cyclic mastalgia.³⁴

5. Limitations

This systematic review study was faced with a number of limitations. For instance, different studies had used different tools to measure the severity and duration of cyclic mastalgia, their outcomes were not measured consistently over time and the dosage and administration routes used for vitamin E and the other supplements, such as herbal medicines, were not similar in all the studies. Due to certain limitations, especially language-wise, it is not certain whether or not all the RCTs on the subject have been successfully included in this review study. The weaknesses of this study include the poor quality of the articles published on the subject, and only one study was low risk of bias in terms of all the criteria. Most studies had not fully explained their allocation concealment step, and some studies had reported their results on

mastalgia with median and standard deviation, and despite the emails sent to their author, no response was received. Some studies had not reported on their sample attrition after the intervention. Other limitations of the study include the lack of access to the studies' protocol to assess reporting bias in them. Also considering that

6. Conclusion and implication to practice

The present study showed that, compared to placebos, vitamin E can reduce the severity and duration of breast pain. Due to the high heterogeneity of the reviewed studies, the researchers recommend further research using a standard tool based on the CONSORT statement. These studies are also recommended to compare the effectiveness of vitamin E with other treatments (such as vitamin B6 and fish oil), so that publication biases in these studies can be assessed by funnel plots. Also, considering that major part of the reviewed articles (11 out of a total of 14 articles) have been conducted in Iran, future studies should be done to explore whether the mainstream research on traditional medicines is influenced by the orthodox culture of preferring traditional herbal medicine over modern agent.

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