ORIGINAL ARTICLE

Therapeutic Effects of Vitamin E on Cyclic Mastalgia

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■ **Abstract:** Cyclic mastalgia is one of the most prevalent disorders among fertile women. To date, hormonal agents, despite their side effects, have been widely used for treatment of this ailment. This study was performed to clarify the therapeutic effects of Vitamin E (Vit E) as a safe treatment for cyclic mastalgia among fertile women. This study was conducted as a double blind clinical trial; 150 women with cyclic mastalgia, referred by three public health centers in Qazvin City in Iran, were enrolled in the trial and randomly divided into two distinct case and control groups; each containing 75 patients. The severity and duration of breast pain were measured according to both the Cardiff Breast Pain Chart and the Visual Analog Scale. Simple, chewable tablets of either Vit E or a placebo were prescribed twice a day for 4 months for case and control participants, respectively. Follow-up was performed at the end of both the second and the fourth months and, at that time, the severity, duration and side effects of intervention were evaluated. The administration of Vit E had significant curative results as tested at both the 2- and 4-month benchmarks. Chi-square testing indicated that after both 2 and 4 months of therapy, the efficacy demonstrated by the Vit E recipient case group was superior to that of the group that received a placebo. Applying the Mc Nemar Test, it also was shown that there was no significant difference in the benefits received between treatment courses of 2 versus 4 months. A 2-month prescription of Vit E has positive therapeutic effects on cyclic mastalgia. Given its lack of significant side effects, Vit E, therefore, can be considered a safe alternative to hormonal therapies currently being used in the treatment of cyclic mastalgia. ■

Key Words: breast pain, cyclic mastalgia, vitamin E

Mastalgia is defined as moderate to severe pain in breasts persisting for more than 5 days. Although mild premenstrual breast pain continuing less than 5 days is often considered normal, severe pain continuing for more than 5 days may contradict normal daily activities and require some medication (1,2).

Recent studies have revealed that over 70% of all women under the age of 55 have experienced breast pain; approximately 45% have mild pain and 25% are negatively affected by moderate or severe pain lasting more than 5 days (1). Mastalgia is one of the major causes of breast pain for women utilizing primary care clinics (2). In approximately two thirds of mastalgic women, pain interferes with routine daily activities; with 10% of affected women requiring medication (3).

Cyclic mastalgia is the most prevalent type of mastalgia, responsible for 60–70% of all clinical forms of mastalgia. Pain severity changes throughout the menstrual cycle; generally aggravated in the luteal phase (between ovulation and menses) and disappearing by the initiation of menses. Nevertheless, it may persist in different degrees throughout the entire menstrual cycle (2).

The exact etiology of cyclic mastalgia still remains unknown, although some causes including hormonal changes (i.e., elevated levels of estrogen, decreasing levels of progesterone, increases in the estrogen–progesterone ratio, increased prolactin, reduced excretion of follicle-stimulating and luteinizing hormone, lower levels of androgens, decline in the ratio of unsaturated to saturated fatty acids, and oversensitivity of receptors), psychiatric changes, and nutritional changes have been considered; as have been water retention and an increase in body weight and/or breast size (1–3). In support of these causation hypotheses, anti-estrogen agents, such as Bromocriptine, Danazol, analgesics, and other drugs have been recommended for treatment—as have certain herbal supplements such as evening primrose oil (EPO)—despite their displaying limited proven success (2,3).

Patients receiving the above mentioned treatments should generally undergo careful clinical and

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radiologic examinations to provide adequate assurance that no serious underlying diseases (especially breast cancer) are the cause of the related pain or discomfort (1–4). Recently, based upon a finding of both normal levels of hormones and appropriate numbers of hormonal receptors in these patients, a so called concept of ''alteration in receptor sensitivity'' has been suggested as a possible approach to consider.

Women suffering from cyclic mastalgia have been found to have different proportion of fatty acid esters (5) than women who do not exhibit symptoms. Specifically, the plasma levels of *Estearic* and *Palmitic* saturated fatty acid esters have been found to be higher in women with cyclic mastalgia, whereas *Linolenic*, *Dehydrogamma Linolenic,* and *Arachedonic* (all essential unsaturated fatty acid esters) were decreased. As the behavior of a receptor can be altered by fluctuations in the unsaturated–saturated ratio of essential fatty acids, increasing this ratio results in simultaneously increasing the receptors' sensitivity (6). This accounts for why a low fat diet regimen can reduce the bioavailability of prolactin, even though its serum level is normal (7). Accordingly, this behavior also explains why a mastalgic patient, despite having normal serum levels of hormones, can have certain responses and be more sensitive to medicinal intervention.

If this supposition were found to be reliable, prescription of essential fatty acids or the application of agents modifying the fatty acids ratio in plasma may offer indisputable benefits in treatment of mastalgia (6,8). Vitamin E (Vit E) has been found to have an antioxidant virtue (9) with the ability to prevent the oxidation of unsaturated fatty acids and, consequentially, both decrease the above-mentioned ratio and inhibit the receptors to become more inclined to hormonal influence. Moreover, Vit E has exhibited no measurable negative side effects in recommended dosages.

Thus, we conducted this study to clarify whether there could be any therapeutic benefits in prescribing Vit E for women suffering from cyclic mastalgia.

MATERIALS AND METHODS

Sample Selection

This was a double blind, randomized clinical trial, carried out between 2003 and 2005 in three separate clinics affiliated with Qazvin University of Medical Sciences in Iran with the approval of the University's Board of Ethics. The study was performed utilizing 150 fertile women (ages 20-year old to premenopausal) who complained of periodic breast pain which continued more than 5 days each month and had affected them for more than 6 months.

These women were selected from 500 affected women who fulfilled the requirements of Questionnaire No. 1 which included testing according to the Cardiff Breast Pain Chart and Visual Analog Scale (VAS). This selection process occurred over a 2-month period with 182 women initially returning for a second round after 2 months with a final enrollment of 160 who had a pain severity score above 4, pain duration of more than 5 days and uniform nutritional patterns (e.g., limited dietary intake of Vit E and methylxantines such as tea and coffee). Affected women, regardless of their current condition, underwent a careful clinical evaluation by a surgeon to determine that there were no abnormal clinical findings such as breast mass or breast infection. Sonography and mammography were also performed, when appropriate to insure proper candidate screening. We also excluded women with a history of hormone therapy, use of oral contraceptive pills, a positive history of medical treatment for relief of breast pain during the 3 months prior to examination, and pregnant or lactating women.

Accordingly, the 160 remaining women were divided randomly via an encoding system into two groups of case and control, each containing 80 participants. Affected women in both groups were then matched by the following: age, marital status, marital age, gravid, menstrual age, history of lactation, postpubertal onset of cyclic mastalgia, location of their pain, history of using analgesic agents (or any other treatments routinely used for calming cyclic mastalgia), positive family history, history of trauma, history of invasive breast procedures, discharges from breast, pain in one or both breasts, and impression of pain during sexual relations.

Clinical Management and Study Procedure

Subjects were further divided based upon the perceived severity of their pain. Patients in each group were then divided into two classes; those with moderate pain (scores between 4 and 7) and those with severe pain (scores between 7 and 9). Measurement of pain severity, pain duration and confirmation of

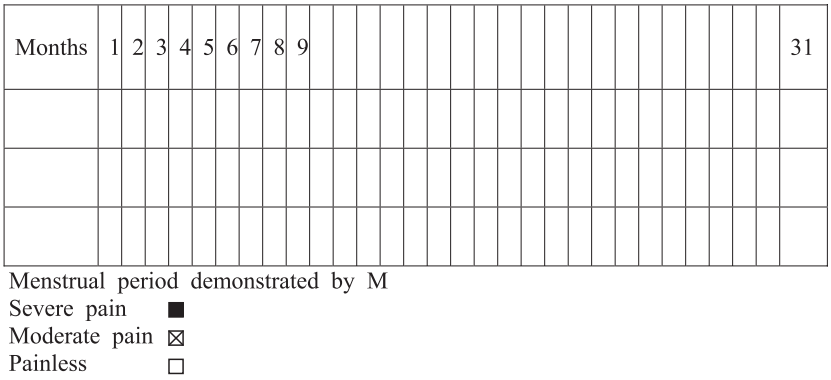

Figure 1. Cardiff breast pain chart (daily chart of breast pain).

the diagnosis of cyclic mastalgia was determined by applying the *VAS* and also the *Cardiff Breast Pain Chart*.

Trial participants, double blindly, received simple oral and chewable tablets of Vit E (200 mg dosage based upon previous researches in this field) or a placebo twice a day for a period of 4 months. Follow-up was conducted at the end of the second and fourth months via Questionnaire No. 2, wherein VAS related and certain other questions to ascertain side effects were inserted. Subsequently, a decoding process was performed and five patients were excluded in each group of case and control because of simultaneous use of other confounding drugs, conflicting mismatches in nutritional patterns with other participants and/or irregular usage of Vit E or the placebo. Ultimately, 150 participants remained in the study; 75 in each group.

Analytical and Statistical Methods

Effectiveness of the treatment was defined by either a reduction in the subjective severity of pain to a lower pain severity class (i.e., from moderate to mild one) or a decrease in pain duration to less than 5 days based upon the *VAS*, the primary method used in physiotherapy testing. It consists of a horizontal line scored between 0 and 10 with zero indicating a painless condition and 10 corresponding to an intolerant painful situation. The *Cardiff Breast Pain Chart* has been utilized and is a daily chart for monitoring breast pain as shown in Figure 1.

Statistical analysis was performed applying the chi-square test, the Mc Nemar test and Student's *t*-test. A value of $p < 0.05$ was considered to be statistically significant.

RESULTS

There was no significant difference between two groups of case and control by age ($p = 0.147$), before-treatment pain duration ($p = 0.830$) and pain severity degree ($p = 0.377$). The "effectiveness" of Vit E and placebo were defined within each group by dividing participants into *effective* and *non-effective* categories. To ascertain any differences in the effectiveness of a 2 months administration of Vit E versus a placebo between the two case and control groups, a chi-squared test was applied which resulted in display of a significant difference ($p < 0.05$) (Chart 1). The same results were achieved by measuring both groups after 4 months of administration of those agents ($p < 0.000$) (Chart 2).

To determine the difference between the effectiveness of a 2 versus 4 months administration of Vit E in each case group, the Mc Nemar test was applied. The result showed no considerable difference between those receiving Vit E ($p = 1$). The same result was

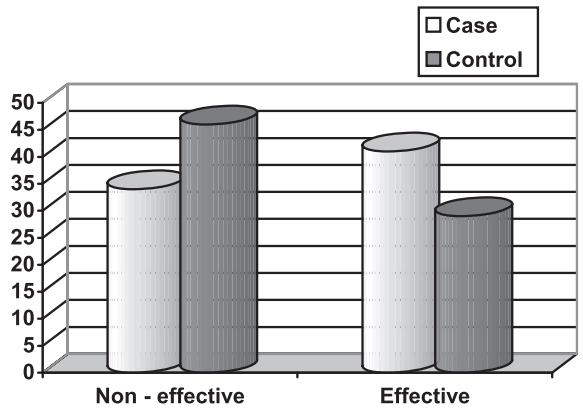

Chart 1. Efficacy of vitamin E and placebo in case and control during second month.

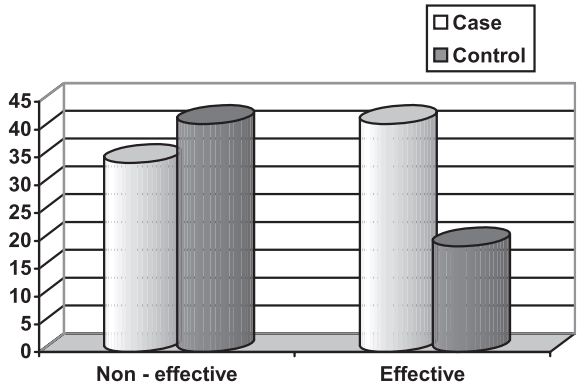

Chart 2. Efficacy of vitamin E and placebo in case and controls during fourth month.

obtained from the control group administered the placebo (p = 0.1).

Side effects between case and control groups were evaluated by analyzing the Chi-squared test results. However, this revealed no significant difference between the 2-month results (p = 1) and the 4-month results (p = 0.757).

CONCLUSION

Based on the above-mentioned results, we found a dramatic outcome in 2 and 4 months use of Vit E compared with a placebo. However, the therapeutic effects were negligible, whether a course was administered for 2 versus 4 months. In other words, no additional improvement occurred from 4 months usage as opposed to 2 months usage.

In 1997, Khanna et al. compared the results of a Danazol recommended prescription versus a Vit E course of treatment. Whereas Vit E reduced pain in 41% of studied patients with no apparent side effects, Danazol had similar pain reduction results in 72% of the study participants. However, one third of study participants taking Danazol developed other side effects (10).

Meyer et al. (11) carried out a study on 105 affected women in 1990 but could not ascertain a curative impact resulting from Vit E administration. However, his lack of conclusion may be resulted from regarding the breast pain as an exclusive symptom of overall ''breast disease,'' rather than viewing breast pain resulting from mastalgia as a distinct medical condition per se.

Ernester, in 1985, studied 201 women with mastalgia. He also could not definitively confirm Vit E's efficacy (1,12). However, this conclusion was a consequence of his interpreting breast pain as one of the symptoms of fibrocystic disease. Therefore, in that study, mastalgia was not studied or considered as a distinct disease.

In 2004, Bespalov *et al.* conducted a trial on 66 patients by utilizing ''Karnet''; a dietary supplement containing β-carotene, α-tocopherol, ascorbic acid, and garlic powder. The result was a reduction in the severity of mastalgia, premenstrual syndrome, oligomenorrhea, and dysmenorrhea and there was a regression in symptoms of fibromatosis 75% of participants receiving Karnet compared with 45% receiving the placebo. The authors, therefore, recommended it as a useful supplement in the treatment of benign breast masses (13).

Accordingly, we have concluded that the accepted protocol for the management of mastalgia (1,2), should initially be the prescription of a course of Vit E for 2 months after an exacting evaluation of the patient has provided adequate assurance of a lack of serious disease or malignancy. Our study shows that this may lead to the subsiding the symptoms in approximately 70% of patients complaining of breast pain (14). For the remaining 30% who may return with continuing breast pain complaints, EPO (an over the counter supplement consisting of unsaturated fatty acids and Vit E) could be prescribed as the next step in treatment and, if the results are unsatisfying, Danazol will be recommended as a second choice.

However, it should be noted that EPO is an expensive agent, with each capsule costing approximately US$2. Because evening primrose does not grow naturally in many countries, including Iran (except in some specially planted, preserved areas), obtaining it presents a high economic burden. In contrast, Vit E is produced in many countries, is relatively inexpensive, has no discernible side effects at the doses recommended; therefore, offering an acceptable, cost-effective option. Therefore, in consideration of the varying socioeconomic status of patients worldwide, it is reasonable to recommend Vit E as the first treatment course option in the treatment of cyclic mastalgia with Danazol (considering its cost and side effects) remaining the second choice if Vit E therapy does not resolve the problem and EPO is not cost-effective.

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REFERENCES

1. Millet AV, Dirbas FM. Clinical management of breast pain: a review. *Obstet Gynecol Surv* 2002;57:451–61.

2. Smith RL, Pruthi S, Fitzpatrick LA. Evaluation and management of breast pain. *Mayo Clin Proc* 2004;79:353–72.

3. Semih K, Yavus A, Cemal TE, *et al.* Symptomatic treatment of premenstrual mastalgia in premenopausal women with lisuride maleate: a double-blind placebo controlled randomized study. *Fertil Steril* 2001;75:718–23.

4. Padden DL. Mastalgia: evaluation and management. *Breast J* 1999;5:162–5.

5. Gateley CA, Maddox PR, Prichard GA, *et al.* Plasma fatty acid profiles in benign breast disorders. *Br J Surg* 1992;79:407–9.

6. Horrobin DF. The effect of gamma-linolenic acid on breast pain and diabetic neuropathy: possible non-eicosanoid mechanism: prostaglandin, leukotrienes and essential fatty acids. *Gynecol Obstet* 1993;48:101–4.

7. Sforza M, Vertemati G, Russo R. Update on mastalgia. *Minerva Chir* 1995;50:435–7.

8. Sharma AK, Mishra SK, Salila M, *et al.* Cyclic mastalgia: is it a manifestation of aberration in lipid metabolism? *Indian J Physiol Pharmacol* 1994;38:267–71.

9. Gallagher ML. Vitamins. In: Mahan LK, Escott-Stump S, eds. *Krause's Food Nutrition & Diet*, 11th edn. Philadelphia, PA: Saunders, 2004:88–90.

10. Khanna AK, Tapodar J, Mirsa MK. Spectrum of benign breast disorders in a university hospital. *J Indian Med Assoc* 1997;95:5–8.

11. Meyer EC, Sommers DK, Reitz CJ, *et al.* Vitamin E and benign breast disease. *Surgery* 1990;107:541–51.

12. Ernester VL, Goodson WHD, Hunt TK, *et al.* Vitamin E and benign breast disease: a double blind randomized clinical trial. *Surgery* 1985;97:490–4.

13. Bespalov VG, Barash Niu, Ivanova OA, *et al.* Study of an antioxidant dietary supplement "Karinat" in patients with benign breast disease. *Vopr Onkol* 2004;50:467–72.

14. Barros AC, Mottola J, Ruiz CA, *et al.* Reassurance in treatment of mastalgia. *Breast J* 1999;5:162–5.