

Clinical effectiveness of vitamin E and vitamin B6 for improving pain severity in cyclic mastalgia

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ABSTRACT

Background: Recent attempts have been focused on employing chemical and natural supplemental agents for treatment of cyclic mastalgia. Among various agents, the potential effects of vitamins remain questionable. In the present study, we examined the efficacy of two types of these vitamin supplements (vitamin E and vitamin B6) in improving pain severity in cyclic mastalgia.

Materials and Methods: In a randomized double-blinded clinical trial, 80 patients suffering from cyclic mastalgia were randomly assigned to receive 200 IU of vitamin E daily or 40 mg/day of vitamin B6 for 2 months. Written informed consent was obtained from all participants. Severity of breast pain was detected by the Cardiff breast pain score during one menstrual cycle before and two menstrual cycles after the intervention. Data were analyzed using *t*-test, Chi-squared test, analysis of variance (ANOVA), and regression with SPSS version 19 and $P < 0.05$ was considered significant.

Results: There was no significant difference in the mean of severity of cyclic mastalgia during one menstrual cycle before the intervention between the vitamin E and B6 groups (9.1 ± 2.1 and 8.4 ± 3.1 , respectively), but the difference was significant during the first cycle (5.1 ± 1.6 and 5.2 ± 2.5 , respectively) and the second menstrual cycle (2.3 ± 1.0 and 2.6 ± 2.0 , respectively) in the two groups after the intervention. The trend of changes in pain severity score showed significant downward trend of pain severity score within the study period in both the treatment groups ($P < 0.001$), while these trends were similar in both groups when examined by the repeated-measure ANOVA test. By multivariable linear regression analysis adjusted for baseline variables, we found that both the treatment regimens resulted in similar reduction in breast pain severity ($P = 0.067$).

Conclusions: Both regimens containing vitamin E and vitamin B6 are similar in reducing breast pain severity in cyclic mastalgia.

Key words: Breast pain, cyclic mastalgia, vitamin B6, vitamin E

INTRODUCTION

Some women's breasts are unusually tender and lumpy, with symptoms of pain and dull heaviness that vary with the menstrual cycle. This condition is called cyclic mastalgia and is often associated with premenstrual syndrome. Among women, the reported prevalence of mastalgia ranges from 41 to 79%, and the most common type is associated with menstruation. Cyclic mastalgia typically occurs monthly before the beginning of the menstrual period, is of mild severity, and is relieved within 7 days of the onset of menses. Spontaneous remission often

occurs, but many women experience cyclic mastalgia for years, often with increasing severity until menopause. In some women, this pain interferes with activity, relationships, and quality of life. Cyclic mastalgia interferes with sexual activity (48%), Physical and social activities (21%), and employment or education (8%).^[1]

Cyclical mastalgia may be associated with excessive use of mammograms with unnecessary, ineffective, or undesirable self-medication. When the lumps become significant enough to be called cysts, the condition is called fibrocystic breast disease. Besides discomfort, perhaps the worst problem of this condition is that it can mimic the appearance of breast cancer on mammograms, leading to false alarms. To make matters worse, fibrocystic changes can also hide true cancers, and some evidence hints that women with

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Submitted: 23-Jul-14; Accepted: 26-Jul-15

Access this article online

Quick Response Code:



Website:
www.ijnmrjournal.net

DOI:
10.4103/1735-9066.170003

variables and the Chi-square test (or Fisher's exact test if required) for the categorical variables. Trend of changes in pain severity score within the study period (during one menstrual cycle before and two menstrual cycles after the intervention) was examined by repeated-measure analysis of variance (ANOVA) test. The change in pain severity score was also examined by multivariate regression analysis to examine the treatment efficacy of the treatment protocols, with the baseline variables considered as probable potential confounders. *P* values of 0.05 or less were considered statistically significant. All the statistical analyses were performed using SPSS version 19.0.

RESULTS

As shown in Table 1, the two groups treated with vitamin E and vitamin B6 were comparable in terms of baseline characteristics including age, age of marriage, socioeconomic level, body mass index, marital status, as

Table 1: Baseline characteristics and clinical data of the study population

Characteristics	Mean (SD)		P value
	Vitamin E group (n=40)	Vitamin B6 group (n=40)	
Age (years)	31.35 (8.86)	31.23 (9.82)	0.953
Mean body mass index (kg/m ²)	22.31 (4.23)	22.00 (4.05)	0.788
Marriage age >20 years old (%)	34 (85.0)	27 (77.5)	0.207
Occupational state (%)			
Worker	22 (55.0)	17 (42.5)	0.263
Housewife	18 (45.0)	23 (57.5)	
Marital status (%)			
Single	6 (15.0)	13 (32.5)	0.086
Married	34 (85.0)	27 (67.5)	
Educational level (%)			
Primary	10 (25.0)	30 (75.0)	0.152
Secondary or higher	5 (12.5)	35 (87.5)	
Number of parity	2.10 (0.96)	1.88 (1.02)	0.311
Breastfeeding (%)	27 (67.5)	17 (42.5)	0.025
Age of menarche	12.55 (0.78)	14.05 (1.11)	<0.001
Menstrual period (day)	6.50 (1.17)	6.50 (0.87)	0.998
Regular menstrual cycle (%)	34 (85.0)	32 (80.0)	0.556
Premenstrual syndrome (%)	33 (82.5)	40 (100)	0.012
Chronic pelvic pain (%)	-	8 (20.0)	0.003
Family history of breast cancer (%)	-	5 (12.5)	0.055
Regular exercise activity (%)	24 (60.0)	20 (50.0)	0.369
History of depression (%)	-	6 (15.0)	0.011
History of anxiety (%)	13 (32.5)	11 (27.5)	0.626

SD: Standard deviation

well as the number of parity and menstrual regularity. Also, family history of breast cancer, exercise activity, and history of anxiety were similar between both groups. However, breastfeeding was reported to be more in the group treated with vitamin E and the mean age of menarche was also lower in this group compared with vitamin B6 group. Also, the prevalence of some underlying comorbidities including premenstrual syndrome, pelvic pain, and history of depression was higher in the latter group. There was no significant difference in the mean of severity of cyclic mastalgia during one menstrual cycle before the intervention between the vitamin E and B6 groups (9.1 ± 2.1 and 8.4 ± 3.1 , respectively), but the difference was significant in the two groups during the first cycle (5.1 ± 1.6 and 5.2 ± 2.5 , respectively) and the second menstrual cycle (2.3 ± 1.0 and 2.6 ± 2.0 , respectively) after the intervention. The trend of changes in pain severity score showed significant downward trend of pain severity score within the study period in both the treatment groups ($P < 0.001$) [Figure 1], while these trends were similar in both groups when examined by the repeated-measure ANOVA test [Table 2 and Figure 2]. By multivariable linear regression analysis adjusted for baseline variables [Table 3], it was found that both the treatment regimens resulted in similar reduction in breast pain severity. Vitamins E and B6 are the most effective and least toxic agents available for the treatment of breast pain [$\beta = 0.807$, standard error (SE) = 0.433, $P = 0.067$].

DISCUSSION

Adding an antioxidant agent to first-line therapeutic regimes for treatment of cyclical mastalgia has been shown to be an effective schedule. Recently, direct attention has been paid toward using vitamins to facilitate pain relief in these patients. It has been suggested that use of adequate levels of vitamins as co-factors in the proposed metabolic pathways involving this complaint may be fully beneficial.^[19] Although some controlled trials could demonstrate the effects of vitamins in relieving cyclical mastalgia pain, some others failed to support the efficacy. Thus, previous studies gave questionable results with conflicting evidence.^[20-22] In a similar randomized trial of Iranian women suffering from mastalgia, administration of 200 mg twice daily could effectively reduce pain severity both 2 and 4 months after treatment, compared with the placebo group.^[23] In another trial, daily doses of 1200 IU vitamin E alone or in combination with evening primrose oil taken for 6 months decreased the severity of cyclical mastalgia.^[24] Also, a study similar to the present trial was conducted in the United Kingdom by Goyal and Mansel, who used a combination treatment arm of antioxidants and minerals which included beta-carotene, vitamin C, vitamin B6, zinc, niacin, and selenium in a coconut oil base and essential fatty acids. The investigators obtained equivocal

Table 2: Level of pain severity in the two treatment groups

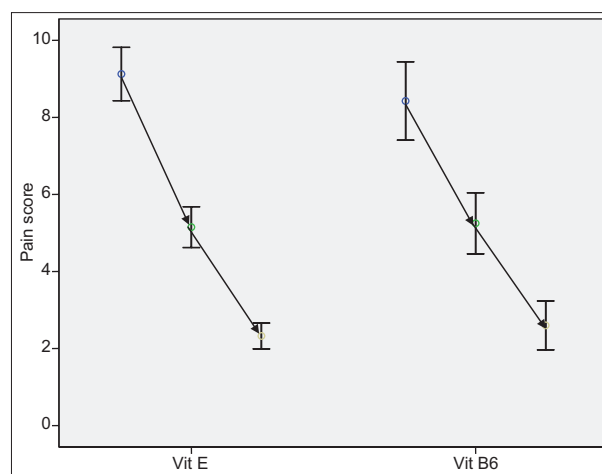
Characteristics	Frequency (%) (n=40)		P value
	Vitamin E group	Vitamin B6 group	
On admission (cycle 0)			
Mild	3 (7.5)	11 (27.5)	0.065
Moderate	22 (55.0)	19 (47.5)	
Severe	15 (37.5)	10 (25.0)	
One month later (cycle 1)			
Mild	32 (80.0)	34 (85.0)	0.069
Moderate	-	3 (7.5)	
Severe	8 (20.0)	3 (7.5)	
Two months later (cycle 2)			
None	3 (7.5)	4 (10.0)	0.999
Mild	37 (92.5)	36 (90.0)	
Moderate	-	-	
Severe	-	-	

Table 3: Multivariate linear regression model for comparing the effect of drugs on pain severity

Characteristics	Beta	SE	P value
Type of medication	0.807	0.433	0.067
Age	0.072	0.061	0.237
Occupational state	1.431	0.412	0.001
Marital status	2.901	0.494	<0.001
Educational level	-0.577	0.505	0.258
Number of parity	-0.759	0.632	0.234
Breastfeeding	0.437	0.565	0.441
Age of menarche	-0.117	0.196	0.554
Menstrual regularity	-2.583	0.516	<0.001
Premenstrual syndrome	2.847	0.882	0.002
History of depression	3.570	0.993	0.001
History of anxiety	-1.200	0.410	0.005
Family history of breast cancer	1.972	0.814	0.018
Regular exercise activity	-0.077	0.388	0.844

SE: Standard error

results in the reduction of breast pain symptoms.^[25] Three clinical trials have been performed, and all have shown vitamin E to be no better than placebo in the treatment of benign breast disease. In the first trial, 50 patients were asked whether their breast pain was better, worse, or unchanged after 2–3 months of therapy. In each group, 40% reported improvement.^[26] The second trial did not assess breast pain, but found no reduction in nodularity.^[27] The third trial found no reduction in nodularity or mammographic density, and although a larger proportion of women in the vitamin E group reported reduction in breast tenderness, this was statistically not significant.^[28] Contrarily, some studies could not find beneficial effects of supplemental vitamins on mastalgia, probably because of small sample size or inappropriate

**Figure 2:** Trend of the changes in the pain severity score in the Vitamin E group and vitamin B6 group [although in both groups, this trend was gradually reducing ($P < 0.001$), the trend was similar across the two groups ($P = 0.807$)]

nature of the study designs including ignoring adequate inclusion criteria or incorrect adjusting for confounders.^[29-31] In uncontrolled studies, vitamin B6 has been used to treat cyclical mastalgia with mixed results. A small ($n = 42$), double-blinded, controlled study found that vitamin B6 did not significantly reduce cyclical mastalgia at a dose of 200 mg daily, as compared with a placebo.^[31] Considering the key role of oxidation and inflammation processes in the appearance and expansion of cyclical mastalgia, it is believed that the use of vitamin supplements, especially of our studied vitamins, can successfully decrease the pain severity related to this phenomenon. However, it seems that the dosages of vitamins, duration of administration, as well as using them concurrently with other standard therapeutic regimens can all potentially influence the clinical results of these regimens, and thus, examining different regimens containing these vitamins in different doses and durations should be considered.

CONCLUSION

Both regimens containing vitamin E and vitamin B6 can similarly reduce breast pain severity in cyclic mastalgia. It seems that the dosages of vitamins, duration of administration, as well as using them concurrently with other standard therapeutic regimens can all potentially influence the clinical results of these regimens, and thus, examining different regimens containing these vitamins in different doses and durations should be considered.

ACKNOWLEDGMENTS

The authors would like to thank the staff of Hamadan University of Medical Sciences, Hamadan, Iran, for their valuable support and participation. This article is the result of a research project that

was approved by the Research Deputy of Hamadan University of Medical Sciences. The project has been funded by the Research Deputy of Hamadan University of Medical Sciences.

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How to cite: Shobeiri F, Oshvandi K, Nazari M. Clinical effectiveness of vitamin E and vitamin B6 for improving pain severity in cyclic mastalgia. *Iranian J Nursing Midwifery Res* 2015;20:723-7.

Source of Support: The project has been funded by the Research Center for Child and Maternity Care, School of Nursing and Midwifery, Hamadan University of Medical Sciences, Hamadan, Iran, **Conflict of Interest:** The authors declare that they have no conflicts of interest in this article.