Paediatrica Indonesiana

VOLUME 51 January • 2011 NUMBER 1

Original Article

Effectiveness of vitamin E as a treatment of primary dysmenorrhea in pubertal adolescents

Wagito, Siska Mayasari Lubis, Melda Deliana, Hakimi

Abstract

Background Primary dysmenorrhea is a common complaint among adolescents. Absenteeism from work and school are associated with the severity of symptoms. Vitamin E is an alternative treatment for primary dysmenorrhea.

Objective To evaluate the effectiveness of vitamin E as a treatment of primary dysmenorrhea.

Methods We conducted a randomized, double-blind, controlled trial from August to October 2009. We included female adolescents with primary dysmenorrhea in this study. Subjects were divided into 2 groups by simple randomization. Each group received either 200 units of vitamin E or a placebo twice daily, beginning two days before menstruation and continuing until the third day of menstruation. Treatment was repeated for three menstrual cycles. Subjects recorded the severity and duration of pain in a daily diary. Data was analyzed using Chi-square, Mann-Whitney U-test, and independent t-test.

Results One hundred-sixteen primary dysmenorrhea subjects enrolled in our study. By simple randomization, they were divided into two groups of 58 subjects each. There were no statistically significant differences between the two groups in the severity and duration of pain before the start of treatment and after 1 month of treatment. After treatment for 2 months and 3 months, there were statistically significant differences in pain severity (P=0.013, 95%CI -0.54 to -0.11; and P=0.0001, 95%CI -0.67 to -0.26, respectively) and pain duration (P=0.025, 95%CI -0.65 to -0.07 and P=0.007, 95%CI -0.75 to -0.12, respectively) between the 2 groups.

Conclusion Vitamin E was effective in treatment of primary dysmenorrhea in pubertal adolescents after 2 and 3 months of treatment. **[Paediatr Indones. 2011;51:41-6]**.

Keywords: *vitamin E, primary dysmenorrhea, pubertal adolescent.*

Dysmenorrhea is pain that occurs during menstruation.[1] Prevalence estimates vary from 45% to 75% of pubertal adolescents. Furthermore, absenteeism from school and work as a result of dysmenorrhea ranges from 13% to 51%, with 5% to 14% often absent due to the severity of symptoms.[2] An epidemiological study in Egypt reported 75% of pubertal adolescents experienced dysmenorrhea, with 20.3% reporting absenteeism from school due to severity of symptoms.[3]

Primary dysmenorrhea usually occurs at the first 6 to 12 months after menarche, and is always associated with ovulatory cycles. Secondary dysmenorrhea is menstrual pain associated with pelvic pathology.[2,4] Some literature recommend the use of analgesic drugs such as non-steroidal anti-inflammatory drugs (NSAIDs), cyclo-oxygenase-2 inhibitors (COX-2) or oral contraceptives that have been proven effective in relieving pain.[5,6] Other treatment options such as physical exercise, transcutaneous electrical nerve stimulation, behavioral intervention, and dietary

This study has been presented at 4th Annual Scientific Meeting of Child Health, Medan, February 22nd – 24th, 2010.

From the Department of Child Health, Medical School, University of North Sumatera, Adam Malik Hospital, Medan.

Reprint request to: Wagito, MD, Department of Child Health, Medical School, University of North Sumatera, Adam Malik Hospital, Jl. Bunga Lau No.17, Medan, 20136. Tel. 62-61- 8361721/ 8365663. Fax. 62-61-8361721. E-mail: *drwagitowijaya@gmail.com*

supplementation or traditional medicine have also shown satisfactory results.[7] Vitamin E is an alternative treatment without side effects that has been proven beneficial in reducing pain that occurs in primary dysmenorrhea.[8,9] Vitamin E acts to inhibit the release of arachidonic acid and its conversion into prostaglandins (PGs) through the enzymes phospholipase A2 and cyclo-oxygenase.[10] This study was designed to confirm the effectiveness of vitamin E as a treatment of primary dysmenorrhea.

Methods

We conducted a randomized, double-blind controlled trial from August to October 2009, at four junior/senior high schools in Medan. We included females aged 12 to 18 years, who met the diagnostic criteria for primary dysmenorrhea, had regular menstrual cycles within the past 6 months, had long menstrual cycles (every 21 to 35 days), and had good nutritional status. We excluded patients using other drugs for dysmenorrhea, those with obesity or poor nutritional status, and those with pelvic abnormalities.

We divided subjects into two groups by simple randomization: 58 patients to receive vitamin E and 58 patients to receive a placebo. Group I received 200 IU of vitamin E, two times daily in morning and evening, given from 2 days before menstruation until the third day of menstruation, and repeated for 3 months. Group II received a placebo in same manner and duration as group I. A questionnaire was used to identify primary dysmenorrhea and to establish the severity and duration of the pain. The severity of pain was measured with pain rating scales (0= no pain, 10= awful pain) and further classified into mild (0-3), moderate (4-6), or severe (7-10). The duration of dysmenorrheal pain was recorded in days. We collected the pain severity and duration data from each group in daily diaries given every month for 3 months.

We measured anthropometric values from each patient before the study began. Weight was measured using Camry® scales (sensitivity to 0.1 Kg) and height was measured using a 2M stature meter (sensitivity to 0.5 cm). Nutritional status was measured by body mass index (BMI)/weight in kilograms (kg) divided by height in meters square (m^2). We plotted the BMI values on the Centers for Disease Control and Prevention (CDC) growth charts 2000. Obesity was defined as BMI $\geq 95^{th}$ percentile, overweight as BMI 85^{th} - $<95^{th}$ percentile, good nutritional status as BMI 5^{th} - $<85^{th}$ percentile, and poor nutritional status as BMI $<5^{th}$ percentile.

Both vitamin E and the placebo were packed in capsules of similar color and shape. Neither researchers nor patients knew which drugs were given. If pain from dysmenorrhea still continued until the fifth day, patients were allowed to take ibuprofen (200 mg every 8 hours). We obtained informed consent from patients and this study was approved by the Research Ethics Committee of Medical School, University of Sumatera Utara.

All data collection was processed, analyzed and presented using the Statistical Package for the Social Sciences (Windows version 15.0; SPSS Inc, Chicago). Statistical comparisons between categorical data were determined using Chi-square and Mann-Whitney U-test. Independent t-test was used to determine the association between nominal and numerical data. Significance was set with $P<0.05$ and a 95% confidence interval.

Results

We screened a total of 750 female students, and found 540 students with dysmenorrhea, of whom 349 did not meet inclusion criteria and 75 refused to participate. The remaining 116 girls were included in the study, and divided into 2 groups. Each group was comprised of 58 students, who received either vitamin E (group I) or the placebo (group II). After three months of follow-up, no girls dropped out of either group. (**Figure 1)**

The average age in vitamin E group was 194.9 months and 190.0 months in the placebo group. The education level mode in the vitamin E group was senior high school level 2 with 36 students (62%), and for the placebo group was senior high school level 1 with 36 students (62%). Other than lower abdominal pain, the most common symptom of dysmenorrhea was headache, found in 12 girls (21%) and 10 girls (17%) in the vitamin E and placebo groups, respectively. Only 2 students (3%) in the vitamin E group and 3 students (5%) in the placebo group took analgesics during dysmenorrhea. (**Table 1**)

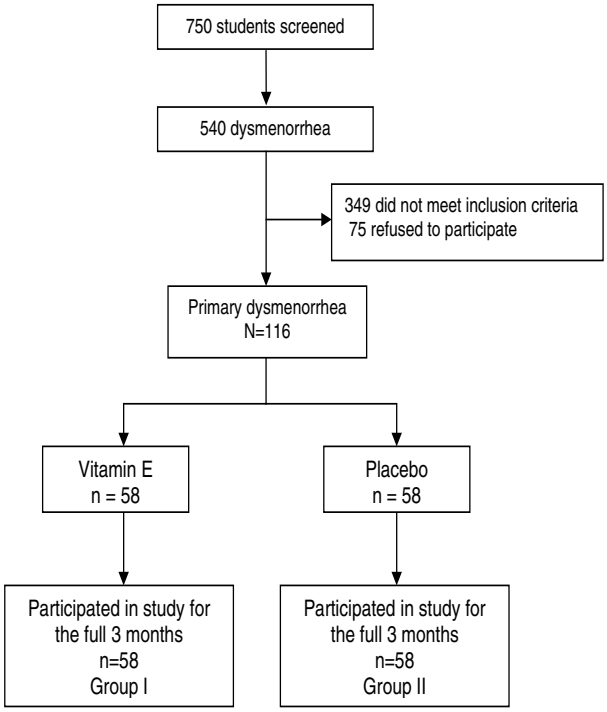

Figure 1. Study profile

Table 2 showed the outcomes at baseline and after treatment for 1 month, 2 months, and 3 months. There were statistically significant reductions in the degree of pain in both groups at two and three months, but the decrease in pain severity was significantly greater in the vitamin E group than in the placebo group (P=0.013, 95%CI -0.54 to -0.11; P=0.0001, 95%CI -0.67 to -0.26, respectively).

We also found no statistically significant difference between the 2 groups in the pain duration after 1 month of treatment (P=0.140, 95%CI -0.62 to 0). However, after 2 and 3 months of treatment we observed statistically significant differences (P=0.025, 95%CI -0.65 to -0.07; P=0.007, 95%CI -0.75 to -0.12, respectively). (**Table 3**)

Discussion

We found that the prevalence of dysmenorrhea was 72% from 750 female students at four junior/senior high schools in Medan. We noted only 10.4% of student absences from school were due to severity of pain. Similar prevalences were found in secondary school adolescents in northwest Ethiopia and in higher secondary school in India.[11,12]These prevalence rates were lower than those observed in a study reported in the United States on Hispanic students. They reported a prevalence of dysmenorrhea of 85% in the 3 preceding menstrual cycles, with school absence as high as 38%.[13] Variations in school absenteeism rates among these studies may be related to different cultural perceptions and responses to various gradients of pain.[14]

We found that the average ages of menarche in the vitamin E group and placebo group were 12.1 years and 11.9 years, respectively, earlier than that

Table 1. Baseline characteristic

Characteristic	Vitamin E n=58	Placebo n=58
Level of education, n(%)		
Junior high school level 1	3 (5)	0
Junior high school level 2	9 (15)	0
Junior high school level 3	9 (15)	9 (15)
Senior high school level 1	1 (2)	36 (62)
Senior high school level 2	36 (62)	13 (22)
Mean age, months (*SD*)	194.9 (14.90)	190.0 (10.72)
Mean weight, kg (*SD*)	38.9 (3.05)	36.7 (4.20)
Mean height, cm (*SD*)	148.6 (9.89)	150.5 (8.28)
Mean age at menarche, months (*SD*)	133.0 (13.84)	131.6 (13.66)
Mean length of menstruation, days (*SD*)	28.7 (1.92)	29.2 (2.07)
Symptoms due to dysmenorrhea, n (%)		
Headache	12 (21)	10 (17)
Nausea and vomiting	0	2 (3)
Diarhea	3 (5)	1 (2)
Analgesics used, n (%)	2 (3)	3 (5)

Table 2. Pain severity at baseline, 1, 2 and 3 months of treatment

Pain severity (with treatment)	Vitamin E n (%)	Placebo n (%)	95% CI	P
At baseline			-0.06 to 0.41	0.338
Mild	9 (15.5)	13 (22.4)		
Moderate	33 (56.9)	35 (60.3)		
Severe	16 (27.6)	10 (17.2)		
1 month			-0.33 to 0.12	0.599
Mild	20 (34.5)	15 (25.9)		
Moderate	32 (55.2)	36 (62.1)		
Severe	6 (10.3)	7 (12.1)		
2 months			-0.54 to -0.11	0.013
Mild	26 (44.8)	13 (22.4)		
Moderate	30 (51.7)	37 (63.8)		
Severe	2 (3.4)	8 (13.8)		
3 months			-0.67 to -0.26	0.0001
Mild	35 (60.3)	14 (24.1)		
Moderate	22 (37.9)	37 (63.8)		
Severe	1 (1.7)	7 (12.1)		

Table 3. Duration of pain at baseline, 1, 2 and 3 months of treatment

Duration of pain	Vitamin E (days)	Placebo (days)	95% CI	P
At baseline	2.1 (0.84)	2.1 (0.88)	-0.31 to -0.32	0.967
1 month with treatment	1.6 (0.73)	1.9 (0.95)	-0.62 to 0	0.140
2 months with treatment	1.4 (0.67)	1.7 (0.89)	-0.65 to -0.07	0.025
3 months with treatment	1.2 (0.71)	1.6 (0.91)	-0.75 to -0.12	0.007

Value in mean (SD)

reported in other studies. The Third National Health and Nutrition Examination Survey (NHANES) reported that the average age of menarche in American teenagers was 12.43 years.[15-17] In addition, a descriptive study in Hong Kong and a cross-sectional survey in Malaysia, found a similar average menarche age in pubertal adolescents, 12.3 years.[18,19] The age of menarche in each population is worth studying, because it may be affected by race, ethnicity, and environmental factors.[16,17]

Previous studies have found an average length of menstrual cycles of 21 to 35 days, with an average number of days of bleeding of 3 to 7 days, and blood loss of 30 to 40 ml per day.[7,15] Menstrual cycles are often irregular in early gynecological life. However, by the third year after menarche, 86.9% of pubertal adolescents had a normal menstrual cycle of 21 to 35 days.[18] For these reasons, one of our inclusion criteria was a menstrual cycle duration in the normal range of 21 to 35 days. The average menstrual cycle duration in the vitamin E and placebo groups were 28.7 days and 29.2 days, respectively.

Our study subjects were all of good nutritional status, with a body mass index (BMI) of 5th to 85th percentiles. Nutritional status affects the occurrence of dysmenorrhea in pubertal adolescents. Some studies mentioned that obesity was associated with the occurrence of primary dysmenorrhea.[4,5,20] However, other studies did not find a relationship between nutritional status and the occurrence of primary dysmenorrhea.[19,21]

The most frequent clinical symptom of dysmenorrhea was cramping pain in the lower abdomen which spread to the thigh and waist areas. Other symptoms were headache, nausea, constipation or diarrhea, and vomiting. Pain symptoms generally appeared on the first day of menstruation, peaked within 24 hours, and disappeared after 2 days.[5,7,22] In our study, all patients experienced lower abdominal pain. Another common symptom, headaches, were in as many as 12 students (20.7%) in the vitamin E group and 10 students (17.2%) in the placebo group. In contrast, a cross-sectional study in Thailand found that cramping pain in the lower abdomen was the most

frequently reported complaint among adolescents (78%), followed by low back pain (58.9%), and mood changes (56.9%). Other symptoms reported were fatigue, diarrhea and headache at frequencies of 42.9%, 18.7% and 26.2% respectively.[20]

Vitamin E, composed of four tocopherol and tocotrienol components, is known to have antioxidant activity. α-tocopherol has antioxidant properties that can prevent chronic disease associated with oxidative stress.[23] Two Iranian studies reported vitamin E to be effective in reducing symptoms and degree of pain caused by dysmenorrhea. In addition, they reported that both vitamin E and a placebo caused a reduction in pain duration.[8,9] Similarly, we observed that both vitamin E and placebo reduced the duration of pain from primary dysmenorrhea, but vitamin E had the greater effect.

The severity of pain measured at baseline in our study showed that a moderate degree of pain was most common. Similar with a study of dysmenorrhea among Thai adolescents that revealed mild to moderate pain severity in 47.5% subjects.[20] However, their subjects had a longer latency of pain-evoked potentials, a higher psychophysical rating of pain, and a higher level of anxiety state. These findings were evident across the entire menstrual cycle and not only during menstruation. The augmentation of pain perception may be part of the development of dysmenorrhea.[24]

There were some limitations noted in our study, such as lack of patient supervision toward compliance on taking the medicines. Monitoring only consisted of checking the number of drugs returned by patients after the study. In addition, some recall biases might have been occurred when completing the questionnaire. Potential misclassification of dysmenorrhea and its severity were minimized by clear explanation of the definitions to all participants.

In conclusion, vitamin E is useful in reducing the severity and duration of pain in dysmenorrhea after 2 and 3 months of treatment, and can be an alternative treatment of primary dysmenorrhea in pubertal adolescents.

References

1. Fleischman A, Gordon C. Adolescent menstrual abnormalities. In: Lifshitz F, editor. Pediatric endocrinology. 5th ed. New York: Informa; 2007. p. 349-63.
2. Proctor M, Farquhar C. Diagnosis and management of dysmenorrhea. Br Med J. 2006;332:1134-8.
3. El-Gilany AH, Badawi K, El-Fedawy S. Epidemiology of dysmenorrhea among adolescent students in Mansoura, Egypt. Eastern Mediter Health J. 2005;11:155-63.
4. Calis KA. Dysmenorrhea. [cited Sep 2008]. Available from: http://www.emedicine.com /med/topic606.htm
5. Lefebvre G, Pinsonneault O, Antao V, Black A, Burnett M, Feldman K, et al. Primary dysmenorrhea consensus guideline. J Obstet Gynaecol Can. 2005;27:1117-30.
6. Nasir L, Bope ET. Management of pelvic pain from dysmenorrhea or endometriosis. J Am Board Fam Pract. 2004;17:s43-7.
7. Mayo JL. A healthy menstrual cycle. Clin Nutr Ins. 1997;5:1-8.
8. Ziaei S, Faghihzadeh S, Sohrabvand F, Lamyian M, Emamgholy T. A randomised placebo-controlled trial to determine the effect of vitamin E in treatment of primary dysmenorrhea. Br J Obstet Gynaecol. 2001;108:1181-3.
9. Ziaei S, Zakeri M, Kazemnejad A. A randomised controlled trial of vitamin E in the treatment of primary dysmenorrhea. Br J Obstet Gynaecol. 2005;112:466-9.
10. Wu D, Mura C, Beharka AA, Han SN, Paulson KE, Hwang D, et al. Age-associated increase in PGE2 synthesis and COX activity in murine macrophages is reversed by vitamin E. Am J Physiol. 1998;275:C661-8.
11. Zegeye DT, Megabiaw B, Mulu A. Age at menarche and menstrual pattern of secondary school adolescents in northwest Ethiopia. BMC Women's Health. 2009;9:29-36.
12. Agarwal AK, Agarwal A. A study of dysmenorrhea during menstruation in adolescent girls. Indian J of Community Med. 2010;35:159-64.
13. Banikarim C, chacko MR, Kelder SH. Prevalence and impact of dysmenorrhea on Hispanic female adolescents. Arch Pediatr Adolesc Med. 2000;154:1226-9.
14. Goldstein-Ferber S, Granot M. The association between somatization and perceived ability: roles in dysmenorrhea among Israeli Arab adolescents. Psychosomatic Med. 2006;68:136-42.
15. Braverman PK, Sondhelmer SJ. Menstrual disorders. Pediatrics in Review. 1997;18:17-26.
16. Chumlea WC, Schubert CM, Roche AF, Kulin HE, Lee PA, Himes JH, et al. Age at menarche and racial comparisons in US girls. Pediatrics. 2003;111:110-3.
17. Anderson SE, Dallal GE, Must A. Relative weight and race influence average age at menarche: results from two nationally representative surveys of US girls studied 25 years apart. Pediatrics. 2003;111:844-50.

18. Chan SC, Yiu KW, Yuen PM, Sahota DS, Chung KH. Menstrual problems and health-seeking behavior in Hong Kong Chinese girls. Hong Kong Med J. 2009;15:18-23.
19. Lee LK, Chen PCY, Lee KK, Kaur J. Menstruation among adolescent girls in Malaysia: a cross-sectional school survey. Sin Med J. 2006;47:869-74.
20. Tangchai K, Titapant V, Boriboonhirunsarn D. Dysmenorrhea in Thai adolescents: prevalence, impact and knowledge of treatment. J Med Assoc Thai. 2004;87:s69-73.
21. Singh A, Kiran D, Singh H, Nel B, Singh P, Tiwari P. Prevalence and severity of dysmenorrhea: a problem related to menstruation, among first and second year female medical students. Indian J Physiol Pharmacol. 2008;52:389-97.
22. Reddish S. Dysmenorrhea. Aust Fam Phys. 2006;36:842-9.
23. Brigelius-Flohe R, Traber MG. Vitamin E: function and metabolism. J Fed Am Soc Exp Biol. 1999;13:1145-55.
24. Granot M, Yarnitsky D, Itskovitz-Eldor J, Granovsky Y, Peer E, Zimmer EZ. Pain perception in women with dysmenorrhea. Obstet Gynecol. 2001;98:407–11.