Impact of Vitamin E on Reducing Primary Dysmenorrhea among University Students: A Single-Blind Randomized Controlled Trial

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ABSTRACT

Background: Primary dysmenorrhea is a common complaint among adolescent girls and women of reproductive age, which can be severe enough to negatively affect the quality of their life. Therefore, the present study aimed to assess its impact on primary dysmenorrhea severity among university female students.

Methods: This single-blind, randomized controlled trial was conducted on 82 female university students with primary dysmenorrhea, who were allocated to either an intervention group (vitamin E) or a comparison group (placebo) and treated during two successive menstrual cycles. Dysmenorrhea severity was measured using the Visual Analogue Scale at baseline and during the two cycles.

Results: The median dysmenorrhea scores were not significantly different between both groups at baseline or during the first cycle after the intervention. However, the median dysmenorrhea score was significantly reduced in the vitamin E group during the second cycle. Most students in the vitamin E and placebo groups had moderate dysmenorrhea at baseline, being 73.2% and 85.4%, respectively. During the...
Introduction

Dysmenorrhea, which refers to menstruation-associated pain, is one of the most prevalent gynecologic conditions affecting menstruating women. Primary dysmenorrhea refers to lower abdominal cramps that may occur immediately before or during menstruation in the absence of other disorders. In contrast, secondary dysmenorrhea refers to painful menstruation caused by pelvic disorders such as endometriosis, leiomyomas, pelvic inflammatory disease, adenomyosis, endometrial polyps, and cervical stenosis (outlet obstruction). Therefore, it can be associated with other clinical presentations such as dyspareunia, dysuria, abnormal bleeding, or infertility.

Although the pathophysiology of primary dysmenorrhea is not fully understood, one of the most accepted hypotheses is that increased secretion of uterine prostaglandin F2 (PGF2) and prostaglandin E2 (PGE2) significantly contributes to ischemia and hypoxia, resulting in dysrhythmic uterine contractions, reduced blood flow and production of anaerobic metabolites. The frequency of dysmenorrhea varies from 45% to 97% across different age and ethnic groups. Primary dysmenorrhea affects the quality of life, causing women to miss social activities, sports events and educational classes.

Dysmenorrhea is often treated using a variety of methods, including chemotherapy and complementary medicine. Non-steroidal anti-inflammatory drugs (NSAIDs) and oral contraceptive pills (OCPs) are the most commonly used drugs for treating dysmenorrhea. The role of prostaglandins in causing dysmenorrhea justifies the administration of NSAIDs. However, long-term use of NSAIDs has been associated with side effects such as headache, dizziness, drowsiness, nausea, vomiting, anorexia, gastrointestinal bleeding, acute exacerbation of asthma, acne and dysuria.

In the era of complementary and alternative medicine, herbs, yoga, psychotherapy, relaxation, massage, minerals (calcium and magnesium), vitamins (E, B and C), hydrotherapy, hypnosis, acupressure and acupuncture have all been tried to alleviate dysmenorrhea. Most adolescent girls use non-pharmacologic alternatives for treating dysmenorrhea or self-medicate with over-the-counter pain relievers.

Vitamin E has been shown to improve primary dysmenorrhea by reducing the severity of pain in about 7% of Taiwanese patients. It modulates the activity of the phospholipase A2 and cyclo-oxygenase enzymes that convert arachidonic acid to prostaglandins and can increase the levels of endogenous opioids that alleviate pain. Vitamin E is abundant in a wide variety of natural products, including sunflower seeds, wheat germ oil, almonds, peanuts, avocados, spinach, red sweet peppers, kiwifruit and mango. However, its largest quantities are found in nuts, seeds and some oils.

Although a number of earlier studies have demonstrated the efficacy of vitamin E in relieving dysmenorrhea, the evidence is still insufficient, and
several published reviews have emphasized the need for further research on this issue. Therefore, the present study aimed to assess the impact of vitamin E on reducing primary dysmenorrhea severity in university female students compared to a placebo in Sana’a city.

2. Methods

2.1. Study design, participants and setting

From December 2021 to March 2022, a single-blind randomized clinical trial (RCT) was conducted among female students at the Faculty of Medicine and Health Sciences, University of Science and Technology in Sana’a, Yemen. One hundred and fifty female students in the first and second levels of Medicine and Nutrition & Dietetics programs were assessed for eligibility to participate in the study. Students were considered eligible for inclusion in the study if they were single between 18 and 25 years of age, had primary dysmenorrhea with no increase over time and had regular menstrual cycles. Those having a pelvic disease or a history of abdominal or pelvic surgery, or receiving NSAIDs were excluded from the study. Based on inclusion criteria, 150 students were eligible to be enrolled in the study.

2.2. Randomization and blinding

Of the 150 female students assessed for eligibility at enrollment, 58 were excluded because they did not meet the inclusion criteria for primary dysmenorrhea. Thus, 92 students were included in the trial. However, only 82 students were available for the trial, as the dropout rate at the beginning of the intervention was 11%. These 82 students were randomly allocated to either an intervention group (vitamin E) or a comparison group (placebo) at a ratio of 1:1, with 41 students in each group. All randomized students finished the study, and their data were statistically analyzed (Figure 1). The randomized lists were blinded to all participating students, but not to the investigator. In addition, vitamin E and placebo gel capsules were similar, and their covers were identical with codes known only to the principal investigator.

2.3. Data collection

At the beginning of the study, data about the students’ age, age at first menarche, duration of menstrual cycle and dysmenorrhea severity were collected using a pre-designed data collection sheet. The severity of dysmenorrhea was measured using the Visual Analogue Scale (VAS) during the last menstruation before intervention (month 0). A scale of scores from 0 to 100 was constructed using a ruler to measure the distance (in mm) along a 10-cm line between the “no pain” anchor and the student’s mark. Dysmenorrhea severity was categorized as none (0–4 mm), mild (5–44 mm), moderate (45–74 mm), or severe (75–100 mm). VAS measurements were also recorded during the first and second menstrual cycles after the intervention.

2.4. Intervention

Vitamin E (Pharco Pharmaceuticals, Alexandrina, Egypt) was given to students in the intervention group at a total dose of 400 mg per day split into two doses for five days (two days before and three days during menstruation), while a placebo was given to the comparison group at the same dose regimen. Vitamin E and a placebo were administered to the respective groups during two consecutive menstrual cycles.
Then, the students were asked to record any differences in dysmenorrhea they felt between these two cycles after the intervention compared to the cycles before the intervention.

2.5. Data analysis

Data were analyzed using IBM SPSS Statistics, version 23 (IBM Corp., Armonk, NY, USA). The independent samples t-test and Mann–Whitney U test were used to test differences between normally distributed and non-normally distributed mean scores of dysmenorrhea, respectively. Statistical significance was considered at a $P$-value of $<0.05$.

3. Results

3.1. Characteristics of participants

Table (1) shows that the mean age at randomization was 20.8±1.4 years for female students in the vitamin E group compared to 21.2±1.6 years for those in the placebo group, with no statistically significant difference ($P = 0.182$). The mean age at the first menarche was 13.1±1.4 years for students in the vitamin E group compared to 13.2±1.2 years for those in the placebo group, with no statistically significant difference ($P = 0.729$). On the other hand, the mean duration of the menstrual cycle was significantly lower ($P = 0.039$) among students in the vitamin E group compared to those in the placebo group, being 5.2±1.4 days vs. 6.0±2.0 days, respectively.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Vitamin E group (N=41)</th>
<th>Placebo group (N=41)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at randomization (years)</td>
<td>20.8 (1.4)</td>
<td>21.2 (1.6)</td>
<td>0.182</td>
</tr>
<tr>
<td>Age at first menarche (years)</td>
<td>13.1 (1.4)</td>
<td>13.2 (1.2)</td>
<td>0.729</td>
</tr>
<tr>
<td>Duration of menstrual cycle (days)</td>
<td>5.2 (1.4)</td>
<td>6.0 (2.0)</td>
<td>0.039</td>
</tr>
</tbody>
</table>

3.2. Impact of vitamin E on dysmenorrhea severity

Table (2) shows no statistically significant difference in the median dysmenorrhea scores between students in the vitamin E and placebo groups at baseline ($P = 0.644$). Although the reduction in the median dysmenorrhea score was higher in the vitamin E group than in the placebo group during the first cycle after the intervention, the difference was not statistically significant ($P = 0.059$). In contrast, there was a significant reduction ($P = 0.008$) in the median dysmenorrhea score in the vitamin A group compared to the placebo group during the second cycle after the intervention.

<table>
<thead>
<tr>
<th>Time of pain scoring</th>
<th>Vitamin E group (N=41)</th>
<th>Placebo group (N=41)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysmenorrhea score</td>
<td>Mean (IQR)</td>
<td>Mean (IQR)</td>
<td></td>
</tr>
<tr>
<td>At baseline</td>
<td>6 (1.5)</td>
<td>6 (1.3)</td>
<td>0.644</td>
</tr>
<tr>
<td>First cycle after intervention</td>
<td>4 (2.3)</td>
<td>5 (2.8)</td>
<td>0.059</td>
</tr>
<tr>
<td>Second cycle after intervention</td>
<td>3 (2.0)</td>
<td>4 (2.5)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

3.3. Distribution of dysmenorrhea severity between vitamin E and placebo groups

Table (3) shows that most students in the vitamin E and placebo groups had moderate dysmenorrhea at baseline, being 73.2% and 85.4%, respectively. After the intervention, most students in the vitamin E group had mild dysmenorrhea, being 56.1% and 61% during the first and second cycles, respectively. In contrast, most students in the placebo group had moderate dysmenorrhea after the intervention, being 58.5% and 56.1% during the first and second cycles, respectively.
Table 3: Distribution of dysmenorrhea severity between vitamin E and placebo groups of female university students in Sana’a, Yemen

<table>
<thead>
<tr>
<th>Dysmenorrhea severity categories</th>
<th>Vitamin E group (N=41)</th>
<th>Placebo group (N=41)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>30 (73.2)</td>
<td>35 (85.4)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>11 (26.8)</td>
<td>6 (14.6)</td>
<td></td>
</tr>
<tr>
<td>First cycle after intervention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>23 (56.1)</td>
<td>12 (29.3)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>13 (31.7)</td>
<td>24 (58.5)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>5 (12.2)</td>
<td>5 (12.2)</td>
<td></td>
</tr>
<tr>
<td>Second cycle after intervention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>25 (61.0)</td>
<td>13 (31.7)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>14 (34.2)</td>
<td>23 (56.1)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>4 (9.8)</td>
<td>5 (12.2)</td>
<td></td>
</tr>
</tbody>
</table>

4. Discussion

Primary dysmenorrhea is a common complaint among females of all ages and can negatively affect their quality of life. Numerous pharmaceutical and traditional approaches have been tried to alleviate the severity of dysmenorrhea. Therefore, the present RCT aimed to determine whether vitamin E supplementation alleviates the severity of primary dysmenorrhea in university students compared to a placebo and whether it can be a candidate for use as an alternative to prescription drugs. Accordingly, the impact of vitamin E on reducing dysmenorrhea pain was evident during the second menstrual cycle after supplementation as shown by a significantly lower mean dysmenorrhea score among students receiving vitamin E supplements compared to those receiving placebos. In addition, the majority of students who received vitamin E supplements experienced mild dysmenorrhea during the first and second cycles as opposed to the majority of students who received placebos, who mostly experienced moderate dysmenorrhea.

The findings of the present RCT are consistent with those previously reported in two independent RCTs, which found that vitamin E supplements had a statistically significant impact on reducing dysmenorrhea scores when compared to placebos. They also observed greater reductions in the duration of dysmenorrhea and the amount of bleeding. Likewise, significant reductions in the severity of primary dysmenorrhea after supplementation with vitamin E have been reported for pubertal adolescents in Indonesia, female students in Iran and unmarried women in Pakistan. It is noteworthy that vitamin E has been suggested as a potential medicine for the treatment of primary dysmenorrhea. In line with the present RCT is what was reported for single females aged less than 25 years in Syria, where dysmenorrhea severity reduced by 26.5% during the first cycle after vitamin E supplementation and to 38.8% during the second cycle after supplementation. Similarly, significant reductions in the severity of primary dysmenorrhea after supplementation with vitamin E have been reported for pubertal adolescents in Indonesia, female students in Iran and unmarried women in Pakistan. It is noteworthy that vitamin E has been suggested as a potential medicine for the treatment of primary dysmenorrhea.

5. Conclusion

Vitamin E can significantly reduce the severity of primary dysmenorrhea when administered in doses of 200 mg twice daily for two days before menstruation and three days thereafter. It can therefore be considered when treating primary dysmenorrhea.

Acknowledgments

The authors thank university students who participated in the study.

Ethical approval and consent

The Medical Ethics Committee at the Faculty of Medicine and Health Sciences, University of Science and Technology in Sana’a, Yemen approved this study (MECA No.: EAC/UST240). Informed consent was obtained from students before starting the study after explaining to them...
its purpose. The privacy of participants and confidentiality of data were ensured. Participants were also informed that they have all the right to withdraw from the study without giving a reason.

**Conflict of Interest**
The authors declare no conflicts of interest.

**Funding**
None.

**References**


