

Effect of vitamin E vaginal suppository on atrophic vaginitis among postmenopausal women

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Abstract

Introduction: Urogenital atrophy is a common problem after menopause, and results from declining estradiol levels and may causes symptoms that can significantly affect quality of life. The aim of this study was to determine the effect of the vaginal suppository of vitamin E in the treatment of atrophic vaginitis.

Materials & Methods: This randomized, double-blind controlled trail study was carried out on 42 postmenopausal women with of vaginal atrophy symptoms. The women were randomized in two groups to take vaginal suppository containing 1 mg vitamin E (n=20) or placebo (n=22) for 8 weeks. The symptoms of vaginal atrophy, vaginal pH and maturation value were measured and compared in both groups before and after treatment. Data were analyzed using t-test and Chi square in SPSS version 16.

Results: The results showed that the symptoms of atrophy were relieved significantly in recipient vitamin E group ($p < 0.001$). A significant decrease in vaginal pH was detected in recipient vitamin E group compared to placebo group ($p < 0.001$). In addition, the mean maturation index was significantly higher in vitamin E group compared with placebo group ($p < 0.002$).

Discussion: The results showed that vitamin E relieves symptoms of vaginal atrophy. Therefore, the use of vitamin E vaginal suppositories is recommended for the women with vaginal atrophy who do not want or cannot receive a topical estrogen treatment.

Keywords: Menopause, Vaginal Atrophy, Maturation Index, Vitamin E, Vaginal pH.

Introduction

Study on physical and psychological health of middle-aged women initially focuses on the menopause as a predictable change in their lives (1). Menopause is one of the most critical stages of life, which is considered the most important health concerns for women in middle age. During this period, women undergo many changes that may take several years (2).

Natural menopause is the cessation of menstruation in women, which occurs due to the cessation of ovarian follicular activity and results in the termination of the woman's reproduction period. Thus, a woman is considered menopausal whenever has at least 12 months of amenorrhea unrelated to pregnancy, lactation, or other hormonal disorders (3, 4). The average age of menopause is estimated at 50-52 years of age (5). In the study by Mohammad et al, which is considered the largest and most

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Received: 17 Dec 2012

Accepted: 16 March 2013

detailed study in Iran, the mean (\pm standard deviation) of age of menopause was 50.4 ± 4.3 years in the country (6).

Menopause is accompanied by a number of early and late complications (7). The symptoms of menopause seem to be numerous, all of which has not been experienced by a certain person (8). Epidemiological studies suggest that 65-85 percent of women experience unpleasant symptoms of menopause (9). More changes and menopausal symptoms are associated with estrogen deficiency (10). Low levels of circulating estrogen cause some undesirable changes in all organs whose health and performance depend on the presence of estrogen (11). The lack of estrogen causes the sensitivity of the vaginal tissue to impact, which causes 15 percent of postmenopausal bleeding (12). Urogenital atrophy leads to a decrease in the size of the uterus, ovaries, vagina and vulva channel.

Vaginal atrophy leads to loss of collagen, elastin and smooth muscles in the vagina (13). Vaginal symptoms include dryness, dyspareunia, and recurrent vaginal infections, whereas urinary symptoms may include dysuria, urgency, and recurrent urinary tract infections (4). The symptoms resulting from vaginal atrophy are experienced by 15 percent of women almost before the age of menopause and 40-57 percent of postmenopausal women (14). In a study by Barlow, about 49 percent of women had experienced urinary-genital symptoms for a while (15). In another study by NouhJah, the outbreak of genitourinary diseases in postmenopausal women was 46.1 percent (10).

There are several methods to improve vaginal atrophy, including hormonal and non-hormonal methods. Hormonal methods are based on the topical use of systemic low-dose estrogen alone or with progesterone, in three forms: cream, vaginal ring or vaginal tablet. Non-hormonal methods include vaginal moisturizers and

lubricants, oils, vitamin E (16) as well as vitamin D (17). Certain specific vitamins are essential for maintaining the healthy uterus and vagina so that the organs are wrinkled and dried, if not lubricated by the vitamin. Among the others, vitamin E is the best (18). As a fat-soluble vitamin with strong antioxidant properties, vitamin E is involved in the metabolism of all cells and prevents the tissue damage caused by oxidants (11). Vitamin E plays a key role in the stabilization of estrogen levels, so that it can improve menopause symptoms, including hot flashes, irritability, insomnia, dizziness, palpitations, shortness of breath and vaginal dryness (2). As an active healing substance, it can be used locally on the skin because of the antioxidant and anti-inflammatory properties (11). Vitamin E is also available as oil (2), which if used topically, can reduce vaginal dryness (18).

Ziaei et al, conducted a study on the effect of vitamin E on hot flashes in postmenopausal women, which examined the percentage of vaginal epithelial cells before and after treatment with vitamin E. They found that vitamin E had a beneficial effect in reducing the frequency and severity of hot flashes. However, in relation to the percentage of superficial and parabasal cells, no significant difference was observed before and after treatment (19). In addition, in a study entitled "Vitamin E in the Menopause", McLaren et al, concluded that vitamin E had the effect of slowly restoring and might reduce dyspareunia as a result of improving atrophic lesions in lower reproductive system. Vitamin E does not cause rapid changes in clinical features of the lower reproductive system, but it seems that long-term use of high doses can improve 50% of age-dependent vulvovaginal lesions. Vaginal smears vary rarely; there is no parity between the maturation of vaginal cell, and

relief of symptoms; and cervix is not also stimulated to secrete mucus (20).

Given that menopause is an undeniable event occurs in women life, which is experienced by almost all women, and considering the problems (such as vaginal atrophy) that are experienced by at least 50% of women in postmenopausal period, this study was conducted to examine the effect of vitamin E in the treatment of vaginal atrophy in postmenopausal women.

Materials and Methods

This study was conducted as a randomized double-blind clinical trial on qualified postmenopausal referred women to No. 1 Health Center, Ahvaz during September 2010 to April 2011.

Reviewing different papers (16) as well as the statistical consultant, 22 patients for each group were selected as sample size.

At the beginning of research, vitamin E and placebo suppositories weighing $1\pm0/04$ g, which contain SUPPOCIRE AM PELLETS (GATTEFOSSE, France) (semi-synthetic fatty acid triglycerides) as the base for all suppositories, as well as 1 mg of vitamin E was prepared in the industrial laboratory of the Faculty of Pharmacology of Ahvaz Jundishapur University of Medical Sciences. Then, drug and placebo were placed in the same and similar envelopes and statistical consultant encoded using a random number table so that the researcher and the patients were not aware of the drug prescribed.

Inclusion criteria included: Age 45-65 years, amenorrhea for at least 12 months or having a hormones test with FSH levels greater than 40 international units, normal pap smear in the past three years, symptoms of vaginal atrophy, vaginal pH above 5, vaginal superficial cells less than or equal to 5%, and having sexual activities.

Exclusion criteria also included: Vaginal infections, genital infections, the use of sex hormones in the past eight weeks, vaginal bleeding of unknown cause, and plenty consumption of phytoestrogens such as soybean, red clover, fenugreek, vitex, during the last month.

The procedure was as follows:

Among all postmenopausal women referring to No. 1 Health Center, located in the East of Ahvaz, 115 women were interviewed, and research subject was shared with them in compliance with ethical considerations.

Following obtaining the informed consent from qualified women to enter the study, a demographic questionnaire was completed in first visit, and then physical examination was performed including examination of women's vulva, vagina and cervix in terms of infections, sores, lesions and abnormal discharges. The subjects who did not have the symptoms were selected for the study.

The symptoms of vaginal atrophy were examined including inflammation, redness, and vulvovaginal attrition and pap smear was performed for all patients who have not been tested in the past 3 years. Then, the sample of vaginal cells was taken by scraping the side walls of the vagina on the surface of cervix with a wooden spatula and was fixed on glass slides. In addition, to determine the pH of the vagina, pH paper was in contact with the side wall of the vagina for 5 seconds.

The pH paper color was compared to pH EM-ALERT, and the results were recorded. In addition, the mental symptoms of vaginal atrophy were assessed in accordance with 4-degree self-assessment scale of composite score including irritation, itching, the feeling of vaginal dryness and dyspareunia, as follow:

The severity of each symptom was determined by the patient, to which the

researcher then gave a score in terms of the 4-point scale (0= absent, 1= mild, 2 = moderate, 3= severe). Finally, the composite score was calculated by adding the numbers related to each symptom. Subsequently, cytological samples in order to be examined were sent to the Shafa Hospital's pathology laboratory within a maximum period of two days.

After each slide was stained as blind by two pathologists, it was studied to determine the percentage of basal, intermediate and superficial vaginal cells, as follows: A total number of 100 cells were counted; and the percentage of each cell type was expressed, which was used in the following equation to determine the maturation value (MV) of vaginal cells.

$$MV = (\% \text{superficial cells}) + (0.5 \times \% \text{intermediate cells})$$

If the pap smear had normal results and the vaginal atrophy was confirmed by examinations and maturation index of vaginal cells, patient was recalled to the clinic by phone. Finally, 44 patients were randomly divided into two groups of treatment with vitamin E (22 patients) and placebo (22 patients).

Vitamin E and placebo suppositories were placed in 44 envelopes, each containing 35 suppositories that was used for 8 weeks and was randomly coded by another person, so follows:

The numbers 1 to 44 for each pharmaceutical envelopes was selected using a table of random numbers, so that each person could receive a number corresponding to random numbers. After referring to the clinic in the first visit, the subject received a package containing vaginal suppositories with some necessary instructions on how to use a suppository daily for a continuous 14 days; and the suppository was then placed in deep into the vagina before bedtime every other day until the end of two months. A record form for daily use of the drug

was provided to the patient; and the date of subsequent visits was set for eight weeks after the start of treatment. At the final visit (56th day after treatment), the composite score scale, cytological sample, and vaginal pH test were conducted once again for the patient; and samples were sent to the pathology laboratory for evaluation of vaginal atrophy.

For all efficacy variables, statistical analysis was carried out by SPSS version 16. Descriptive statistics were performed for each variable. Statistical analysis was performed using independent t-test and Chi-square test to compare patients' baseline characteristics and the genital scores, MV, and vaginal pH at basal condition and at the end of the study in the two groups. Paired t test was used for the comparison of the parameters in two groups. Data are expressed as Mean \pm SD; the significance level was set up at p less than 0.05.

Ethical considerations

This trial was approved by the Research Ethics Committee of Ahvaz Jundishapur University of Medical sciences (No. 18.ETH). Women completed informed written consent form. Each woman was assigned an ID code, ensuring data set anonymity. Women could withdraw from the study at any point.

Results

In this study, 42 patients completed the study: Two patients in the vitamin E group were excluded due to not referring for follow-up or not taking drugs.

The average age of the vitamin E and placebo groups was 54.9 ± 5.16 and 53.77 ± 5.3 , respectively. The majority of patients in both groups were aged between 51-55 years; and independent t-test showed no significant differences between the two groups ($p=0.491$). In addition, the mean duration of menopause in

the vitamin E group and in the placebo group were 82.75 and 74.18 months, respectively, in which no significant difference was found between the two groups using Independent t-tests ($p=0.685$).

The results also indicated that mean composite score of the vagina before and after treatment showed a statistically significant difference ($p<0.001$) in the vitamin E group, while there was no significant difference ($p=0.05$) in this context in the placebo group.

The mean composite score of vaginal symptoms before treatment showed no significant difference between the two groups ($p=0.431$). However, after 8 weeks of treatment, statistically significant differences were observed between the two therapeutic groups and relief of vaginal symptoms in the vitamin E group was significantly higher when compared with the placebo group ($p=0.001$) (Table 1).

The independent t-test for each group showed significant differences between the groups in relation to vaginal pH before treatment ($p=0.450$).

Using paired t-test, mean vaginal pH before and after the study showed statistically significant difference in the vitamin E group ($p<0.001$) and in the placebo group ($p<0.03$).

A comparison between the two therapeutic groups showed that statistically significant difference can be seen in relation to vaginal pH after treatment, and that vitamin E further reduced vaginal pH ($p<0.001$) (Table 2).

The paired t-test showed that the mean maturation index of vaginal cell before starting treatment in the vitamin E group was 9.55 ± 6.36 , which reached 24.5 ± 8.78 at the end of treatment.

Vaginal cell maturation index before and after treatment in this group showed significant difference ($p<0.001$). In addition, the paired t-test showed that the mean maturation value of vaginal cells before treatment in the placebo group was 8.02 ± 4.62 , which reached 17.72 ± 4.19 . Vaginal cell maturation index before and after treatment showed statistically significant difference ($p<0.001$) in this group.

A comparison between the vitamin E and placebo groups using independent t-test also showed that the mean maturation index of vaginal cells before treatment had no significant difference between these two groups ($p=0.376$). However, the mean maturation value of vaginal cell was significant in the two groups after 8 weeks of treatment ($p<0.002$) (Table 3).

Table 1: Composite score of vaginal symptoms (CSVs) comparison before and after treatment in two groups

Parameters	Vitamin E Group Mean \pm SD	Placebo Group Mean \pm SD	p-value
CSVs before treatment	4.650 \pm 2.41	6.95 \pm 1.58	0.431
CSVs after treatment	0.650 \pm 0.875	5.95 \pm 1.73	0.001
p- value	0.001	0.05	

Table 2: Vaginal pH before and after treatment comparison in two groups

Parameters	Vitamin E Group Mean \pm SD	Placebo Group Mean \pm SD	p-value
Vaginal pH(before treatment)	6.17 \pm 0.862	6.34 \pm 0.569	0.450
Vaginal pH(after treatment)	5.125 \pm 0.666	5.95 \pm 0.615	0.001
p-value	0.001	0.03	

Table 3: The comparison of vaginal maturation value before and after treatment in two groups

Parameters	Vitamin E Group (Mean \pm SD)	Placebo Group (Mean \pm SD)	p-value
Vaginal maturation value (before treatment)	9.55 \pm 6.36	8.02 \pm 4.62	0.376
Vaginal maturation value (after treatment)	24.50 \pm 8.78	17.72 \pm 4.19	0.002
p-value	0.001	0.001	

Discussion

The findings indicated that vitamin E was effective in improving vaginal atrophy.

Regarding the first objective of the study, i.e. examining the effect of vitamin E vaginal suppository on vaginal maturation index, the results showed that vitamin E was significantly more effective and increased more the maturation of vaginal cells although both vitamin E and placebo increased vaginal cell maturation index. In this regard, a study entitled "The effect of vitamin E on hot flashes in postmenopausal women conducted by Ziaei et al. in Tehran a daily 400 IU of vitamin E and a soft gel as placebo were prescribed for two groups over four weeks. As it was a crossover study, a drug displacement was made during an interval of one week to eliminate the transfer effect of drugs after the first treatment period, i.e., wash out. This phase lasted for 4 weeks. The comparison of percentages of vaginal superficial and parabasal cells before and after treatment in

this study showed that no significant difference was observed in the subject and control groups, and that vitamin E did not increase the maturation of vaginal cells (19). The results of the research were inconsistent with the present study, probably due to the systemic administration of vitamin E in this study.

Regarding another objective of this study i.e., examining the effect of vitamin E vaginal suppositories on the relief of symptoms of vaginal atrophy, the results showed that vitamin E could relieve the symptoms of vaginal atrophy so that the relief of symptoms was observed at the second week after treatment. In this regard, a study was conducted by Costantino et al, with the aim of examining the effect of vaginal suppositories containing hyaluronic acid, vitamins A and E on the treatment of vaginal atrophy in postmenopausal women. Vaginal suppository was administered daily for patients for a

continuous 14 days, and then every other day. Results of this study showed a significant decrease in the vaginal dryness, burning, dyspareunia, and other symptoms in the first week after treatment (10), which is consistent with those of this research.

The McLaren et al, also conducted a study entitled "Vitamin E in the menopause", in which the effect of vitamin E on hot flashes, sexual function, reproductive system, vagina, cervix and urethra were examined. A dose of 18.500 mg of vitamin E in the form of α -tocopherol were administered for 47 patients during a period of 42 days. The researchers concluded that vitamin E had the effect of slowly restoring, and had reduce dyspareunia as a result of improving atrophic scars in the lower reproductive system. Although, vitamin E did not cause rapid changes in clinical features in the lower reproductive system, high dose and long-term use appeared to improve 50% of age-dependent vulvovaginal ulcers. Vaginal smears vary rarely; there was no similarity between the maturation of vaginal cells, and relief of symptoms; and cervix was not also stimulated to secrete mucus (20). As a fat-soluble vitamin with strong antioxidant properties, vitamin E is involved in the metabolism of all cells and prevents the tissue damage caused by oxidants (10). As an active healing substance, it can be used locally on the skin because of the antioxidant, anti-inflammatory properties (10), and if used topically, can reduce vaginal dryness (18). In the books of midwifery, the use of vitamin E suppositories as lubricant is recommended for the treatment of vaginal atrophy (21). In this study, the placebo also decreased the vaginal pH and increased the vaginal cell maturation value. One possible explanation could be the

use of semi-synthetic fatty acid triglyceride as a base for the preparation of suppositories, which can improve the vaginal atrophy in the pH range and the value of examining vaginal cells, due to the slippery made in the vaginal environment. Further studies will be necessary for accurate analysis in this regard.

The study was performed as double-blind and samples were randomly entered in the study. This type of sampling has clear strengths in empirical studies. All subjects in the study had a natural menopause, while menopause caused by radiation therapy and hysterectomy – oophorectomy were also included in most previous studies. In addition, since all phases of the study (including sample selection, initial assessment, examination and sampling) were conducted only by the researcher, it had added more accuracy to the study.

Cultural and social issues with respect to the age of the subjects were among the constraints in this study, which cause impatience, unwillingness and fear of the study results. In addition, in this study no adverse effects were observed in the therapeutic group.

Conclusion

The results showed that vitamin E relieved symptoms of vaginal atrophy. Therefore, the use of vitamin E vaginal suppositories is recommended for the women with vaginal atrophy who do not want or cannot receive a topical estrogen treatment.

Further studies will be necessary for accurate analysis in this regard.

Acknowledgments

This research was financially supported by the Research Deputy of Ahvaz Jundishapur University of Medical Sciences. The study was recorded in the Iranian Registration of Clinical Trials (IRCT201105026364N1). In the end, the staff of the Ahvaz No. 1 Family

Health Care Center, Osveh Pharmaceutical Company, patients participating in this study, and all those who helped us in this study, especially Ms. Marziyeh Mohammadian, are sincerely appreciated.

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