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The comparison of hyaluronic acid vaginal tablets with estradiol vaginal tablets in the treatment of atrophic vaginitis: a randomized controlled trial

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Abstract
Objective To compare the effectiveness of the vaginal tablets of hyaluronic acid and estrodiol for the treatment of atrophic vaginitis.
Materials and methods Forty-two postmenopausal women with symptoms of atrophic vaginitis were randomized to take vaginal tablets of 25 μg estradiol ($n = 21$) (group I) or 5 mg hyaluronic acid sodium salt ($n = 21$) (group II) for 8 weeks. The symptoms of atrophic vaginitis were evaluated by a self-assessed 4-point scale of composite score and the degree of epithelial atrophy was determined as, none, mild, moderate and severe. Vaginal pH and maturation index were measured and compared in both the groups.
Results The symptoms were relieved significantly in both the groups ($P < 0.001$). The relief of symptoms was significantly superior in group I compared with group II ($P < 0.05$). A significant decrease in epithelial atrophy and vaginal pH were detected in both the groups ($P < 0.01$) after treatment. The vaginal maturation values were also significantly improved at both study groups ($P < 0.001$). The mean maturation value was significantly higher in group I when compared with group II ($P < 0.001$).
Conclusion Both treatments provided relief of vaginal symptoms, improved epithelial atrophy, decreased vaginal pH, and increased maturation of the vaginal epithelium. Those improvements were greater in group I. Hyaluronic acid vaginal tablets can be used in patients with atrophic vaginitis who do not want to or can not take local estrogen treatment.

Keywords Atrophic vaginitis · Hyaluronic acid · Vulvovaginal complaints

Introduction

Follicular depletion of the ovary results in the decline of endogenous estrogen production at menopause. The vagina and other estrogen-dependent tissues gradually undergo atrophic changes. Low-estrogen levels leads to increase basal and parabasal cells in relation to superficial cells at cytology. The loss of estrogen-dependent cellular maturation in the vagina can result in atrophic vaginitis, with symptoms of dryness, soreness, irritation, discharge and dyspareunia [1]. Because of the decrease in estrogen at menopause, the lactobacilli decrease as well and the vaginal environment shifts toward alkalinity. This alkaline pH allows vaginal epithelium more susceptible to infection by colonization of the fecal flora. Although postmenopausal atrophic vaginitis is a common condition in elderly women, only a small percentage of those affected population sought help fort her symptoms [1, 2]. The management options for

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atrophic vaginitis range from nonhormonal home remedies to several forms of local or systemic estrogen therapy. Water-based lubricants, vaginal moisturizers, vitamin E oil are some of the nonhormonal treatment options [3]. In symptomatic women who have no other indications for systemic hormone replacement or prefer not to use systemic therapy, local vaginal treatment with estrogen is also an effective option in reversing atrophic vaginal changes and relieving symptoms [2, 4]. Because vagina looses collagen and water-retaining ability at menopause, hyaluronic acid can be used in adjuvant of the repairing processes of the atrophic and dystrophic states of the vagina and senile dryness due to estrogen deficiency. [1, 5] The aim of this study is to compare the effectiveness of the hyaluronic acid vaginal tablets with estradiol vaginal tablets for the treatment of atrophic vaginitis.

Materials and methods

This randomized, controlled study was conducted at Bakirkoy Dr. Sadi Konuk Training and Research Hospital, menopause outpatient clinic. During the 8-week study, the efficacy of 25 μg estradiol vaginal tablets (Vagifem, Novo Nordisk Inc. USA) were compared with the vaginal tablets containing hyaluronic acid sodium salt 5 mg, asiatic centella oil extract 60 mg, calendula oil extract 60 mg, aloe vera oil extract 60 mg, essential oil of melaleuca 2 mg, semi-synthetic glycerides, bht, isopropyl paraben, isobutyl paraben, butyl paraben (Farma-Derma srl Italy). The study was approved by the local ethics committee, and written informed consent was obtained from each participant before the start of study procedures. Sexually active women aged 45 years or older with moderate to- severe vaginal dryness and soreness were enrolled ($N = 48$). All participants had serum E2 concentrations of 20 pg/mL or less, with 5% or less superficial vaginal cells. Participants were also required to be at least 12 months postmenopausal, with an endometrial thickness of 5 mm or less as determined by transvaginal ultrasonography. Known or suspected history of breast carcinoma, hormone-dependent tumor, genital bleeding of unknown cause, acute thrombophlebitis or thromboembolic disorder associated with estrogen use, vaginal infection requiring treatment, allergy to the test drug or its constituents, or any serious disease or chronic condition that could interfere with study compliance were among the criteria for exclusion. The use of any investigational drug within the 30 days preceding screening, any homeopathic preparation within the 7 days preceding study drug initiation, and any exogenous corticosteroid or sex hormones within the 8 weeks preceding study drug initiation were prohibited.

Patients were randomized to take 25 μg estradiol vaginal tablets daily for 14 days, and subsequently, one tablet twice per week (group I) or vaginal tablets containing hyaluronic acid sodium salt 5 mg once in a day (group II) for 8 weeks, respectively. The participants were also instructed to insert the tablets at the same time each day. Six patients discontinued the study: three in group I (one because of lost at follow-up and 2 because of noncompliance) and three in group II (2 because of lost at follow-up and 1 because of noncompliance). Evaluations for efficacy of the treatment modalities occurred at eighth week. The symptoms of atrophic vaginitis evaluated in a composite vaginal score, including vaginal dryness, soreness, irritation, discharge, and dyspareunia. However, vaginal discharge was excluded from the composite vaginal symptom score because vaginal discharge was rated as none or mild by the majority of participants. Therefore, the primary efficacy endpoint was the change in the composite score of the vaginal symptoms (dryness, soreness, irritation and dyspareunia). Assessments of these vaginal symptoms were conducted at baseline (week 0) and week 8. The severity of each symptom was self-assessed and received a grade based on a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). A composite score of these symptoms (mean of the individual symptom scores for dryness, soreness, irritation and dyspareunia) was then generated. Additional efficacy assessments included the determination of vaginal health by examination of epithelial atrophy (degree of epithelial integrity and thickness, vaginal secretions and color), vaginal pH and vaginal cytology. The degree of epithelial atrophy was determined by 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). Vaginal pH was measured by a pH indicator strip inserted into the vagina in intervals in 4-point scale, respectively (pH < 5 (0), 5–5.49 [1], 5.5–6.49 [2], and more than 6.49 [3]). Vaginal cell samples were analyzed blindly by an experienced cytologist to determine the percentages of parabasal, intermediate, and superficial cells. The vaginal maturation value was calculated according to the formula, maturation value = (0×% of parabasal cells) + (0.5×% of intermediate cells) + (1.0×% of superficial cells). The sample size would provide an 80% power in detecting a difference in change from baseline score of 0.5 between two groups with an assumed standard deviation (SD) of 0.85 for the primary efficacy endpoints (change from baseline in composite score of vaginal dryness, soreness, irritation and dyspareunia).

For all efficacy variables, statistical analyses were carried out by NCSS 2007 & PASS 2008 Statistical Software (UT, USA). For univariate analysis, continuous data were reported as median and mean ± SD. During the evaluation of studying data, the qualitative data were evaluated using Student's t test and Mann–Whitney U test. Paired t test and Wilcoxon-signed rank test were used for the comparison of

the parameters in two groups. The results were given in 95% confidence interval and significance was accepted at $P < 0.05$ level.

Results

Mean age of the patients in group I (51.86 ± 4.35) and group II (52.95 ± 4.80) was not significantly different ($P > 0.05$). The patients were menopausal for 5.29 ± 3.03 years in group I and 4.67 ± 3.13 years in group II, respectively ($P > 0.05$). Three of the patients in group I and 4 of the patients in group II were hysterectomized because of benign conditions like fibroids. The frequencies of symptoms before and after treatment in two groups are presented in Table 1. The composite score of vaginal symptoms was not significantly different at the beginning of the treatment. The relief of symptoms was significantly detected in both study groups ($P < 0.001$) after 8 weeks of treatment. The relief of vaginal symptoms was significantly superior in group I when compared with group II, respectively ($P < 0.05$) (Table 2). The degree of epithelial atrophy was significantly severe in group II $P < 0.05$), a significant decrease was detected in both groups ($P < 0.01$) after treatment (Table 3). The vaginal pH was significantly decreased in both groups ($P < 0.01$) after treatment, while the decrease was more prominent in group I (Table 4). The vaginal maturation values were also significantly improved in both study groups ($P < 0.001$) after 8 weeks of treatment, while the mean maturation value was significantly higher in group I when compared with group II, respectively ($P < 0.001$) (Table 5).

Table 2 The comparison of composite score of vaginal symptoms before and after treatment in two groups

	Group I Median ± SD	Group II Median ± SD	*P*
Composite score of vaginal symptoms before treatment	9.71 ± 1.93	9.24 ± 1.92	0.427
Composite score of vaginal symptoms after treatment	2.67 ± 1.53	3.86 ± 1.39	0.012*
P	0.001**	0.001**	

Student's *t* test

Paired sample test

* $P < 0.05$; ** $P < 0.01$

Table 3 The comparison of epithelial atrophy before and after treatment in two groups

		Group I *n* (%)	Group II *n* (%)	*P*
Epithelial atrophy (before treatment)	1 (Mild)	1 (4.8%)	0 (0%)	
	2 (Moderate)	20 (5.2%)	16 (76.2%)	
	3 (Severe)	0 (0%)	5 (23.8%)	
	Median	2	2	0.012*
Epithelial atrophy (after treatment)	0 (None)	3 (14.3%)	2 (9.5%)	
	1 (Mild)	18 (85.7%)	18 (85.7%)	
	2 (Moderate)	0 (0%)	1 (4.8%)	
	Median	1	1	0.419
P		0.001**	0.001**	

Mann–Whitney *U* test

Wilcoxon-signed rank test

* $P < 0.05$; ** $P < 0.01$

Discussion

The quality of life of menopausal women can be negatively affected by vulvovaginal atrophic changes. More than a half of postmenopausal women will have urogenital discomfort associated with estrogen deficiency [2, 6, 7]. In recent prospective cohort study, 510 postmenopausal women have reported dyspareunia (10%) and vaginal dryness (9.6%) [8].

Table 1 The frequency of vaginal complaints before and after treatment in two groups

Group	Severity of symptoms	Dryness before treatment (%)	After treatment	Soreness before treatment	After treatment	Irritation before treatment	After treatment	Dyspareunia before treatment	After treatment
I	None	0 (0)	5 (23.8)	0 (0)	8 (38.9)	0 (0)	6 (28.6)	0 (0)	9 (42.8)
	Mild	0 (0)	15 (71.4)	1 (4.8)	13 (61.9)	1 (4.8)	15 (71.4)	0 (0)	12 (57.3)
	Moderate	9 (42.8)	1 (4.8)	10 (47.6)	0 (0)	13 (61.9)	0 (0)	12 (57.2)	0 (0)
	Severe	12 (57.2)	0 (0)	10 (47.6)	0 (0)	7 (33.3)	0 (0)	9 (42.8)	0 (0)
II	None	0 (0)	1 (4.8)	0 (0)	3 (14.2)	1 (4.8)	2 (9.5)	0 (0)	3 (14.2)
	Mild	0 (0)	17 (80.9)	1 (4.8)	17 (80.9)	0 (0)	18 (85.7)	1 (4.8)	16 (76.1)
	Moderate	13 (61.9)	3 (14.3)	12 (57.3)	(4,8)	13 (61.9)	1 (4.8)	13 (61.9)	2 (9.5)
	Severe	8 (38.1)	0 (0)	8 (38.9)	0 (0)	7 (33.3)	0 (0)	7 (33.3)	0 (0)

The frequencies are presented as number of patients and percentage

Table 4 The comparison of vaginal pH before and after treatment in two groups

pH		Group I *n* (%)	Group II *n* (%)	*P*
Vaginal pH (before treatment)	2 (5.5–6.49)	19 (90.5%)	15 (71.4%)	
	3 (>6.49)	2 (9.5%)	6 (28.6%)	
	Median	2	2	0.120
Vaginal pH (after treatment)	0 (<5.0)	3 (14.3%)	0 (0%)	
	1 (5.0–5.49)	18 (85.7%)	15 (71.4%)	
	2 (5.5–6.49)	0 (0%)	6 (28.6%)	
	Median	1	1	0.003**
P		0.001**	0.001**	

Mann–Whitney *U* test

Wilcoxon-signed rank test

* $P < 0.05$; ** $P < 0.01$

Table 5 The comparison of vaginal maturation value before and after treatment in two groups

	Group I (mean ± SD)	Group II (mean ± SD)	*P*
Vaginal maturation value (before treatment)	4.38 ± 0.80	4.14 ± 0.85	0.358
Vaginal maturation value (after treatment)	71.19 ± 12.96	44.40 ± 9.32	0.001**
P	0.001**	0.001**	

Student's *t* test

Paired sample test

** $P < 0.001$

The common treatment up to the 1990s has been the oral hormone replacement therapy (HRT), but this treatment has been consequently re-considered due to its adverse effects. In addition to previous study [2], it is found that although many women use oral HRT, urogenital symptoms may persist and many women can get additional benefits Vaginal administration of low-dose estradiol tablets offers safe and convenient local relief of vaginal symptoms [6, 7]. Studies have shown that vaginal estrogen preparations can result in rapid and efficient absorption of estrogen into systemic circulation [9–11]. Although it was reported as low-dose preparation that contain 25 μg of E2 effectively relieve symptoms of atrophic vaginitis without unwanted systemic side effects [11–13], it should be noted that according to the NAMS position statement in 2007, the optimal treatment regimen and minimum effective dose for local vaginal estradiol preparations have not been established. Closer surveillance may be required for women at high risk for endometrial cancer, and they are still considered at risk in case of prolonged use [14]. In this statement, NAMS points out the first-line treatments include nonhormonal vaginal lubricants and moisturizers [14]. That is why nonhormonal options that are available should be considered in relieving coital discomfort in these women and such alternatives include vaginal moisturizers, acupuncture, natural estrogen, herbal supplements or plant estrogens [15]. In this study, we have studied the effect of hyaluronic acid in atrophic vaginitis. Because vagina also looses collagen and water-retaining ability at menopause, hyaluronic acid is used as adjuvant of repairing processes of the atrophic and dystrophic states of the vaginal mucosa, senile dryness also due to estrogen deficiency. Tea et al. [5] studied the efficacy and safety of hyaluronic acid vaginal tablets in 95 patients suffering from hormone or chemotherapy-induced atrophic vaginitis due to breast cancer. They have found a significant reduction (70%) in symptoms of atrophic vaginitis [5]. Morali et al. [16] performed a clinical trial to investigate, the effects of a alternative medical device in the form of a gel, containing hyaluronic acid, liposomes, phytoestrogens from humulus lupulus extract and Vitamin E, with the aim of testing its safety and efficacy in post-menopausal women with urogenital atrophy. One hundred post-menopausal women assigned to the vaginal application of 2.5 g of gel/day for 1 week followed by two applications/week for 11 weeks. The results showed a marked effect of the tested product on the vaginal dryness and on all other symptoms and signs with statistically significant reductions since the first week of treatment [16]. We have also found comparable results with those two trials. In our study, we have found significant improvement in vaginal symptoms, epithelial atrophy, vaginal pH and vaginal maturation index. This improvement was more significant in the patients who take vaginal estrogen tablets except in determination of epithelial atrophy. This may be due to subjective evaluation of the patients. The primary goals of vaginal atrophy management are symptom relief and reversal of atrophic anatomic changes and we have found significant reduction in vaginal complaints with the vaginal hyaluronic acid tablets. Although we believe that studies with high number of patients are needed to define the efficacy of hyaluronic acid vaginal tablets as the first-line treatment of atrophic vaginitis, and it can also be used in patients who do not want to or cannot take local estrogen treatment.

Conflict of interest statement None.

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