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A comparison of hyaluronic acid and estradiol treatment in vulvovaginal atrophy

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Abstract. – OBJECTIVE: This study aims to compare the effects of vaginal estrogen and hyaluronic acid on vulvovaginal atrophy.

PATIENTS AND METHODS: This randomized controlled study included a total of 300 patients, with 150 patients in each group (Group E and Group H). The VHI score was determined based on a pre-treatment evaluation conducted by a gynecologist. After one month of receiving vaginal estrogen in Group E and vaginal hyaluronic acid in Group H, the patients were re-evaluated by their physicians.

RESULTS: A statistically significant difference was found between the pre- and post-treatment VHI scores in Group E and Group H (p = 0.000; p = 0.000). No statistical difference was found between Group E and Group H in terms of treatment efficacy (p = 0.712). The pre- and post-treatment complaints of dryness, itching, dyspareunia, burning, and dysuria were found to be statistically significant in Group E and Group H (p = 0.000; p = 0.000; p = 0.000; p = 0.000; p = 0.000 in Group E, respectively) (p = 0.000; p = 0.000; p = 0.000; p = 0.000; p = 0.000 in Group H, respectively). No statistical difference was observed regarding dyspareunia, dysuria, and burning complaints (p = 0.632; p = 0.106; p = 0.128, respectively). However, hyaluronic acid was found to be significantly more effective for itching complaints (p = 0.002), while estrogen was found to be significantly more effective for dryness complaints (p = 0.012).

CONCLUSIONS: Hyaluronic acid and estrogen were equally effective in vaginal treatment. Hyaluronic acid may be preferred for patients in whom hormonal therapy is contraindicated or for those who prefer non-hormonal therapy.

Key Words:
Vulvovaginal atrophy, Hyaluronic acid, Estrogen, Treatment of vulvovaginal atrophy.

Introduction

Vulvovaginal atrophy (VVA), also known as the genito-urinary syndrome of menopause (GSM), is a condition characterized by dryness, itching, burning, dyspareunia, and urinary symptoms resulting from a decrease in estrogen levels in the blood[1,2]. The average age of menopause is approximately 46-50 years, and the average life expectancy of women is 82 years in Turkey[3,4]. This indicates that women spend 58% of their lives in the menopausal period. Due to the decrease in estrogen levels in VVA, lactobacilli decrease in vaginal flora, and the pH becomes alkaline, which leads to thinning of the epithelium, increased susceptibility to trauma, and decreased resistance to fecal infection[5]. This occurs not only during natural menopause, but also in patients receiving tamoxifen, aromatase inhibitors, and other medications for breast cancer[6]. Vulvovaginal atrophy (VVA) negatively affects patients' sexual health and quality of life[7].

Oral Hormone Replacement Therapy (HRT) is highly effective in relieving all symptoms of Vulvovaginal Atrophy (VVA), including vasomotor complaints[8]. However, this treatment should not be administered to patients with certain diseases such as breast cancer, genito-urinary cancer, a history of endometrial hyperplasia, liver diseases, cardiovascular diseases, migraines, etc. It is also known that perceptions of HRT have changed since the first results of the Women's Health Initiative (WHI) study were reported in 2002. However, there is still a bias against recognizing the benefits and risks of HRT among many women and clinicians[8]. Therefore, efforts to find non-hormonal treatments have intensified in recent years.

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Hyaluronic acid is a glycosaminoglycan found in the matrix. It plays a role in the proliferative differentiation of the vaginal epithelium and enhances the adhesion of desmosomes and vaginal epithelial cells to each other[9]. Furthermore, hyaluronic acid enhances the defense of vaginal tissues against microbiota by improving the moisture retention in the tissues[10]. In hypo-estrogenic states, the levels of Type I and III collagen decrease, resulting in reduced tissue strength[11].

Postmenopausal vulvovaginal atrophy/genitourinary syndrome of menopause (VVA/GSM) is an influential factor affecting various aspects of women's health. Many international literatures indicate that VVA/GSM symptoms should be addressed since these symptoms severely affect women's quality of life and sexual functioning.

The objective of this randomized controlled trial was to compare the effects of hyaluronic acid and estradiol and to determine their impact on VHI. The secondary objective was to investigate the effect of VVA/GSM on symptoms.

Patients and Methods

This randomized, controlled, monocentric, prospective, comparative (before/after) study was conducted in Koru Ankara Hospital from April 2023 to September 2023.

The clinical study approval can be verified at https://www.turkiye.gov.tr/saglik-titck-ebys2 using the code E-66175679-514.99-983380. Ethics Committee approval was obtained from Ankara Etlik City Hospital, with the reference number AEŞH-EK1-2023-024. Informed written consent was obtained from the volunteers who were included in the study. The study was registered at www.clinicaltrials.gov under the number NCT06144814. The power analysis for the study was conducted.

Inclusion criteria: age over 40 years, FSH value above 25 pg/ml, LH value above 20 pg/ml, E2 value below 15 pg/ml, endometrial thickness of 5 mm or less, and absence of menstruation for 12 months.

Exclusion criteria: patients receiving Hormone Replacement Therapy (HRT); patients with genital organ malignancy or breast cancer; patients with vaginal bleeding of unknown cause; patients with a history of thrombophlebitis, thromboembolism, or thrombophilia; patients with acute or chronic cardiovascular diseases; patients with allergies to estrogen or hyaluronic acid; patients with vaginal infection; and patients with acute or chronic liver diseases. Patients eligible to participate in the study were required to report at least one of the following symptoms: vaginal dryness, burning or irritation, lack of lubrication during intercourse, sexual discomfort or pain during intercourse, dysuria, or recurrent urinary tract infection.

A total of 300 patients were included in the study and randomized into two groups, with 150 in each group. Informed written consent was obtained from the volunteers who willingly participated in the study. Group I received 10 μg of vaginal estradiol (Vagifem® Novo Nordisk, Bagsvaerd, Denmark), one tablet daily for two weeks and two tablets per week for the following 2 weeks. Group II received 5 mg of vaginal hyaluronic acid daily for 14 days, followed by two days a week for the subsequent two weeks. Hyaluronic acid gel for vaginal use was supplied by ORTHOGEN® (GİNHYAL, Çankaya, Ankara, Turkey). The treatment period lasted 1 month in both groups.

Before receiving treatment, patients who consented to participate in the study were examined by a gynecologist, and their Vaginal Health Index (VHI)[12] score was determined. After the completion of the treatment period, the patients underwent re-evaluation by the same physician, and the VHI score was obtained once more. The VHI is the most common score based on vaginal elasticity, secretions, pH, presence of petechiae on the epithelial mucosa, and hydration assessment. The vaginal atrophy index ranges from 5 to 25, with < 15 indicating atrophy.

Vaginal pH was measured by placing pH paper on the anterior wall of the vagina. A value of > 5 pH was defined as decreased estrogen activity[13]. The effect on the primary outcome, the VHI index, was investigated.

Side effects were defined as burning and allergic reactions to the medications administered vaginally during treatment.

Statistical Analysis

Statistical analysis was performed using SPSS 2013, Version 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables are expressed as mean, median, and standard deviation. For pre- and post-treatment comparisons, *t*-tests, independent *t*-tests by Wilcoxon, and Mann-Whitney tests were utilized. Categorical variables were presented as the number and percentage of pa-

Table I. Demografic characteristic of the patients.

	Groups E n = 150 mean	Groups H n = 150 mean	*p*-value
Age (year)	51.81	50.63	0.085[t]
BMI kg/m^2	24.89	24.78	0.025[t]
Menapousal duration (year)	5.36	4.25	0.019[t]
Fsh mIU/dl	58.55	58.29	0.903[t]
Parity	3.4	3.2	0.251[t]
Gynecological surgery	7.8	7.6	0.125[t]

[t]Independent sample *t*-test.

tients. The comparison between groups was conducted using the Pearson Chi-square test for independent attributes or the Fisher exact test, if applicable. $p < 0.05$ was considered statistically significant.

Results

A total of 300 patients, with 150 in each group, were included in the study. Group E was labeled as estrogen, and Group H was labeled as hyaluronic acid. No statistical difference was observed between the two groups of patients included in the study regarding the mean age, BMI, menopausal years, parity, FSH, and previous gynecological operations *(*$p = 0.085$*;* $p = 0.025$*;* $p = 0.019$*;* $p = 0.903$*;* $p = 0.125$) (Table I).

In Group E, a statistically significant difference was found regarding pre- and post-treatment VHI scores ($p = 0.000$). In Group H, the VHI score increased significantly before and after treatment ($p = 0.000$). Nevertheless, there was no statistical difference in treatment efficacy between Group E and Group H ($p = 0.712$) (Table II).

The most common complaints reported by the patients were dryness (89%), itching (75%), dyspareunia (70%), and dysuria (65%). Patients' pre- and post-treatment complaints were evaluated. In group E, all pre- and post-treatment complaints (dryness, itching, dyspareunia, burning, and dysuria) were found to be statistically significant ($p = 0.000$, $p = 0.000$, $p = 0.000$, $p = 0.000$, $p = 0.000$, respectively). In group H, all pre- and post-treatment complaints (dryness, itching, dyspareunia, burning, and dysuria) were determined to be statistically significant ($p = 0.000$, $p = 0.000$, $p = 0.000$, $p = 0.000$, $p = 0.000$, respectively).

There was no statistical difference between the two groups in terms of the effect of hyaluronic acid and estrogens on dyspareunia, dysuria, and burning complaints ($p = 0.632$, $p = 0.106$, $p = 0.128$). However, the complaint of itching was statistically significantly higher in Group H ($p = 0.002$). In terms of dryness complaints, Group E was statistically more effective than Group H ($p = 0.012$) (Table III).

Discussion

In a randomized clinical study involving a total of 42 patients, Ekin et al[14] reported that symptoms of vaginal atrophy improved, vaginal pH decreased, and the vaginal maturation index showed improvement in the group that received both estrogen and hyaluronic acid. However, this improvement was also reported to be higher in the group receiving estrogen. In this study, the researchers did not use pure hyaluronic acid. Instead, they used vaginal tablets that contained hyaluronic acid along with various herbal extracts.

Jokar et al[15] compared the effects of hyaluronic acid and estrogen on 52 patients in a randomized controlled clinical trial. They reported that hy-

Table II. VHI score comparison within and between groups.

	Groups E n = 150 mean	Groups H n = 150 mean	*p*-value
VHI Score before	7.84	7.97	0.425[t]
VHI Score after	20.35	20.24	0.712[t]
p-value	0.000**	0.000**	

[t]Independent sample *t*-test retest. **Dependent sample *t*-test.

Table III. Comparison of complaints by groups and after treatment.

	Group E	*p*-value within groups	Cramer's V	Group H	*p*-value within groups	Cramer's V	*p*-value between groups
Dysuria	Before After	$p = 0.000^c$	0.970	Before After	$p = 0.000^c$	0.868	$p = 0.106$*
Dryness	Before After	$p = 0.000^c$	0.860	Before After	$p = 0.000$	1	$p = 0.002$*
Dyspareunia	Before After	$p = 0.000^c$	0.972	Before After	$p = 0.000^c$	1	$p = 0.632$*
Itching	Before After	$p = 0.000^c$	1	Before After	$p = 0.000^c$	0.901	$p = 0.012$*
Burning	Before After	$p = 0.000^c$	0.970	Before After	$p = 0.000^c$	0.889	$p = 0.128$*

[c]Independent Chi-square. *The Chi-Square test.

aluronic acid was more effective than estrogen in treating VVA/MGS. The results of our study showed that hyaluronic acid and estrogen increased the VHI score to the same degree, and that no statistical difference was found between the groups.

In the complaint-based evaluation, we found that hyaluronic acid was more effective in treating dryness, while estrogen was more effective in alleviating itching. We believe that the water retention property of hyaluronic acid enhances its effectiveness in addressing the issue of dryness.

Studies[16] show that hyaluronic acid is effective in treating symptoms of VVA/MGS in both oncologic and estrogen-naïve patient groups. Delia et al[16] reported in a randomized controlled trial of 180 individuals undergoing treatment for cervical cancer that patients who received hyaluronic acid, which also included vitamins A and E, experienced significantly fewer symptoms of VVA/MGS compared to those who did not receive it. Carter et al[17] demonstrated that treatment with hyaluronic acid improved vaginal health and enhanced sexual function in a prospective study involving 104 patients with breast cancer and endometrial cancer receiving aromatase inhibitors.

In a multicenter randomized controlled trial comparing hyaluronic acid and estrogen in 144 patients, Chen et al[18] reported a statistically significant improvement in VVA/MGS complaints in both groups, and the study found no significant difference in the effects between the groups. The findings of our study align with the results of this study.

Almost all studies reported a statistically significant improvement in symptoms of VVA/MGS with the use of hyaluronic acid. Nonetheless, the results of comparisons between estrogen and hyaluronic acid showed that estrogen is superior to hyaluronic acid and that both substances have similar effects, but hyaluronic acid is more effective than estrogen. We assume that the rationale for this is related to the fact that hyaluronic acid was used at various doses and ranges in the studies. Moreover, some experiments used not only pure hyaluronic acid but also preparations containing other components (various vegetable oil extracts, vitamin E, vitamin A, etc.). Unfortunately, the literature does not provide sufficient information on the effect of these components on the effectiveness of hyaluronic acid.

In this study, we investigated the short-term effects. Today, patients with VVA/MGS symptoms demand agents that can promptly alleviate symptoms and provide quick relief. Of course, it is essential that the treatment provides long-term benefits. However, the patient's commitment to the treatment and medication relies on their satisfaction with the results within a short period of time[18]. Patients are more likely to discontinue medication if they do not experience sufficient benefits within a short period of time of using the medication[18]. Both HRT and hyaluronic acid therapy are forms of replacement therapy and do not have a curative effect. Long-term results can be achieved when treatment is maintained.

The ideal treatment agent is one that is effective in a short period of time, cost-effective, user-friendly, and has minimal side effects. In terms of usage, both agents are administered vaginally, and there is no risk of overdose. Since all

vaginal products containing hyaluronic acid also include additional active ingredients (vitamin E, vitamin A, etc.), it was not possible to compare their costs. However, in 2023, vaginal preparations containing estrogen and vaginal products with hyaluronic acid as the main component have comparable prices in Turkey. Therefore, vaginal hyaluronic acid is an alternative for patients who cannot use estrogen or prefer not to undergo hormone therapy.

The strengths of our study are that it is a randomized clinical trial and that the use of pure hyaluronic acid reduces the side effects compared to other complex preparations.

The limitations of the study are the exclusion of long-run effects from its scope.

Conclusions

In light of all this data, it has been shown that hyaluronic acid has a positive effect on the symptoms of VVA/MGS, similar to estrogen. Therefore, hyaluronic acid treatment may be an alternative for patients who cannot use or prefer not to use hormone therapy.

All authors have read and approved the submission of the manuscript, and the manuscript has not been published and is not being considered for publication elsewhere in whole or in part in any language.

Conflict of Interest
The authors declare that they have no conflict of interests.

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Authors' Contribution
BB and JA conceived and designed the study; BH, JA, and MV collected the data and performed the data analysis. JA wrote the draft of this manuscript. BB and MV edited the manuscript.

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Ethics Approval
Ethics Committee approval was obtained from Ankara Etlik City Hospital, with the reference number AEŞH-EK1-2023-024. The study was registered at www.clinicaltrials.gov under the number NCT06144814.

Informed Consent
Written informed consent forms were gathered by each patient before the study.

Availability of Data and Materials
The corresponding author is available to share experience and data upon reasonable request.

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