Arch Gynecol Obstet (2013) 288:1199–1201
DOI 10.1007/s00404-013-3068-5

NEWS AND VIEWS

Is vaginal hyaluronic acid as effective as vaginal estriol for vaginal dryness relief?

Petra Stute

Published online: 1 November 2013

Summary

In a multicenter, randomized, controlled, open-label, parallel-group trial hyaluronic acid vaginal gel (Hyalofemme®) was compared to estriol vaginal cream (Ovestin®) in women with vaginal dryness due to various causes [1]. A total of 144 supposedly postmenopausal women below age 70 years were randomized in a 1:1 ratio to either receive hyaluronic acid vaginal gel (5 g per application) or estriol vaginal cream (0.5 g cream per application = 0.5 mg estriol) every 3 days for a total of ten applications, respectively. Exclusion criteria included vaginal infections, conventional contraindications to estrogens, use of vaginal products other than the investigational compounds, being unmarried, pregnant, or breastfeeding. The aim of the study was to test for non-inferiority of hyaluronic acid vaginal gel compared to estriol vaginal cream. The primary efficacy end point was the percentage (%) improvement in vaginal dryness, with the secondary end points being the percentage (%) improvements in vaginal itching, burning, and dyspareunia. Efficacy was assessed by using a visual analog scale (VAS) (0–10; 0 = absent, 10 = intolerable) at baseline (V0), during telephone contact after the third administration (V1), and at the final visit after the tenth administration (V2). Safety parameters included vaginal pH, endometrial thickness, and a vaginal smear for vaginal microecosystem assessment. Adverse events were recorded according to international guidelines. 133 women completed the study. At baseline, participants' characteristics did not differ significantly. Mean age was 54 years, time since menopause was 5 years on average, and cause of menopause was mostly natural. However, mean menstrual cycle days were also reported, although according to inclusion criteria only postmenopausal women were eligible for the study. At V1, an improvement in vaginal dryness was reported by about 49 % of women using hyaluronic acid vaginal gel, and by 53 % of women using estriol vaginal cream ($p = 0.31$). At V2, the percentage improvement rates were 84 and 89 % ($p = 0.13$), respectively. Improvement rates for vaginal itching, burning, and dyspareunia at V2 were about 86, 85, and 57 % for hyaluronic acid vaginal gel, and 82, 87, and 62 % for estriol vaginal cream ($p > 0.05$), respectively. After treatment, vaginal pH was significantly lower in estriol-treated women compared to those having received hyaluronic acid. Endometrial thickness did not differ between groups. In the majority of women, the vaginal microenvironment remained unaffected by treatment. However, the proportion of women whose abnormal vaginal microecological results became normal was higher in women using estriol vaginal cream. Adverse events (suspected to be) related to the investigational compounds were minor and included vaginal infection and genital itching. The authors concluded that hyaluronic acid vaginal gel was not inferior to estriol vaginal cream in women presenting with vaginal dryness. They suggest using hyaluronic acid vaginal gel not only as an alternative treatment to vaginal estrogens, but also to consider its general use in women presenting with vaginal dryness of any cause.

Background

Vulvovaginal irritation is a frequent complaint among postmenopausal women who do not use hormone therapy.

P. Stute (✉)
Department of Obstetrics and Gynecology,
Inselspital Bern, Effingerstraße 102, 3010 Bern, Switzerland
e-mail: petra.stute@insel.ch

Common symptoms of vaginal atrophy include dryness, itching, burning, and dyspareunia [2]. The prevalence is up to 45 % in midlife and older women [3]. In healthy vagina, glycogen-derived glucose is converted into lactic acid helping to maintain an acidic vaginal pH between 3.5 and 4.5. As estrogen-dependent glycogen content is gradually lost during peri- and postmenopause, exfoliation of the vaginal epithelium is decreased and leads to reduced normal lactobacilli flora and vaginal pH changes. The increased vaginal pH and thinning of the vaginal epithelium then increase the risk of mechanical weakness of the vulvovaginal structures [2]. However, vaginal symptoms may also be associated with the use of certain medications (e.g. antidepressants, antihistamines), medical conditions (e.g. diabetes mellitus, obesity, autoimmune disorders, allergy), and lifestyle factors (e.g. smoking, excessive use of soap, stress), respectively. Thus, also premenopausal women may be affected. The North American Menopause Society (NAMS) recently updated their recommendations for the management of symptomatic vulvovaginal atrophy (VVA) in postmenopausal women [4]. Nonprescription therapies such as vaginal lubricants and moisturizers are considered first-line therapies. In general (water, silicone, or oil based), lubricants may be used during sexual intercourse for reduction of friction-related irritation of atrophic tissue. Additionally, nonhormonal, long-acting vaginal moisturizing agents can decrease vaginal pH to premenopausal levels, although they do not improve the vaginal maturation index [4]. Hyaluronic acid is a glycosaminoglycan and part of the extracellular matrix. Relative to its molecular weight, it may bind huge amounts of water making it a promising ingredient for a moisturizer. Indeed, hyaluronic acid vaginal gel has been studied in postmenopausal women previously [5, 6]. Prescription therapies such as low-dose vaginal estrogen therapy (ET) are considered second-line therapies. Internationally, there are various approved ET products that are equally effective at the recommended doses. The recommended dose for estriol vaginal cream, for example, is 0.5 mg once daily during the first 3 weeks, followed by 0.5 mg twice weekly. For a new product to be approved for symptomatic VVA treatment, pharmaceutical companies are recommended to follow FDA guidance [7]. Herein, VVA is defined by the following criteria: 5 % or less superficial cells on vaginal smear (maturation index), vaginal pH >5.0, and at least one moderate or severe symptom of VVA. The primary efficacy analyses should demonstrate a statistically significant improvement versus placebo from baseline to week 12 of treatment in all three of the following parameters: (1) maturation index (decrease of parabasal vaginal cells and increase in superficial vaginal cells), (2) lowering of the vaginal pH and (3) the moderate to severe symptom identified by the subject as being most bothersome to her.

Comment

In the present study, the authors claim proving the non-inferiority of hyaluronic acid vaginal gel compared to estriol vaginal cream in women with vaginal dryness. However, there are some flaws in the study design, thus hampering this conclusion. First, with respect to the study population, given the menstrual cycle data reported, premenopausal women of unknown number seem to have been included into the study, although per protocol only postmenopausal women were eligible. Inclusion criteria did not request a predefined lower threshold of vaginal symptom intensity. Thus, also women with minor symptom intensity were eligible. Dyspareunia is an important end point in studies investigating vaginal products. However, it is crucial to assess the prevalence and frequency of sexual activity in participants at baseline and across the study; otherwise, no conclusion regarding improvement in dyspareunia can be drawn. Furthermore, various other reasons are known to be related to vaginal symptoms that have not been assessed. Taken together, the study population was very heterogenous. Secondly, with respect to the study design, a randomized-controlled, double-blind trial would have been preferable to reduce bias. According to FDA, the primary efficacy end point should involve vaginal pH, vaginal maturation index and the most bothersome moderate to severe vaginal symptom [7]. In the present study, the primary efficacy end point was subjective, whereas vaginal pH was assessed as safety parameter only. Statistical analysis revealed no between-group differences for any VAS symptom score at V1 and V2, respectively. However, p values for pre-/post-treatment comparisons within each group were not provided. During follow-up at V1 and V2, the number of missing data was quite high. For example, at V2, data of only 40 % of the participants using hyaluronic acid vaginal gel and of 53 % women using estriol vaginal cream were available for statistical analysis with respect to the symptom of vaginal itching. Of course, missing data could also mean that these women did not present with the symptom at baseline, making a comparison between V0, V1, and V2 impossible. Finally, with respect to the intervention, the application modus for hyaluronic acid vaginal gel corresponded to the general recommendation. However, this is not true for estriol vaginal cream. In addition, ten applications in total are usually not sufficient to prove the efficacy for symptomatic VVA treatment, at least in postmenopausal women [7].

In conclusion, due to the limitations mentioned, the present study does not prove the general non-inferiority of hyaluronic acid vaginal gel in comparison to estriol vaginal cream in women with vaginal dryness. However, due to a previous placebo-controlled study and since no major side effects are to be expected with the use of hyaluronic acid

vaginal gel, it may be used as moisturizer in women complaining of vaginal dryness. This treatment strategy is thus in accordance with the updated NAMS recommendations.

References

1. Chen J, Geng L, Song X, Li H, Giordan N, Liao Q (2013) Evaluation of the efficacy and safety of hyaluronic acid vaginal gel to ease vaginal dryness: a multicenter, randomized, controlled, open-label, parallel-group, clinical trial. J Sex Med 10:1575–1584
2. Archer DF (2010) Efficacy and tolerability of local estrogen therapy for urogenital atrophy. Menopause 17:194–203
3. Santoro N, Komi J (2009) Prevalence and impact of vaginal symptoms among postmenopausal women. J Sex Med 6:2133–2142
4. Management of symptomatic vulvovaginal atrophy: 2013 position statement of The North American Menopause Society. Menopause 20:888–902
5. Morali G, Polatti F, Metelitsa EN, Mascarucci P, Magnani P, Marre GB (2006) Open, non-controlled clinical studies to assess the efficacy and safety of a medical device in form of gel topically and intravaginally used in postmenopausal women with genital atrophy. Arzneimittelforschung 56:230–238
6. Grimaldi EF, Restaino S, Inglese S, Foltran L, Sorz A, Di Lorenzo G, Guaschino S (2012) Role of high molecular weight hyaluronic acid in postmenopausal vaginal discomfort. Minerva Ginecol 64:321–329
7. US Department of Health and Human Services FaDA, Center for Drug Evaluation and Research (CDER) (2003) Guidance for industry: estrogen and estrogen/progestin drug products to treat vasomotor symptoms and vulvar and vaginal atrophy symptoms—recommendations for clinical evaluation (draft guidance)