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Postmenopausal vulvovaginal atrophy (VVA) is positively improved by topical hyaluronic acid application. A prospective, observational study

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Abstract. – OBJECTIVE: To evaluate the effectiveness of a topical vaginal preparation containing hyaluronic acid in controlling signs and symptoms correlated with postmenopausal vulvovaginal atrophy (VVA).

PATIENTS AND METHODS: A prospective, observational study has been performed at the Obstetrics and Gynecology Department of the Vita Salute San Raffaele University of Milan, Italy. Forty-six (46) consecutive postmenopausal women complaining of genital discomfort due to postmenopausal estrogen lack have been enrolled. All patients have been investigated by the use of the Vaginal Health Index (VHI) and of a Visual Analogic Scale (VAS) of symptoms at baseline and one month after the end of the study. The treatment protocol consisted of the administration of a hyaluronic acid-based liquid preparation for vaginal use (Justgin®, Just Pharma, Rome, Italy) three times a week, for a total of 8 weeks. Statistical analysis of VHI and VAS scores has been performed by the use of the Wilcoxon signed-rank test for repeated values, assuming a p-value < 0.05 as significant.

RESULTS: Both Vaginal Health Index (VHI) and Visual Analogic Scale (VAS) of genital symptoms showed statistically significant ($p < 0.0001$) improvements at the end of the study protocol. Patients' degree of satisfaction at the end of treatment was reported as high.

CONCLUSIONS: Conventional treatment of the postmenopausal syndrome, either in terms of systemic and genital symptoms, is based on hormonal replacement therapy (HRT). The limitations to this approach are represented by the need to discontinue the treatment after some years and the contraindications that some women present about the estrogens. For these reasons, alternative approaches have been recently investigated and indicate promising perspectives. Hyaluronic acid topical approach with a liquid preparation for vaginal use (Justgin®, Just Pharma, Roma, Italy) to control signs and symptoms of vulvovaginal atrophy (VVA) in postmenopausal women demonstrated significant effectiveness both in terms of objective and subjective improvement.

Key Words:
Menopause, VVA, Vulvovaginal atrophy, Vaginal Dryiness, Dyspareunia, Hyaluronic acid.

Introduction

During women reproductive ages, the vaginal epithelium undergoes changes in response to the level of circulating estrogens. When menopause occurs, circulating estrogens levels show a dramatic reduction. Parallel with the onset of systematic negative effects, the estrogens lack also determines several modifications of the genital tissues; significant cytological transformations follow estrogen reduction, including the proliferation of connective tissue, fragmentation of elastin and collagen hyalinization. These changes may result in granulation, fissures, ecchymosis, telangiectasia and ulcerations, resulting in a condition described as vulvovaginal atrophy (VVA)[1]. The major symptoms of VVA are: decreased vaginal lubrication, leading to vaginal dryness, followed by other vaginal and urinary symptoms, such as burning, itching, bleeding, leucorrhea, dyspareunia and dysuria. These symptoms usually appear some 2-4 years after the onset of menopause. VVA is particularly relevant regarding the prevalence, affecting 20-45% of women. In contrast to postmenopausal vasomotor symptoms, VVA demonstrates a progressive and worsening feature over time and a less likely attitude to solve without targeted interventions. Several surveys have reported that VVA

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symptoms significantly contribute to determine an adverse emotional and physical impact on patients and their partners through unsatisfactory sexual relationships[2,3]. The main therapeutic objective in managing VVA is to relieve genital symptoms as well as trying to restore the vaginal environment to a healthy condition[4]. Historically, vaginal estrogens have been considered the gold standard of treatment for the relief of VVA symptoms; topical estrogen administration has been widely preferred compared to the systemic modality when genital symptoms are the only complaint and, moreover, low-dose vaginal estrogen administration has been proven to reach optimal effectiveness with minimal side effects and systemic absorption[5]. On the other side, the estrogen-based approach represents, in a significant percentage of postmenopausal women, a kind of limiting factor for several reasons: fear of cancer risk increase, personal and/or cultural reasons, or even identified contraindications. In fact, no conclusive data are available about the long-term safety of vaginal administration of estrogens in particular subgroups of patients[6]. In this view, the state-of-the-art position statements about the optimal approach for the relief of VVA symptoms take into great consideration the patients' preferences and willing, the personal needs and the cultural positions. A quite extensive number of non-hormonal vaginal preparations has been suggested in recent years and proposed as an alternative approach, lubricants and vaginal moisturizers being the most frequently prescribed in clinical practice. For this, it is now a good practice to give patients a comprehensive and detailed information about the available options. In the group of non-hormonal treatments, hyaluronic acid owns many of the characteristics that represent a consistent background for the treatment of VVA symptoms[7].

Background

The vaginal epithelium is particularly sensitive to the effects of circulating estrogens in women; at menopause, when a dramatic reduction of estrogens occurs, this epithelium strongly modify its structure, with progressive and worsening atrophic changes. Hyaluronic acid is a natural polysaccharide that represents an important part of the extra-cellular matrix of the skin and cartilage. This substance is able to storage large amounts of water molecules and has a key role due to the properties of formation and conservation of extra-cellular inflation, skin moistening in the case of inflammation and preservation of water equilibrium. Also, it is widely effective in the treatment of skin diseases due to the preservation of tissue consistency, facilitating the cellular migration in cases of inflammation and also the process of improvement and regeneration of damaged tissues[8].

Patients and Methods

The study has been performed between 2015 and 2016 at the Department of Obstetrics and Gynecology of Vita Salute San Raffaele University School of Medicine, Milan, Italy. In this period, 46 consecutive postmenopausal women have been identified, recruited and enrolled in the trial. All patients participated to the trial on a volunteer basis after having received the proposal in the office visits of the Gynecological Department consultations. The selection criteria of cases were based on the presence of patients' complaint of vulvovaginal signs and symptoms correlated with postmenopausal lack of estrogens: vulvovaginal atrophy, genital dryness, vaginal burning, itching and painful intercourses were the major discomforts reported. Exclusion criteria were: previous use of systemic or topical estrogen-based preparations. All patients were extensively informed of the study design and hypothesis and a signed consent was obtained. According to the study design and the preparation administered, Institutional Review Board (IRB) gave exempt to ethical approval. All patients were prospectively enrolled in the trial after having been comprehensively investigated on the basis of: duration of menopause, gynecological visit, Vaginal Health Index (VHI) score, Visual Analogic Score (VAS) of signs and symptoms. VHI is an objective, score-based investigation tool, firstly elaborated and published by Gloria Bachmann[9] and comprising of five vaginal parameters evaluated by clinical inspection: elasticity, fluid volume, pH, epithelial integrity and moisture. Each parameter is graded from 1 (worst condition) to 5 (best condition). The VAS of signs and symptoms was subjectively recorded by patients on a personal diary; the parameters evaluated were: vaginal dryness, burning, itching and painful intercourses. Patients were asked to score their symptoms from 1 (best condition) to 10 (worst condition). The study protocol of treatment was based on the application of a hyaluronic acid-based liquid

preparation for vaginal use (Justgin®, Just Pharma, Rome, Italy) three times a week for a total of 8 weeks. All cases have been again investigated with the use both VHI and VAS of symptoms one month after the end of treatment, At the same time, patients were asked to report their degree of satisfaction, according to a 5-point Likert scale (very satisfied, satisfied, uncertain, dissatisfied and very dissatisfied). Treatment was considered satisfactory when patients were very satisfied or satisfied.

Statistical Analysis

Statistical analysis of VHI and VAS scores has been performed by the use of the Wilcoxon signed-rank test for repeated values, assuming a p-value < 0.05 as statistically significant.

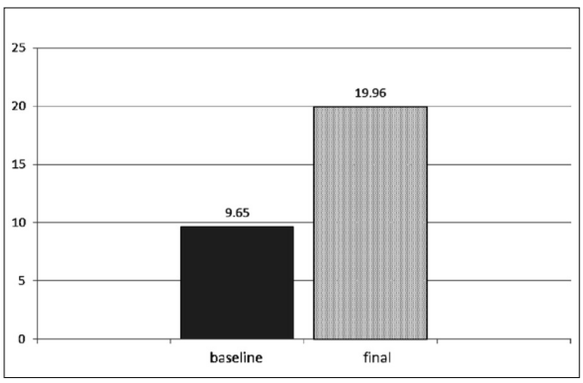

Figure 1. Vaginal Health Index (VHI) mean scores at baseline and after treatment (Wilcoxon signed-rank test: $p < 0.0001$).

Results

The study group consisted of 46 consecutive postmenopausal women; mean age of patients was 57.8 years (min. 49 – max. 67 yrs, 95% CI 8.9 to 10.4) and mean duration of menopause was 6.5 years from onset. All 46 patients completed the trial since neither adverse effects nor spontaneous dropouts were observed. As far as it concerned the Vaginal Health Index (VHI), mean VHI at the enrollment in the trial was 9.65 (min. 5 – max. 16; 95% CI 8.90 to 10.40) underlying that vulvovaginal atrophy objective signs were particularly relevant. When the patients underwent final VHI evaluation one month after the end of the hyaluronic acid-based protocol, mean VHI showed a statistically significant improvement to the value of 19.96 (min. 15 – max. 23; 95% CI 19.38 to 20.54) ($p < 0.0001$) (Figure 1).

With regard to patients' subjective Visual Analogic Scale (VAS) of symptoms – dryness, burning, itching and dyspareunia – a mean value of 7.65, 5.15, 2.21, and 5.63 was reported for the four parameters respectively; it is noteworthy that vaginal dryness (mean VAS 7.65) and painful intercourses (mean VAS 5.63) emerged as the most relevant negative symptoms in this group of patients. On the other end, vaginal itching (mean VAS 2.21) was reported as less invalidating. At the end of treatment, all the baseline VAS scores showed a statistically significant ($p < 0.0001$) improvement as high as 3.95, 2.93, 1.13 and 3.54 respectively; these improvements are summarized in Table I and Figure 2. Concerning the personal satisfaction, according to the 5-point Likert scale, a 95% degree of patients' satisfaction was obtained.

Discussion

VVA is a chronic, progressive and worsening condition depending on the estrogen dramatic decrease that occurs at menopause. According to several surveys published in recent years, the prevalence of VVA among postmenopausal women is particularly relevant, accounting for almost 50% of women. These findings can reasonably underestimate the real dimension of the condition, as these patients are frequently reluctant to complain and report their symptoms,

Table I. Visual Analogic Scale (VAS) mean scores of symptoms.

	Baseline	Final	*p*-value
Vaginal dryiness	7.65	3.95	< 0.0001
Vaginal burning	5.15	2.93	< 0.0001
Genital itching	2.21	1.13	< 0.0001
Painful intercourses	5.63	3.54	< 0.0001

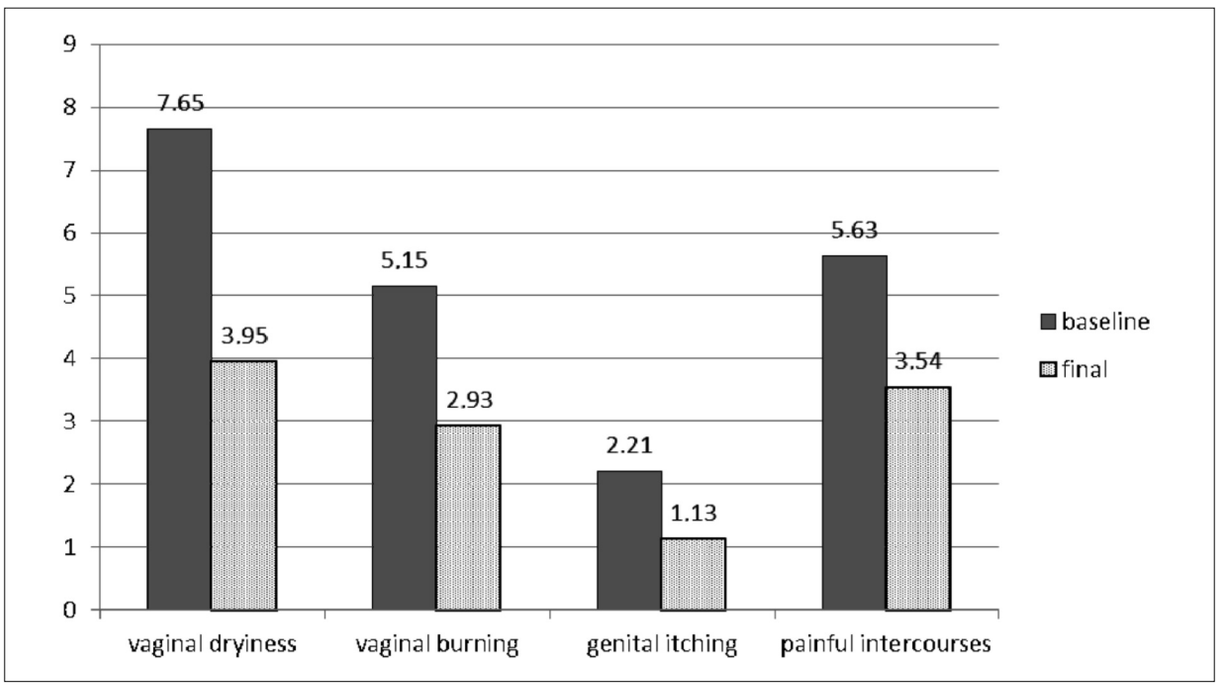

Figure 2. Visual Analogic Scale (VAS) mean scores of symptoms at baseline and after treatment (Wilcoxon signed-rank test: $p < 0.0001$).

GPs are often poorly educated to investigate properly their patients and gynecologists should be encouraged to be proactive. For these reasons, VVA despite its high prevalence remains poorly recognized and undertreated[10]. Based on the available data, systemic estrogen replacement therapy is not recommended for the sole purpose of VVA symptoms treatment. Symptomatic postmenopausal women might derive benefit from systemic hormones, which could improve some aspects of sexual function by addressing bothersome estrogen deficiency symptoms. However, the decision to start a systemic estrogen therapy must be personalized and patients must be adequately informed about the risks and benefits, with particular attention to cardiovascular, thrombotic, and breast cancer risks. There is clear and consistent evidence for the benefits of vaginal estrogen therapy in women who have vaginal symptoms and dyspareunia. Vaginal estrogen therapy and ospemifene are effective and indicated for the treatment of VVA[11,12]. In spite of available reassurances to the contrary, many women still fear estrogen therapy and feel very uncomfortable or present some kind of limitations, according to personal history and/or risk factors. Moreover, no data are available regarding the long-term safety of vaginal estrogen therapy. Alternative options to obtain relief of VVA symptoms include non-hormonal vaginal lubricants and moisturizers, as well as regular sexual activity. Regular use of non-hormonal vaginal lubricants and moisturizers may reduce friction-related irritation of atrophic tissue during vaginal intercourse, thus providing a transient benefit. Recently, very interesting evidence of safety, effectiveness and acceptability of fractional CO_2 laser treatment of VVA symptoms has been reported in the literature[13-16]. As far as it concerns hyaluronic acid, this compound has been largely studied and investigated in many dermatologic, ocular and osteoarticular applications requiring tissue remodeling; vaginal atrophy has also been investigated with promising results[17-19]. The results of the present investigation with a hyaluronic acid-based vaginal liquid preparation commercially available in Italy (Justgin®, Just Pharma, Rome, Italy), strongly supports the indication of such a preparation for the relief of genital symptoms due to VVA. In terms of mechanisms of action details, the high molecular weight hyaluronic acid acts as a protective macromolecule for the vaginal mucosa and also favours the penetration of the low molecular weight molecule into the deeper vaginal layers.

Our results indicate a robust statistical significance of the improvements of symptoms, both objectively by the use of the Vaginal health Index (VHI) and subjectively with a Visual Analogic Scale (VAS) of symptoms, after a 2-month treatment with the hyaluronic acid liquid preparation for vaginal use. In particular, the most significant improvements have been reported as far as it concerned vaginal dryness and painful intercourses, therefore strongly improving the Quality of Life (QoL) of these women; in this view, the patients' degree of satisfaction at the end of the trial was reported as high as 95%. Previous positive results of the use of vaginal hyaluronic acid preparations in symptomatic postmenopausal women[20-22] are available in literature and, even when compared with vaginal estrogen, hyaluronic acid demonstrated similar effectiveness[19]. The results of the present work differ from the previous experiences concerning the hyaluronic acid way of vaginal administration; in fact, all the previously published results refer to vaginal creams and/or suppositories that, as underlined by several surveys, often determine a low degree of satisfaction and compliance, leading to a significant percentage of treatment discontinuation[10]. The liquid preparation, due to its intrinsic characteristics, appears to be very well tolerated and accepted by patients, determining the absence of dropout cases from the study group and contributing to the final degree of satisfaction.

Conclusions

In accordance with the actual statement that postmenopausal women complaining of VVA discomforts should always comprehensively be informed of all the therapeutic available alternatives, and in accordance with experts' opinions that sexual satisfaction and QoL after menopause should be of primary importance for care providers, the results of the present study support the effectiveness of hyaluronic acid in obtaining significant improvements of VVA related symptoms and the inclusion of hyaluronic acid in the pool of effective non-hormonal treatments.

Conflict of Interest

All the authors of the submitted manuscript declare under their responsibility that no financial interests related to the article have to be disclosed.

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