

Effectiveness and safety of vaginal suppositories for the treatment of the vaginal atrophy in postmenopausal women: an open, non-controlled clinical trial

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Abstract. – Menopause, due to the physiological decrease in the estrogens levels, is often associated with many symptoms related to vaginal atrophy such vaginal dryness, dyspareunia, burning, itching, decreasing in libido and therefore a worsening of the quality of life and in particular of the sexual activity.

There are many pharmacological remedies to solve these events, first of all hormone replacement therapy (HRT) that up to the 90s was the therapy of choice for the care of the menopause symptoms. This hormonal therapy, however, has been re-considered due to its side effects.

As alternative, a clinical trial has been performed to investigate the efficacy and safety, in postmenopausal women with urogenital atrophy, of the use of suppositories for vaginal use, containing hyaluronic acid, vitamin E and vitamin A. The trial, according to a open, non-controlled design, was performed on 150 postmenopausal women, 1 vaginal suppository per day, for the first 14 days and then a vaginal suppository, day in and day out, for other 14 days.

The primary endpoint was the evaluation of vaginal dryness assessed by a Visual Analogue Scale (VAS) both by the investigator and the patient. The secondary endpoints were the evaluation of all the other symptoms and signs associated with the vaginal atrophy (itching, burning, dyspareunia, vaginal inflammation or swelling, irritation, assessed by a 4-point scale, presence of vaginal abrasions and irritation), and the recording of the adverse events occurring during the trial.

The patients have not reported adverse effects during the treatment, and the results in terms of effectiveness on the vaginal atrophy symptoms were markedly positive. A high level of compliance was registered.

The product tested can therefore be considered a safe and effective alternative for the treatment of vaginal atrophy symptoms in postmenopausal women, especially when HRT is not recommended.

Key Words:

Medical device, Menopause, Vaginal atrophy, Vaginal dryness, Hyaluronic acid.

Introduction

Menopause is a physiological step in a woman's life, which is associated with a decrease in the estrogens levels, due to a reduction in their endogenous production. Low estrogens circulating levels lead to some negative effects on all those organs whose function and health is linked to their presence. The lower genitor-urinary tract is negatively affected by a decrease in endogenous estrogens production^{1,2}. The vaginal epithelium becomes atrophic and its physiological lubrication is consistently reduced. This modifications lead to many physical discomforts as local itching and dyspareunia. In addition, the thinning of endometrium tissues and the enhancing of the vaginal pH due to estrogens deficiency, leads to increased incidence of vaginal infections and to a marked structural weakness). The vaginal dryness is also responsible for sexual dysfunctions and for libido reduction^{4,5}. The condition of vaginal atrophy is associated with a reduction of estrogens and thus it can be associated to all those women who are in premenopause but that have lower levels of endogenous estrogens for medical (anti-estrogenic drugs administration) or surgical reasons. The aging of female reproductive tract, due to reduced estrogens levels have serious influences on the quality of women's life, especially when its expectation is going to increase⁵.

Hormonal replacement therapy, per systemic or topical way, have been often used, up to the 90s, for the treatment of menopausal effects on the urogenital tract, including those related to vaginal atrophy⁶. The WHI study (Women's Health Initiative) in 2002 and other published studies from that date onwards have changed radically the knowledge about the relationship between the risks and the benefits of the HRT^{7,8}. In particular, with regard to the risks of developing endometrial and breast cancer, the study published in 2005⁹, performed on approximately one million of postmenopausal women treated with HRT, reported a significant increase of the incidence of such cancer forms in women treated with estrogens alone or with a combined therapy (estrogens plus progestin compounds)¹⁰.

An alternative to the HRT was the use of estrogenic products for topical use^{11,12}. However, they are still considered at risk in case of prolonged use.

Considering these last results, there is an increasing need for new safe and effective therapies for the treatment of vaginal atrophy in postmenopausal women, which can be a valid alternative to hormonal therapy¹³.

To reduce the disorders associated with vaginal dryness, in postmenopausal women vaginal moisturizing or lubricants can be effective. The first can have short or long term effects, by improving the balance of intracellular fluids in the vaginal epithelium. The tissues seem to be more trophic and the physical disorders seem to get better.

The vaginal lubricants rather have a short term action as mechanical barrier between the vaginal epithelium and the external environment, and are mainly used to improve the dryness related to sexual activity.

The results of the clinical trial in open, non-controlled design are reported. It investigated the use of vaginal suppositories contain hyaluronic acid, vitamin E and vitamin A, intravaginal administered in women suffering from vaginal atrophy. The trial doesn't include the placebo group, due to the fact that the vaginal administration of a placebo can cause local alterations of the clinical results (e.g. vaginal pH and local epithelial alterations)¹⁴.

Hyaluronic acid sodium salt is a high weight molecule belonging to the class of glycosaminoglycans and consists of repeated disaccharides units (glycuronic acid and N-acetylglucosamine). Hyaluronic acid is able to retain very high amount of water molecules, forming a moisturizing, not greasy and permeable to water and light

film on skin. Hyaluronic acid is the main component of the derma's fundamental substance, and it is widely used in dermatology because it helps to:

- Form extracellular water film;
- Maintain the extracellular swelling;
- Moisturize the skin in case of inflammation.

It then helps to maintain water balance and thus makes the skin smooth and elastic¹⁵. Also plays a key role to maintain the tissues integrity and to ease the cells migration in case of inflammation. Hyaluronic acid inhibits the pericellular migration of viruses and bacteria and sets on its structure the free radicals (antioxidant action), facilitating the healing process and the tissue regeneration^{16,17}. Vitamin E, a fat-soluble vitamin with great antioxidant properties, takes part to the metabolism of all cells. It prevents the degradation of the tissue due to oxidant agents. However, vitamin E, despite the lack of literature, has a rational in this context: it can be used on the skin, because of its properties of antioxidant, anti-inflammatory and healing active agent. Even though few studies have been performed on the effects of vitamin E on vaginal mucosa, the Authors recommend it (taken orally, topically, or vaginally) for certain types of vaginosis¹⁸. In fact, Vitamin E as vaginal suppositories or oil can be used once or twice per day for 3 to 14 days to soothe the vaginal and vulvar mucosa. The use of vitamin E suppositories dates back to 1954 to treat yeast vulvovaginitis¹⁹. A very high soothing effect has been found when they are used once or twice daily for 7 or more days to reduce the symptoms associated with vaginal infections: vaginal irritation, swelling, local redness, burning and itching. The tissue becomes less irritated with a decrease in redness, swelling, and congestion. Vitamin A is a fat-soluble vitamin that has shown to have properties to increase the function of the immune local cells as well as ensure the integrity of morphological and functional vaginal epithelium^{20,21}. The lack of vitamin A also leads to growth inhibition and bones deformation, to serious changes in epithelial structures and reproductive organs^{22,23}.

Materials and Methods

One-hundred and fifty women, aged between 44 to 64, were admitted to participate to the trial,

all in surgical or physiological menopause from even 1 year, presenting vaginal dryness and correlated symptoms. Exclusions criteria were: no compliance to the treatment, genital abnormalities, positive Pap-test within the last three months, vaginal infections (confirmed by microbiological analysis), contact allergy in vulvo-vaginal zone, the use of drugs for vaginal administration in the last 15 days before the beginning of the study, alcohol or drugs abuse, taking part to other studies in the month before the recruitment.

All patients gave a written informed consent to the procedure. The trial was approved by the local Ethics Committee. The study followed the good clinical practice (GCP), and was performed according to an open, non-controlled design to evaluate local and systemic effects of the administration of a preparation of hyaluronic acid, vitamin E and vitamin A (Santes® ovuli, LO.LI. Pharma Srl, Italy) to treat post-menopausal vaginal atrophy.

All the patients were treated with daily application of one suppository, deeply in vagina (in the evening, before going to bed), for 14 days continuously. Then, for other 14 days, the administration of one suppository per day, one day in one day out.

Within the period of the study (4 weeks), four visits were performed: at baseline, after 7 days from the beginning of the treatment (visit 1), after 14 days (visit 2) and at the end of the treatment (day 28) (visit 3).

At baseline visit the exclusion/inclusion criteria were evaluated. Furthermore, demographic, medical and gynecological data were collected. A Pap-test was performed when not available in the last 3 months, urine and vaginal tampons were obtained.

During each visit a gynaecological inspection was done including vulvoscopie, vaginoscopie, cervix, ovarian, uterus and tubal analysis. Registration of objective vaginal symptoms (inflammation, edema, vulvo-vaginal abrasions) and of subjective vaginal symptoms (dryness, itching, burning, dyspareunia) were made.

The evaluation of the vaginal dryness (primary endpoint) was performed according to an analogical scale between 0 (no vaginal dryness feeling) to 10 (unbearable vaginal dryness feeling), by reporting data in the patient's diary.

Other symptoms and signs were evaluated by the investigator using a 4-point scale (1 = absent,

2 = mild, 3 = moderate, 4 = severe). Vaginal abrasions were only assessed as present or absent.

During all the treatment each patient noted daily the symptoms (itching, burning, dyspareunia), evaluating by a 4 points scale (1 = absent, 2 = mild, 3 = moderate, 4 = severe).

Statistical Analysis

Statistical analysis have been performed with SAS (version 8). Data belonging to all the patients that followed the protocol were included in the statistical analysis (PP population). Some results are expressed as means \pm SD. The primary endpoint (vaginal dryness) differences were compared using the two-tailed Student's *t* test for independent data and *chi*² test.

A *P* value < .05 was considered statistically significant.

Analysis of secondary variables has performed by using Friedman test.

Results

Among 165 women recruited for the study, 150 were enrolled. 15 women do not copy with the inclusion criteria. 150 women enrolled, aged between 44 and 64 (mean \pm SD, 51.6 \pm 7.6), with a BMI between 18.1 and 37.47 (mean \pm SD; 24 \pm 10.6) were assigned to the treatment according to the study protocol; demographic characteristics of the patients are reported in Table I.

Twenty patients did not complete the study: four spontaneously abandoned the study, seven did not have compliance to the treatment, nine had a negative follow-up. A total of 130 patients completed the study (PP population).

The vaginal dryness (primary endpoint), measured with VAS scale, decreased in PP population from 7.92 at baseline to 4.22 at visit 1 (7 days after the beginning of the treatment), to 0.84

Table I. Demographic characteristics of the women taking part to the trial.

Patients	Values
Included in the trial	150
Age	51.6 \pm 7.6 (min 44 max 64)
BMI (Body Mass Index)	24 \pm 10.6 (min 18.1 max 37.47)

at visit 2 (14 days), to 0.0 at visit 3 (28 days, end of the treatment). Differences revealed by ANOVA analysis was highly significant ($F = 1029,2$; $P < 0.001$). Multiple comparison confirmed a significant decrease of the symptom, even at the first time point of the study (visit 1, after 7 days), in comparison with the baseline value.

During the baseline visit, the hitching symptom was severe in 106 women and moderate in 24 women; it disappeared progressively during the treatment period and only 4 women still reported the symptom at the end of the treatment (visit 3). The results are reported in Table II. The mean values of hitching, measured with a 4-point scale decreased from 3.82 at baseline, to 2.89 at visit 1, to 1.35 at visit 2 and to 1.03 at visit 3 ($P < 0.001$).

During the baseline visit, burning was present as severe symptom in 93 women, moderate in 26 women and mild in 11. The symptom is progressively disappeared during the treatment. At the end of the treatment only 4 women complained about a mild burning symptom. Data are reported in Table II. The mean values of burning, measured with a 4-point scale decreased from 3.63 at baseline, to 2.45 at visit 1, to 1.31 at visit 2 and to 1.03 at visit 3 ($P < 0.001$).

Dyspareunia, at the baseline visit, was registered as severe symptom in 18 women, as moderate in 78 women and as mild in 34. The symptom decrease progressively and only 5 women reported mild dyspareunia at the end of the treatment. Data are reported in Table II. The

mean values of dyspareunia, measured with a 4-point scale decreased from 2.88 at baseline, to 2.19 at visit 1, to 1.43 at visit 2 and to 1.04 at visit 3 ($P < 0.001$).

During the baseline visit, the inflammation/edema of vaginal mucosa was registered severe in 30 women, moderate in 52 women, mild in 28 and absent in 20; it disappeared progressively during the treatment, and only 5 women still reported the mild symptom at the end of the treatment (visit 3). The mean values of the symptom, measured with a 4-point scale decreased from 2.71 at baseline, to 1.93 at visit 1, to 1.65 at visit 2 and to 1.04 at visit 3 ($P < 0.001$).

During the baseline visit, the vaginal mucosa irritation was severe in 25 women, moderate in 32, mild in 50 and absent in 23 women; it disappeared progressively during the treatment in all the patients. The mean values of the irritation, measured with a 4-point scale decreased from 2.45 at baseline, to 1.78 at visit 1, to 1.34 at visit 2 and to 1.00 at visit 3 ($P < 0.001$).

The compliance to the treatment was complete for 126 patients and partial for the other 4 patients. Data are reported in Figure 1A.

The overall judgement of the product's effectiveness reported by the investigator was optimal in 108 patients, good in 20 patients and moderate in 2 patients. Data are reported in Figure 1B.

The overall judgement of the product's safety was reported by the investigator optimal in 124 patients, good in 4 and sufficient in 2 patients. Data are reported in Figure 1C.

Table II. Subjective symptoms in post-menopausal women treated with the product for 28 days (visit 1 = 7 days; visit 2 = 14 days; visit 3 = 28 days).

		Hitching	Burning	Dyspareunia
Baseline	Absent	0	0	0
	Mild	0	11	34
	Moderate	24	26	78
	Severe	106	93	18
VISIT 1	Absent	0	15	27
	Mild	20	45	53
	Moderate	104	67	48
	Severe	6	3	2
VISIT 2	Absent	95	100	78
	Mild	25	20	48
	Moderate	10	10	4
	Severe	0	0	0
VISIT 3	Absent	126	126	125
	Mild	4	4	5
	Moderate	0	0	0
	Severe	0	0	0

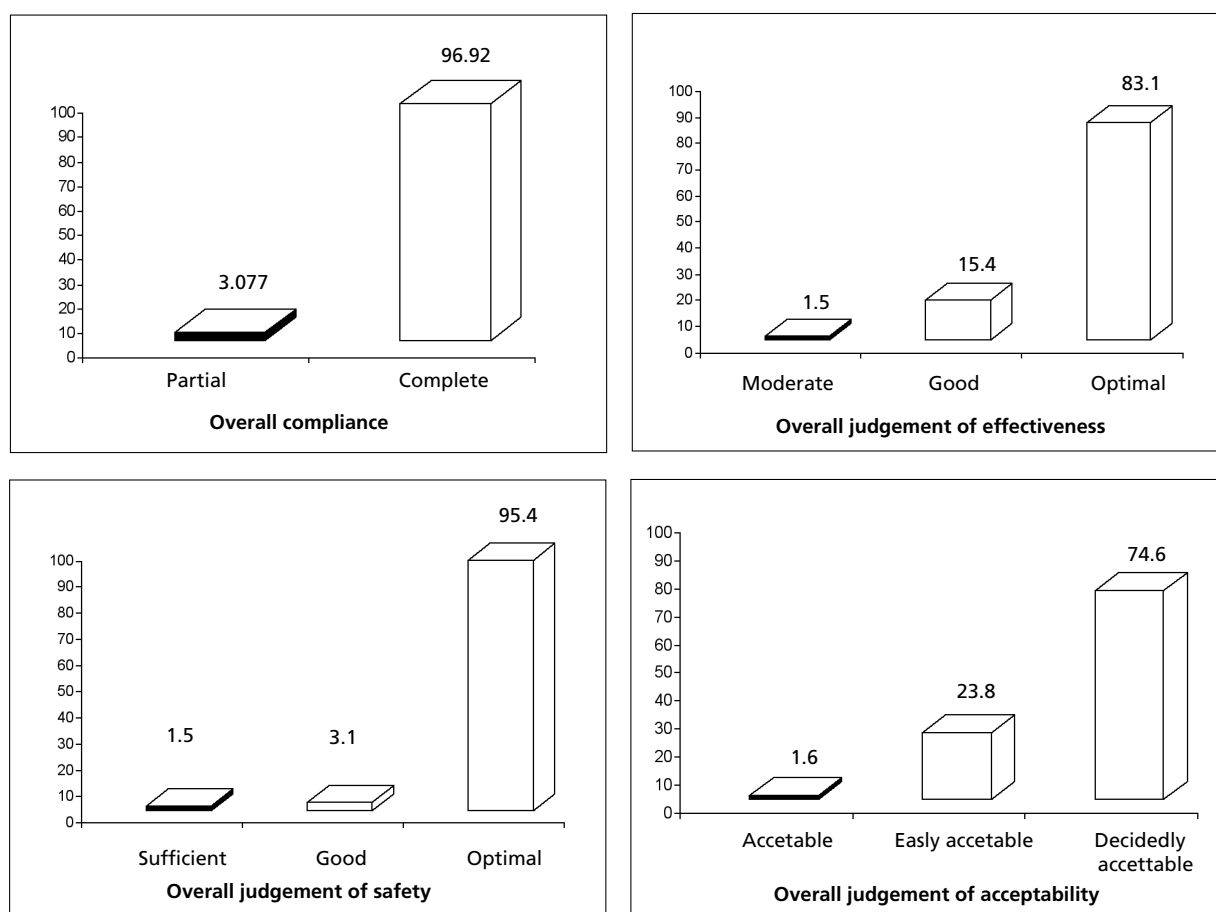


Figure 2. A-D, Overall judgement and compliance in post-menopausal women after 28 days of treatment (data expressed in percentage).

Acceptability of the medical device by the patients was evaluated as decidedly acceptable by 97 patients, easily acceptable by 31 and acceptable by 2 patients. Data are reported in Figure 1D.

Discussion

In the last years is great the need of new therapeutic forms, safe and effective, to restore normal condition in post-menopausal women affected from vaginal atrophy. This new product in suppositories form has been studied in order to be a new alternative form of treatment of the symptoms correlated to genital atrophy.

The trial was assessed on post-menopausal women, in order to evaluate the safety and the effectiveness of this product on the clinical and subjective symptoms correlated to vaginal atrophy.

The results confirmed a favourable safety profile of the product even after a longer period of treatment. The effectiveness on vaginal dryness and on correlated symptoms was good right from the first week of treatment. The overall judgement on effectiveness and safety was optimal for the main part of the patients. The compliance was favourable in almost the whole group of women treated.

The only guidelines available for the study were those correlated to the treatment of vaginal condition: “Guidance for industry. Bacterial vaginosis – Developing antimicrobial drugs for treatment” of FDA (Food and Drugs Administration) that suggest do not use placebo to avoid any alteration of the clinical results¹⁴.

The components of the suppositories are responsible for slowing down the natural process of aging of the vaginal and vulvar tissues and of increasing their natural hydration. Effectiveness of the single components of the product should be investigate separately in further trials.

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