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Low-dose, vaginally administered estrogens may enhance local benefits of systemic therapy in the treatment of urogenital atrophy in postmenopausal women on hormone therapy

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Abstract

Background: When genital atrophy exists, systemic hormone therapy (HT) has a timing until to induce vaginal proliferation and symptomatic relieve. Thus, in order to obtain a prompt improvement, the association of local therapy acting on the genital epithelium to the systemic treatment should be considered. **Objective:** To evaluate the effects of a combined therapy consisting of vaginal estriol with transdermal 17- β -estradiol (50 μ g/day) plus medroxyprogesterone acetate (5 mg/day) per os in shortening the period of uro-genital symptoms. **Subjects and methods:** In a randomized, double blind, controlled with placebo study, 27 women with climacteric symptoms and atrophic vaginitis were treated for 4 months with HT plus vaginal estriol 0.5 mg/day (group E) or placebo (group P). Patients use the local medication daily for the first 3 weeks and twice-weekly thereafter. Before entering in the study, patients were asked about HT and selected for inclusion. In the first visit, electible patients after written informed consent were randomized to receive HT plus local estriol or placebo. All the subjects had baseline studies, including medical history, physical examination, blood and urine analysis. In order to evaluate the effect of local treatment on urinary and genital symptoms, a score for genital, urinary and colposcopic complaints (0 minimum–100 maximum) was developed. This score and Blatt-Kuperman were recorded and performed in every control. **Results:** There were no differences on climacteric symptoms relief between the two groups. Additionally, the improvement in urinary symptoms at the end of the study was similar for both groups (from 16.5 ± 6.1 to 8.5 ± 2.4 for E group and from 15.8 ± 7.8 to 8.8 ± 2.7 for P group; $P < 0.01$ versus basal); however, those women in group E reached significant improvement on urinary complaints since the first month of treatment. Additionally, a significant difference between E and P was observed at months 2 and 3, although no differences were detected at the end of the study. Papanicolaou smear showed reactive or reparative changes and karyopyknotic index exhibited a significant

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increase in superficial cells in both groups and at the end of the study. *Conclusions:* Adding vaginal estriol to HRT may shorten the latency period for urinary symptoms.

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1. Introduction

The main objectives of hormone therapy (HT) in postmenopausal women is to improve the quality of life and to relieve climacteric symptoms that are a consequence of the estrogens deprivation. Estrogens have important physiologic effects on the female lower genital tract throughout adult life, causing symptomatic, histologic, and functional changes. Genitalia atrophy, a manifestation of estrogen withdrawal after menopause, is accompanied by vaginal or urinary symptoms or both such as pruritus, genital discomfort, dysuria, vesical tenesmus and dyspareunia. Additionally, the lack of lactobacillus and the vaginal atrophy may increase the risk of genital and urinary tract infections [1]. Although use of HT in the management of lower urinary tract symptoms has been studied for two decades, only recently has it been tested in randomized placebo-controlled trials and assessed by meta-analysis [2].

More than 50% of postmenopausal women experience moderate or severe symptoms related to atrophic modifications in the genitourinary tract [3]. In Spain, almost one million and a half of women present urogenital complaints due to estrogen deficiency [4]. When these symptoms are present, the use of systemic HT has a timing until the hormonal effect on the genital epithelia induces proliferation and symptomatic relief.

To offer a prompt improvement of these genital symptoms the association of a local hormone therapy to the systemic HT should be considered. The use of local estriol favours the normalization of the cervico-vaginal mucous without endometrial effects, showing the absence of systemic action [5].

In order to investigate the clinical efficacy and safety of the local-systemic combined hormonal therapy we design the present study.

2. Material and methods

2.1. Subjects

A total of 27 early postmenopausal women (time elapsed from the last menstruation >12 months and <8 years) aged between 40 and 64 with genital atrophy symptoms and that had not been submitted to HT in the previous 3 months were included in this open, double blind, randomized, controlled with placebo study. Women with difficulty to understand the survey or with general contraindications for HT use were excluded. In addition, women with hysterectomy and/or oophorectomy were also excluded, since the study was focused on the menopause as a natural and biological process. Alcoholic (>40 g/day) or heavy smoker (>10 cigarettes/day) women were also excluded.

All the patients received 50 µg/day of 17-β-estradiol in transdermal therapeutic systems (two patches for week during 4 weeks) plus medroxyprogesterone acetate (5 mg/day last 10 days) and were randomized to receive 0.5 mg/day of vaginal estriol cream (group E, $n = 13$) or placebo (group P, $n = 14$) daily during the first 3 weeks and twice per week until the end of study. The study period comprised 4 months.

2.2. Study protocol

Before entering in the study, patients were asked about HT and selected for inclusion. In the first visit, electible patients after written informed consent were randomized to receive HT plus local estriol or placebo. All the subjects had baseline studies, including medical history, physical examination, blood and urine analysis. Climacteric symptoms (Blatt-Kuperman), and genital and urinary complaints as well as colposcopy and Papanicolaou smear were recorded and performed in every control by the same investigator (SP).

In order to evaluate the effect of local treatment on urinary and genital symptoms, we developed a score for genital, urinary and colposcopic complaints (0 minimum–100 maximum).

- *Genital symptoms dominion*: include vaginal dryness, vulvar and vaginal itching, dyspareunia, recurrent vaginitis, vaginal relaxation, genital erythema and coitus unattainable (vaginal stenosis). Symptoms were counted according their intensity (0 null to 5 unbearable) and added all in a final score (0 minimum–40 maximum).
- *Urinary symptoms dominion*: include polaquiuria, dysuria, stress incontinence, urgency incontinence, urethritis and urinary frequency. Symptoms were counted according their intensity (0 null to 5 unbearable) and added all in a final score (0 minimum–30 maximum).
- *Colposcopy dominion*: include atrophic colpitis, paleness and petechias. Symptoms were counted according their intensity (0 null to 10 maximum) and added all in a final score (0 minimum–30 maximum).

2.3. Statistical analysis

Results were expressed as mean \pm S.D. To evaluate changes during the follow-up we also used percentages of change ((value – basal value) \times 100/basal

value). Data were analyzed with the program Epi-info 2000, version 1.1.2 (Centers for Disease Control, Atlanta, GA, USA). The treatment efficacy was evaluated by a means comparison (ANOVA) between visits of both groups of treatment with regard to parameters analyzed to calculate the percentage of improvement experienced by every patient in each visit. Percentage differences between groups were evaluated with using Chi-square. Differences in clinical responses between two points during the follow-up were assessed using Mann–Whitney's *U*-test. The analysis was carried out as per "intention to treat". A value of $P < 0.05$ was considered statistically significant.

3. Results

The mean age of the sample was 53.4 ± 2.9 years (range from 40 to 64 years). No significant differences were observed between the groups regarding mean Body mass index, body weight, blood pressure, age and time elapsed since menopause. Of the 27 subjects who were referred to the study, three dropped-out. Patients gave several reasons for default including weight gain, possible side effects particularly erythema in patch application area or vaginal burning and fear about HT.

The occurrence of climacteric symptoms (hot flashes, sweats, insomnia, irritability, lost of concen-

Table 1
Blatt-Kuperman scores at basal situation and at the end of the study

	Group E			Group P		
	Basal	Fourth month	<i>P</i>	Basal	Fourth month	<i>P</i>
Vasomotor instability ^a	6.53 \pm 4.19	1.78 \pm 2.57	<0.001	7.01 \pm 4.81	1.53 \pm 3.17	<0.001
Parestesia	1.87 \pm 1.87	0.57 \pm 1.08	<0.01	1.58 \pm 1.19	0.53 \pm 1.07	<0.01
Insomnia	2.75 \pm 1.99	1.11 \pm 1.42	<0.01	2.59 \pm 1.96	1.09 \pm 0.98	<0.01
Irritability (anxiety)	2.77 \pm 1.97	0.95 \pm 1.31	<0.05	2.48 \pm 1.88	0.90 \pm 1.37	<0.05
Mood disturbance (depression)	2.16 \pm 2.02	0.72 \pm 1.23	<0.01	2.21 \pm 2.12	0.81 \pm 1.04	<0.01
Lack of sexual desire	2.51 \pm 2.16	1.45 \pm 1.58	<0.05	2.57 \pm 2.66	1.45 \pm 1.58	<0.05
Lack of partner's receptiveness	2.26 \pm 2.04	1.31 \pm 1.54	<0.01	2.30 \pm 2.14	1.36 \pm 1.62	<0.05
Fatigue	1.13 \pm 0.98	0.45 \pm 0.69	<0.01	1.27 \pm 1.02	0.47 \pm 0.55	<0.01
Joint pain	1.56 \pm 1.13	0.71 \pm 0.86	<0.05	1.66 \pm 1.78	0.69 \pm 0.71	<0.01
Tachycardia	0.75 \pm 0.91	0.21 \pm 0.50	<0.05	0.81 \pm 0.78	0.19 \pm 0.54	<0.05
Urinary disturbance	0.56 \pm 0.86	0.12 \pm 0.39	<0.05	0.66 \pm 0.74	0.10 \pm 0.14	<0.05
Total score	24.8 \pm 11.2	8.53 \pm 6.74	<0.01	25.8 \pm 12.6	9.03 \pm 7.04	<0.01

Data are percentages of subjects (%) in each point. Group E: HRT plus vaginal estriol; group P: HRT plus placebo. *P* intragroup (basal vs. final). No differences were detected between groups.

^a Hot flashes and excessive sweating.

Table 2
Urinary, genital and colposcopy scores at basal situation and at the end of the study

	Group E		Group P	
	Basal	Fourth month	Basal	Fourth month
Genital score	24.9 ± 12.1	12.5 ± 5.5*	25.5 ± 15	14.5 ± 9.2*
Vaginal dryness	3.5 ± 0.8	0.5 ± 0.4*	3.6 ± 0.9	0.6 ± 0.4*
Vulvar itching	3.0 ± 1.2	1.5 ± 1.0*	3.5 ± 2.0	2.2 ± 1.9*
Vaginal itching	3.0 ± 1.9	1.2 ± 1.0*	3.2 ± 1.4	1.4 ± 1.1*
Dyspareunia	2.8 ± 1.2	2.0 ± 0.8 [#]	2.8 ± 1.4	1.9 ± 0.5 [#]
Recurrent vaginitis	1.9 ± 0.7	0.5 ± 0.4*	2.1 ± 0.9	0.4 ± 0.3*
Vaginal relaxation	2.7 ± 1.7	2.5 ± 1.7	2.5 ± 1.6	2.5 ± 1.0
Genital erythema	2.4 ± 0.7	1.7 ± 1.5 [#]	2.0 ± 0.9	1.9 ± 1.0
Coitus unattainable	1.5 ± 0.9	0.9 ± 0.9 [#]	1.7 ± 0.6	1.0 ± 0.5 [#]
Urinary score	16.5 ± 6.1	8.5 ± 2.4*	15.8 ± 7.8	8.8 ± 2.7*
Polaquiuria	3.5 ± 1.9	1.5 ± 1.0*	3.4 ± 1.6	1.3 ± 1.3*
dysuria	2.9 ± 1.0	1.5 ± 0.4 [#]	3.0 ± 1.3	1.6 ± 0.7*
Stress incontinence	2.5 ± 1.5	2.3 ± 1.7	2.2 ± 1.1	2.0 ± 1.8
Urgency incontinence	3.0 ± 1.9	2.1 ± 0.7 [#]	3.1 ± 2.2	2.4 ± 0.5
Urethritis	1.9 ± 1.2	1.0 ± 0.9	1.4 ± 1.3	1.2 ± 0.9
Urinary frequency	3.5 ± 2.0	0.7 ± 0.8*	3.2 ± 1.7	1.0 ± 0.8 [#]
Colposcopy score	22.5 ± 6.1	9.6 ± 3.7*	23.7 ± 8.9	9.9 ± 4.5*
Atrophic colpitis	9.5 ± 3.4	3.5 ± 2.0*	9.9 ± 4.0	3.6 ± 2.4*
Paleness	8.5 ± 2.2	3.5 ± 2.9 [#]	9.0 ± 3.3	3.4 ± 2.7 [#]
Petechias	5.5 ± 2.4	2.4 ± 1.4 [#]	6.1 ± 2.4	2.8 ± 1.3 [#]

Group E: HRT plus vaginal estriol; group P: HRT plus placebo. P (basal vs. final). No differences were detected between groups.

* $P < 0.01$.

[#] $P < 0.05$.

tration, mood, migraines, etc.) was similar for the two groups at basal situation. At the end of the study a significant decrease in Blatt-Kuperman scores was observed although no differences were detected between groups (Table 1).

The improvement in urinary and genital symptoms at the end of the study was similar for both groups (Table 2) ($P < 0.01$); however, those women in group E reached significant improvement on urinary complaints since the first month of treatment (Fig. 1). Although a significant difference between estriol and placebo groups was observed at months 2 and 3, results were not different at the end of the study.

Monthly colposcopy showed a similar percentage of alterations in both groups with atrophic colpitis, petechias and paleness at basal situation, as well as, no differences were detected at the end of study (Table 2). In addition, Papanicolaou smears demonstrated regenerative changes showing a similar percentage of superficial, intermediate and basal cells in both groups at the end of the study (Fig. 2).

Finally, 13 patients reported local adverse effects during follow up that include burning ($n = 8$ E5,P3;

29.62%), irritation ($n = 10$ E6,P4; 37.03%), and sensation of cream expelling ($n = 2$ P2; 7.40%). No differences were detected between groups regarding the presence of adverse effects. Additionally, most of them ($n = 10$) took place in the first control.

4. Discussion

The female genital and lower urinary tracts share a common embryologic origin, arising both from the urogenital sinus. Both act in response to the effects of sex steroid hormones. Estrogen plays an important role in the function of the lower urinary tract throughout adult life. Estrogen and progesterone receptors have been shown to be present in the vagina, urethra, bladder, and pelvic floor musculature [6]. With extremely low estrogen levels after menopause, atrophy of mucosal surfaces occurs, went together with vaginitis, dyspareunia and stenosis. All these symptoms may affect seriously the quality of life of menopausal women. Dysuria, urgency incontinence and urinary frequency are additional results of mucosal thinning. It is well

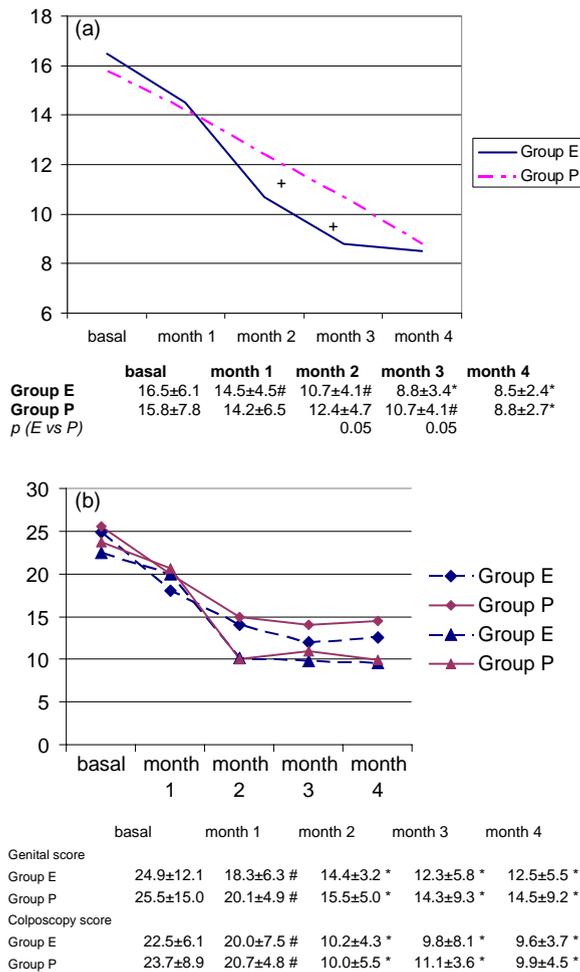


Fig. 1. Urinary score across the follow-up. The improvement in urinary complaints at the end of the study was similar for both groups; however, those women in group E reached significant improvement on urinary complaints since the first month of treatment. Although a significant difference was observed at months 2 and 3, no differences were detected between groups at the end of the study. Group E (HT plus vaginal estriol) group P (HT plus placebo). (* $P < 0.01$ # $P < 0.05$ vs. basal values) (+ $P < 0.05$ E vs. P). BIS: genital (◆) and colposcopy (▲) scores across the follow-up. The improvement in both scores during the follow-up and at the end of the study was similar for both groups. (* $P < 0.01$ # $P < 0.05$ vs. basal values.)

known that HT effectively prevented all these symptoms [7]. In our study, both groups evolved towards the improvement of genital symptoms, but it was more notable in the group treated with vaginal estriol. Our findings are in accordance with other reports on that, the use of local oestrogens was associated with a signifi-

cant decrease of the vaginal pH, with an increase in the index of vaginal presence of lactobaciles, and thereby improvement in uro-genital symptoms and infections prevention [7,8]. Moreover, In a recent, prospective, observational study, rates of cell proliferation throughout the tissues of the lower urinary tract were assessed [9]. Of 59 women studied, 23 were premenopausal, 20 were postmenopausal and HT no-users, and 16 were postmenopausal HT users. Biopsies from the bladder dome, trigone, proximal urethra, distal urethra, vagina, and vesicovaginal fascia adjacent to the bladder neck were evaluated. Women who were HT users had more squamous epithelial cellular proliferation than their estrogen-deficient counterparts.

In postmenopausal women the vaginal atrophy is a frequent complaint of postmenopausal women; symptoms include vaginal dryness, itching, discomfort and painful intercourse. For these reasons, it is very related to the sexual response, therefore the local treatment with estradiol or estriol helps to improve this situation [10]. In fact, dyspareunia seldom brings older women to medical attention and tranquil inquiring may lead to HT of atrophy and enhancement of sexual behavior. Appropriate doses of estrogens may modulate vaginal factors related to enjoyment of sexual intercourse [8]. Systemic hormone therapy treatment for these symptoms is not always necessary [11] and alternative choices are oestrogenic preparations administered vaginally (in the form of creams, pessaries, tablets and the estradiol releasing ring).

In agreement with our data, a recent Cochrane review [11] including 16 trials and 2129 women compared the efficacy of oestrogenic preparations (creams, pessaries, tablets and vaginal ring) with each other in relieving the symptoms of vaginal atrophy, results indicated significant differences favouring the cream, ring, and tablets when compared to placebo and non-hormonal gel.

Data from colposcopy carried out in each visit was similar between both groups, suggesting that the observed tissue alterations are a consequence of the lack of the estrogens since after such a therapy all these changes disappear. Moreover, the low level of estrogens usually are associated with local symptoms [12].

In this study, the reparative changes was observed in a higher percentage in the group treated with local estriol. Additionally, in the karyopyknotic index was observed a total disappearance of basal cells and an

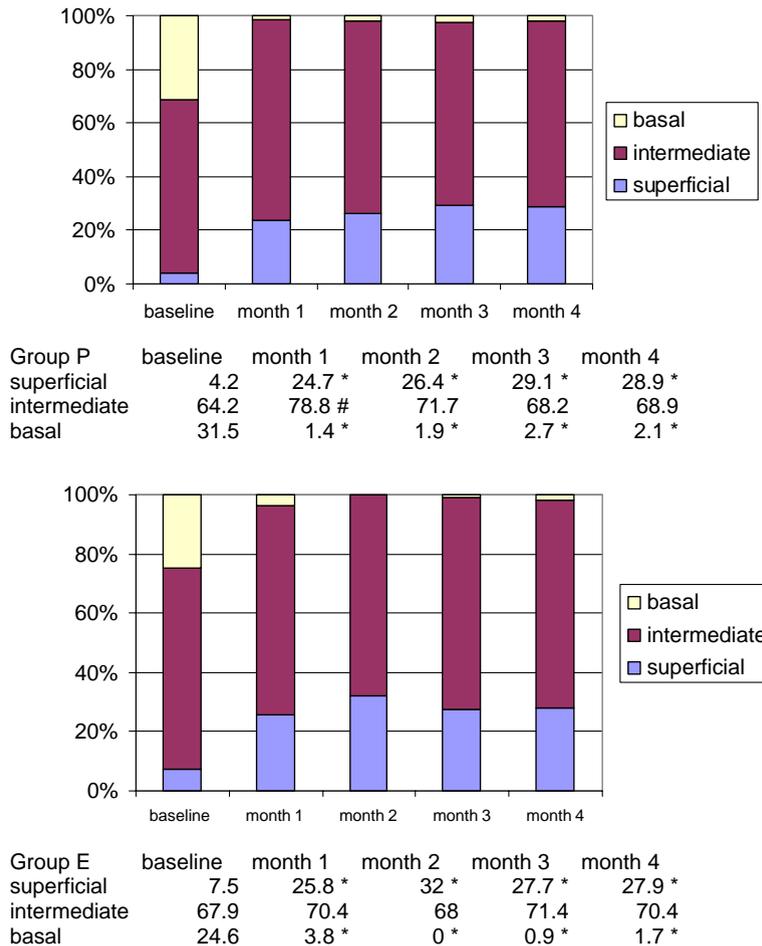


Fig. 2. Papanicolaou smears demonstrated regenerative changes showing a similar percentage of superficial, intermediate and basal cells in both groups during the follow-up and at the end of the study. No differences were detected between groups. (* $P < 0.01$ # $P < 0.05$ vs. baseline.) Results are in percentages.

increase of superficial cells in all treated patients. In the atrophic vagina the estrogens and their metabolites are more easily absorbed [13]. However, as the vaginal epithelization increases the absorption diminishes [14,15]. We have not observed evidences of systemic toxicity in the women who used estriol by local administration and the side effects were limited to burning and irritation with trend to disappearance.

Our data support the hypothesis that estrogen deficiency plays an important role in the etiopathogenia of climacteric and urogenital symptoms and that HT, both local and systemic, also helps to improve this symptoms especially the uro-genital and that local therapy

might even be an acceptable treatment to relieve the atrophic symptoms in the women in whom these symptoms were severe.

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