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ORIGINAL ARTICLE

Treatment of menopausal symptoms with three low-dose continuous sequential 17β-estradiol/progesterone parenteral monthly formulations using novel non-polymeric microsphere technology

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Abstract

Objective: To analyze the short-term efficacy and safety over menopausal symptoms of three low-dose continuous sequential 17β-estradiol (E)/progesterone (P) parental monthly formulations using novel non-polymeric microspheres.

Methods: This was a multicenter, randomized, single blinded study in which peri- and postmenopausal women were assigned to receive a monthly intramuscular injection of 0.5 mg E + 15 mg P (Group A, $n = 34$), 1 mg E + 20 mg P (Group B, $n = 24$) or 1 mg E + 30 mg P (Group C, $n = 26$) for 6 months. Primary efficacy endpoints included mean change in the frequency and severity of hot flushes and the effect over urogenital atrophy symptoms at 3 and 6 months. Safety variables included changes in the rate of amenorrhea, endometrial thickness and histopathology, and local and systemic adverse events.

Results: Compared to baseline at month 6, the three treatment schemes significantly decreased the rate of urogenital atrophy symptoms and the frequency (mean number per day) and severity (mean number graded as moderate and severe per month) of hot flushes. No differences in studied efficacy parameters were observed between studied groups at baseline or at the end of the study. For all groups the most frequent adverse event was pain at the injection site; however they were all rated as mild. At the end of the study peri- and postmenopausal women displayed no significant changes in endometrial thickness or histopathology in all treated groups. The rate of amenorrhea at the end of the study decreased for all studied groups yet was less evident among postmenopausal women as compared to perimenopausal ones.

Conclusions: The three low-dose continuous sequential intramuscular monthly treatments of E/P using novel microsphere technology were effective at reducing menopausal symptoms at short-term with a low rate of adverse events. More long-term and comparative research is warranted to support our positive findings.

Keywords

Hormonal therapy, injectable estradiol, menopause, microspheres, progesterone, vasomotor symptoms

History

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Introduction

More than a decade has passed since the first publication of the results of the Women's Health Initiative (WHI) study that reported a negative cost–benefit ratio and several clinical adverse events with a specific oral hormone therapy (HT) regimen (0.625 mg of conjugated equine estrogens (CEEs) + 2.5 mg of medroxyprogesterone acetate (MPA)) [1]. Despite this, to-date, HT is still the most effective option for the relief of vasomotor and other symptoms related to the menopause [2]. Moreover, current consensus highly recommends the use of lower dosages and the non-oral route for the control of these symptoms [3].

An important goal for HT is to provide clinical efficacy with the lowest possible risk for women [4]; aim that has been evidenced in multiple clinical studies, meta-analyses [5] and a wide variety of hormone presentations offered on the market [6]. A low dose of transdermal estrogen releases 25 μg of 17β-estradiol (E) daily, whereas an ultra-low dose releases 14 μg per day. Low-dose treatments reduce hot flushes between 60% and 70%, whereas with standard dosages this efficacy increases to 80–90% [7]. Despite this, in general, low doses will confer more

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benefits than risks when compared to standard HT doses [8]; hence research regarding HT at low dosages is still an ongoing challenge.

Recently, a new technology called ''*Stable Shaped Particles of Crystalline Organic Compounds*'' was developed for the controlled release of parental products (TechSphere®, Patent Nº US 6,287,693). This technology consists of the creation of non-polymeric crystalline structures in the form of microspheres that use cholesterol as a carrier instead of polymers. Cholesterol has the advantage of being an FDA approved ingredient for the manufacturing of drugs and is of endogenous origin, therefore providing better biocompatibility than polymers. This non-polymeric microsphere technology was used to develop a first of its kind parental HT product for the management of menopausal symptoms. This novel product would contain E microspheres (using cholesterol as carrier) and natural progesterone (P) microspheres (without cholesterol) all in an aqueous suspension, which would allow: (a) an extended E release for 30 days and P for 10–14 days (continuous sequential scheme) while maintaining plasmatic therapeutical concentrations. Estradiol dosages would be up to 30 times lower than those provided by the oral and transdermal route (b) fulfilling current recommendations regarding the use of a low-dose E (0.5–1 mg per month) and the non-oral route (intramuscular [IM]) and (c) incorporating natural P to the parental formulation, hence provide endometrial protection while avoiding the adverse effects of synthetic progestins [9].

The aim of the present research was to analyze the short-term efficacy and safety over menopausal symptoms of three low-dose continuous sequential E/P parental monthly formulations using novel non-polymeric microspheres.

Methods

Study design

This was a multicenter randomized, single-blinded clinical trial with an 8-month follow-up period carried out at five primary care clinics in Mexico City affiliated to the Institute of Social Security for Government Employees (ISSSTE) and in one clinical research unit in Pachuca, near Mexico City. The Institutional Review Board of ISSSTE and the Federal Regulatory Office of the Ministry of Health reviewed and approved the research protocol. The study was conducted according to the provisions of the Declaration of Helsinki and its amendments; hence all women received a thorough explanation about the study before providing signed consent.

Study population

The present study included peri- and postmenopausal women aged 40–65 years with at least three hot flushes per day or 21 per week at baseline. Participants were allocated to randomly receive for six months (every 30 ± 3 days) an IM application of one of the following three continuous sequential schemes for the management of menopausal symptoms: 0.5 mg E + 15 mg P (Group A), 1 mg E + 20 mg P (Group B) and 1 mg E + 30 mg P (Group C). This document reports the outcomes (efficacy and safety) of these three treatments. Perimenopausal women were defined as those having irregular menses or less than 12 menstruations in the last 12 months; and postmenopausal women defined as those having no menses in the last 12 months in addition to a FSH of >40 mIU/mL [10].

All recruited women were otherwise healthy. This was based on background clinical history, general clinical evaluation (including gynecological examination), clinical laboratory parameters, a normal abdominal pelvic ultrasound and mammography and a body mass index (BMI) ± 20% of the ideal range. Participants should not have been administered any type of HT in the previous 90 days. Exclusion criteria were having a chronic condition (diabetes or hypertension), refusal to participate, a history of endometrial hyperplasia or endometrial cancer, hypersensitivity to sex steroids and personal or family history of breast cancer. The appearance of adverse events and/or if participant took a drug that interacted with the treatments being tested were considered as criteria for treatment discontinuation.

The sample size was estimated using a formula for clinical trials with binary outcomes [11]. The assumptions of the hypothesis were that the number of hot flushes would decrease by ≥40% after 4 weeks of exposure to any of the three treatments under study ($P_{\text{endline}} = 0.6$, $P_{\text{baseline}} = 1.0$; $\alpha = 0.05$, $\beta = 0.2$). Treatment safety was expected to be similar among them. The required sample size was 27 participants in each treatment.

Recruitment process

Figure 1 presents the CONSORT Diagram [12] displaying the process of participant recruitment of this study. A total of 214 women were assessed for eligibility of which 111 did not meet the inclusion criteria. Hence, 103 subjects were included and finally randomized to one of the previously mentioned groups: A: $n = 38$; B: $n = 29$ and C: $n = 36$. Four participants of group A discontinued treatment (personal reasons, $n = 3$; adverse event, $n = 1$); five in group B (personal reasons, $n = 4$; adverse event, $n = 1$) and 10 in group C (personal reasons, $n = 4$; adverse events, $n = 6$). This left 84 subjects who completed the 6 months of treatment administration and follow-up (A = 34, B = 24, C = 26).

The research-coordinating center randomly allocated sets of the three treatments to each participating clinic. Treatment sequence was concealed at the study sites according to the list generated at the coordinating center.

Study endpoints

The primary efficacy endpoint was the effect over hot flushes in terms of frequency (decrease of the daily number) and intensity (changes in the total number of moderate and severe hot flashes per month). The secondary efficacy endpoint was the decrease of urogenital atrophy symptoms, such as dysuria, dyspareunia, vaginal atrophy, vaginal dryness and post-coital vaginal bleeding.

Safety variables

The safety variables included changes in the rate of baseline amenorrhea (bleeding and spotting profiles), local and systemic tolerability to the drugs and changes in endometrial thickness and histopathology. Changes in the rate of amenorrhea were evaluated according to the menopausal stage of the participant (peri- and postmenopausal). Local tolerability refers to the appearance of local symptoms or signs, such as pain, edema, skin lesions or color changes at the injection site. Systemic tolerability aimed at identifying whether the adverse events were or were not related to the drug under study.

Follow-up of participants

All participants received treatment for six months and were followed-up for eight months since baseline. Laboratory exams and gynecological examinations were performed only at baseline and at the end of the study (visit six). During each monthly visit, a pregnancy test was performed among perimenopausal women. To ensure compliance each month (for six months) a nurse administered the corresponding treatment. All laboratory tests were processed and interpreted in a certified laboratory. Likewise a certified blinded pathologist examined endometrial biopsies.

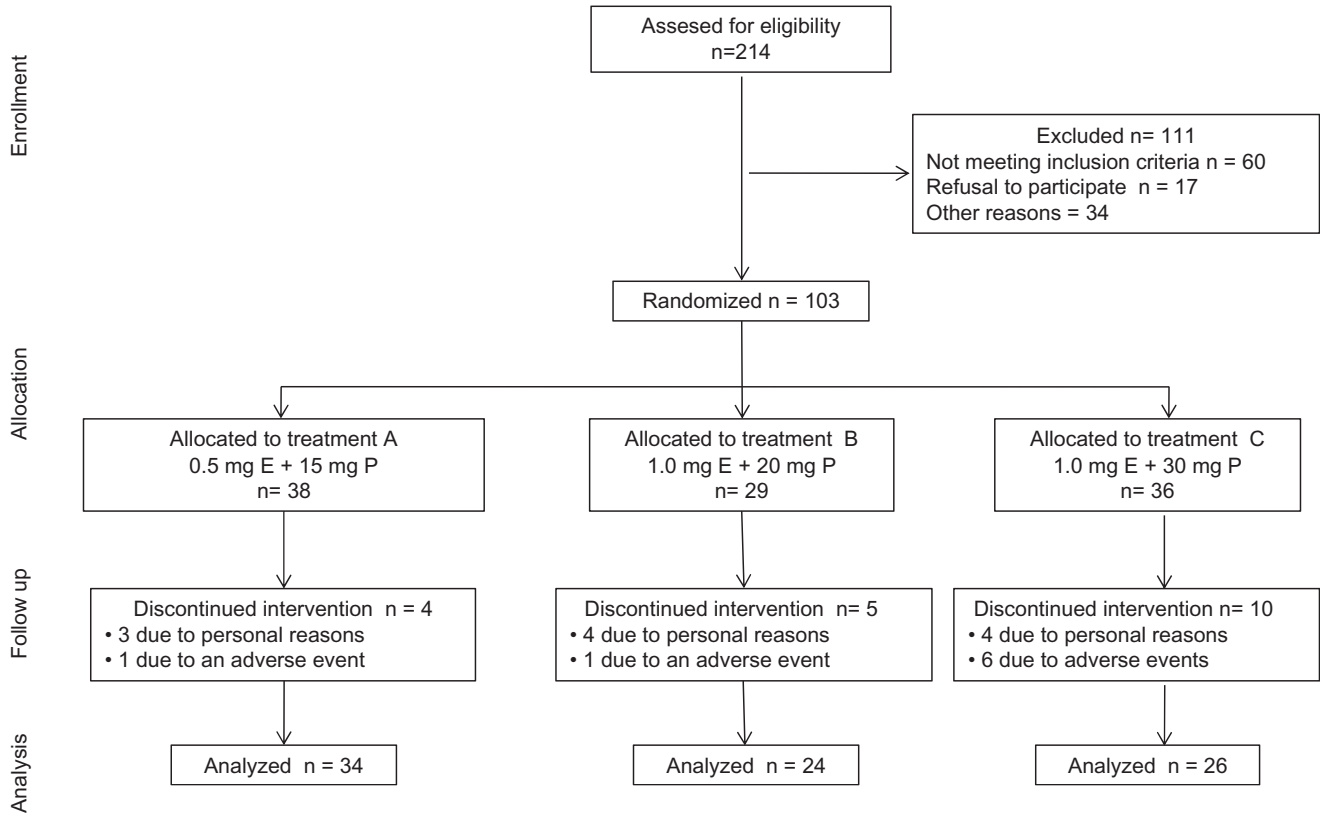

Figure 1. CONSORT Diagram displaying the process of participant recruitment of the study.

Assessment of menopausal symptoms

Hot flushes

Women consenting participation and fulfilling inclusion criteria were provided with a diary in order to register for one month the number and intensity of hot flushes per day. This was considered the baseline determination after which women received the first assigned treatment. Subsequently at each monthly visit she was provided with a new diary which was analyzed by the researcher in the next visit. Hot flush frequency was assessed each month and registered as the mean daily number. Hot flush severity was assessed at baseline and at three and six months and registered as the total number of moderate or severe hot flushes registered during each assessment period.

Symptoms of urogenital atrophy

The following symptoms were assessed at baseline and at three and six months: vaginal dryness, vaginal atrophy, dysuria, dyspareunia and post-coital vaginal bleeding.

Endometrial evaluation

Endometrial changes were evaluated through endometrial biopsies and vaginal ultrasound (endometrial thickness) performed at baseline and at the sixth month. Endometrial hyperplasia was classified according to the International Society of Gynecologic Pathologists [13].

Statistical analysis

Data analysis was performed using the Statistical Package for the Social Sciences version 20.0 (IBM SPSS®, Armonk, NY). Data are presented as mean ± standard deviations, medians (intervals), frequencies and percentages. The Kolmogorov–Smirnov test was used to determine the normality of data distribution. According to this, comparison of continuous data within groups was performed with paired Student's *t*-test and between groups with the Mann–Whitney test. Comparison of percentages was performed with the chi-square test. A p value <0.05 was considered as statistically significant.

Results

Baseline demographic characteristics and reproductive history were similar between studied groups ($p>0.05$) (Table 1). Median age of all participants ranged from 47 to 49 years (interval 38–62). Peri- and postmenopausal women were evenly distributed among the three studied groups ($p>0.05$).

Efficacy

Changes in the mean daily number of hot flushes are presented in Figure 2. Compared to baseline, all treatment groups displayed a significant decrease ($p<0.01$) in the mean daily number of hot flushes at the third and sixth month of follow-up. For all treatment groups, the daily number of hot flushes ranged from 5 to 7 at baseline, from 0.7 to 1.6 at month three and from 0.5 (one every other day) to one per day at month six. No statistically significant differences were observed at each time interval between groups ($p>0.05$).

Assessment of the severity of hot flushes, symptoms of urogenital atrophy and endometrial thickness per treatment group at proposed timelines are presented in Table 2. At baseline, the mean number of monthly moderate and severe hot flushes did not differ among studied groups and ranged from 150.6 to 157.5 and 23.3 to 57.3, respectively. All studied groups displayed a significant decrease at the sixth month in the mean number of monthly registered moderate and severe hot flushes with no differences determined between groups. Moderate severe hot flushes were reduced on average 87% for all groups; whereas for

Table 1. Demographic and baseline characteristics of participants.

Characteristic	Treatments: Group A $n=38$	Group B $n=29$	Group C $n=36$	p Value
Age, median (interval)	49 (38–62)	49 (40–60)	47 (41–56)	0.088
Literacy (%)				
Primary school	42.1	51.7	44.5	0.954
High school	34.2	34.4	33.3	
College	23.7	13.8	22.2	
Occupation (%)				
Employment in the formal market	36.8	41.4	50.0	0.803
Working informally	10.5	10.3	11.1	
Housewives	52.6	48.3	38.9	
Reproductive history				
Pregnancies, median (interval)	4 (1–7)	4 (1–12)	3 (1–6)	0.322
Vaginal deliveries, median (interval)	3 (1–6)	3 (1–9)	2 (1–6)	0.247
Cesarean sections, median (interval)	1.5 (1–3)	2 (1–3)	2 (1–3)	0.850
Practice sex regularly (%)	78.9	62.1	77.8	0.237
Menopause stage (%)				
Perimenopausal women	57.9	51.7	58.3	0.841
Postmenopausal women	42.1	48.3	41.7	

A: 0.5 mg E + 15 mg P; B: 1.0 mg E + 20 mg P; C: 1.0 mg E + 30 mg P.

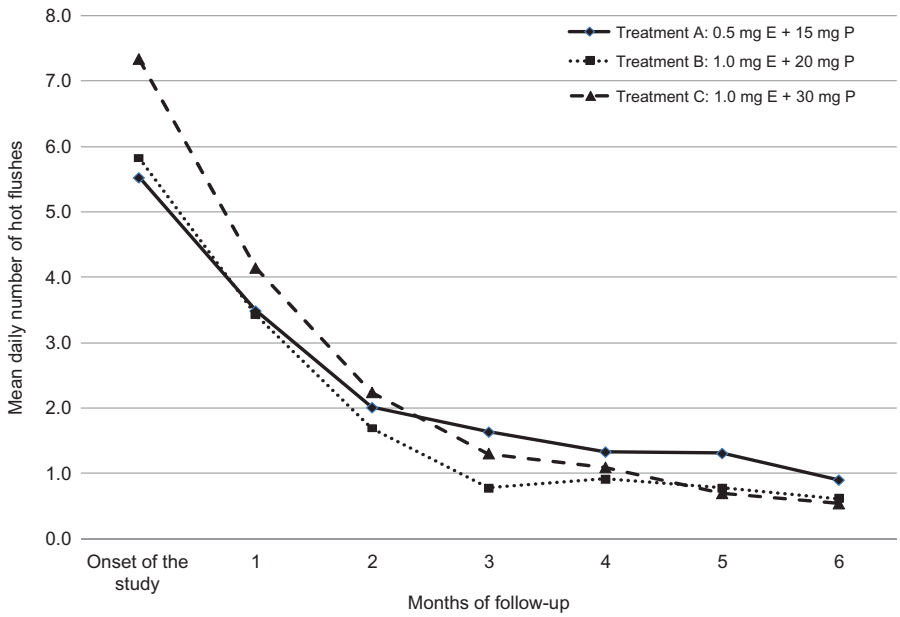

Figure 2. Changes of mean daily number of hot flushes.

severe hot flushes this reduction was 97.3% average for all studied groups.

The percentage of urogenital atrophy symptoms was similar at baseline among studied groups. Vaginal dryness was the most frequent symptom. In general, all studied groups displayed a trend toward a reduction in the percentage of symptoms at the sixth month of evaluation. As with hot flushes there were no differences between groups at month six.

Endometrial thickness among studied groups was analyzed separately for peri- and postmenopausal women. Endometrial thicknesses were similar among studied groups at baseline (for peri- and postmenopausal women); although baseline postmenopausal values were lower than perimenopausal ones. No significant differences were found in endometrial thickness at month six among studied groups (for peri- and also postmenopausal women). Endometrial thickness for postmenopausal women of all studied groups was <5 mm at both baseline and at final evaluation (Table 2).

Safety

Frequency of adverse events among studied groups is displayed in Table 3. Pain at the injection site was most commonly reported for all studied groups (A = 18.4%, B = 24.1%, C = 16.6%, $p > 0.05$); however this pain was considered for all women as mild. Participants receiving treatment A reported mastalgia and myalgias in 2.6%. Those receiving treatment C reported myalgias, nervousness and induration of the injection site in 2.8%.

The percentage of amenorrhea among studied groups throughout the 6-month period is presented in Figure 3 (A for peri- and B for postmenopausal women). At the end of the study period, perimenopausal women of all the groups displayed a lower rate of amenorrhea as compared to baseline (mean 38.7% decrease for all studied groups). All postmenopausal women were in amenorrhea at baseline and at the end of the study a decrease was observed for all studied groups. However, this decrease was less evident as compared to the decrease observed for perimenopausal women.

Table 2. Assessment of the severity of hot flashes, symptoms of urogenital atrophy and endometrial thickness per treatment group at proposed timelines.

	Treatments											
	Group A				Group B				Group C			
Symptoms	Baseline $n=38$	Interim $n=37$	Final $n=34$	*p value	Baseline $n=29$	Interim $n=25$	Final $n=24$	p Value	Baseline $n=36$	Interim $n=29$	Final $n=26$	p Value
Severity of hot flashes												
Moderate												
Total number per month	150.6 ± 108.8	43.6 ± 25.9	25.9 ± 41.2	0.000	153.6 ± 203	23.0 ± 24.3	17.7 ± 39.9	0.000	157.5 ± 189.5	38.9 ± 43.3	16.1 ± 24.1	0.000
Severe												
Total number per month	23.3 ± 50.3	4.7 ± 12.2	1.2 ± 4.1	0.001	31.4 ± 62.8	0.7 ± 3.6	0.9 ± 3.7	0.000	57.3 ± 107.1	2.4 ± 8.7	0.1 ± 0.4	0.000
Urogenital atrophy symptoms												
Vaginal dryness (%)	50.0	24.3	17.6	0.001	58.6	12.0	8.3	0.000	36.1	31.0	23.1	0.407
Vaginal atrophy (%)	42.1	24.3	14.7	0.035	37.9	16.0	4.2	0.006	30.6	13.8	15.4	0.007
Dysuria (%)	28.9	2.7	2.9	0.002	10.3	4.0	0.0	0.097	19.4	10.3	0.0	0.042
Dyspareunia (%)	18.4	5.4	2.9	0.074	17.2	4.0	0.0	0.015	8.3	0.0	3.8	0.368
Post-coital vaginal bleeding (%)	2.6	2.7	0.0	0.368	6.9	0.0	0.0	0.135	5.6	0.0	0.0	0.368

	Group A			Group B			Group C		
Endometrial thickness (mm)	Baseline	Final	p value	Baseline	Final	p value	Baseline	Final	p value
Perimenopausal women	6.72 ± 3.74 ($n=22$)	5.25 ± 3.99 ($n=19$)	0.261	6.64 ± 4.51 ($n=15$)	6.83 ± 6.17 ($n=14$)	0.93	5.98 ± 3.09 ($n=21$)	6.06 ± 3.97 ($n=15$)	0.94
Postmenopausal women	4.02 ± 2.09 ($n=16$)	5.22 ± 5.95 ($n=15$)	0.518	3.92 ± 1.62 ($n=14$)	3.90 ± 2.87 ($n=10$)	0.988	4.18 ± 1.32 ($n=15$)	3.16 ± 1.31 ($n=11$)	0.053

A: 0.5 mg E + 15 mg P; B: 1.0 mg E + 20 mg P; C: 1.0 mg E + 30 mg P. Data are presented as mean ± standard deviations (SD) or percentages (%); evaluation stages: Baseline (at enrollment), interim (third month of follow-up), final (sixth month of follow-up).

*p value obtained when comparing final with baseline; endometrial thickness was assessed at baseline and at the sixth month.

Table 3. Frequency of adverse events per type of treatment.

Signs and symptoms		Treatment A $n=38$ %	Treatment B $n=29$ %	Treatment C $n=36$ %
General symptoms	Headache	–	–	–
Cardiovascular	Palpitation	–	–	–
	Tachycardia	–	–	–
Digestive	Nausea	–	–	–
Musculoskeletal	Arthralgia	–	–	–
	Myalgias	2.6	–	2.8
Nervous	Depression	–	–	–
	Dizziness	–	–	–
	Nervousness	–	–	2.8
Local symptoms	Pain	18.4	24.1	16.6
	Induration	–	–	2.8
	Edema	–	–	–
Special senses	Blurred vision	–	–	–
Urogenital	Increase of endometrial thickness	2.6	–	–
	Pelvic inflammation	–	–	–
	Mastalgia	2.6	–	–

A: 0.5 mg E + 15 mg P; B: 1.0 mg E + 20 mg P; C: 1.0 mg E + 30 mg P.

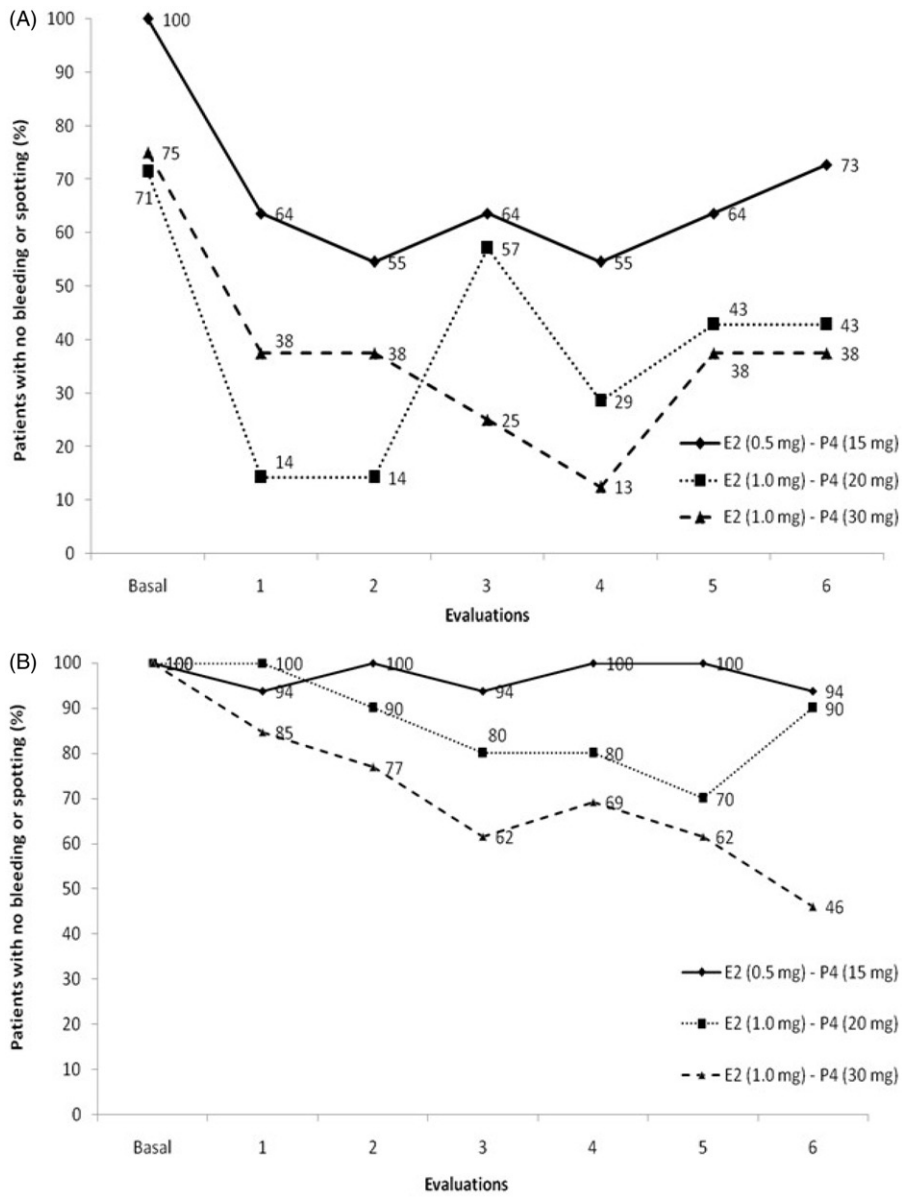

Figure 3. Percentage of amenorrhea during the follow-up among perimenopausal (A) and postmenopausal women (B).

Among postmenopausal women, rate of amenorrhea was lower in group C (46%) as compared to groups A (94%) and B (90%). Participants of all studied groups presented normal endometrial biopsies at baseline with no changes (cancer or hyperplasia) found at the end of study. Equally all mammographic evaluations were normal at baseline and after treatment.

Discussion

The present study found that the three proposed continuous sequential treatment schemes using E and P non-polymeric microspheres were able to effectively reduce menopausal symptoms: hot flushes and symptoms of urogenital atrophy. At week 4 of treatment there was an overall 40% reduction of symptoms; rate that continued to decline at months 3 and 6. Regarding adverse events, all treatment schemes had acceptable local and systemic tolerability.

The aforementioned positive results, although short-term, seem to support the use of E and P non-polymeric microspheres for IM administration. Although this novel form of administration seems interesting, more long-term data are required. Nevertheless, our data may provide the basis to support a safe and innovative way of delivering drugs for the long-term treatment of menopausal symptoms. In this sense, the multiplicity of clinical high risk conditions requiring treatment added to current risk-benefit concerns for HT use have created a complex scenario that urge the need to explore new drug delivery presentations and administration routes. Bearing this in mind transdermal E was created [14]. Our novel microsphere E/P presentation seems to follow the same principle.

Current recommendations are to continue carrying out clinical trials to test the efficacy and safety of low and ultra-low dose HT schemes [15]. The observed efficacy for our microsphere proposed schemes (84–93% reduction in the number of daily hot flushes at month six) is comparable to the efficacy of the standard dose of oral 0.625 mg of CEE that reaches 80–90% reduction [16,17]. Previous studies have reported that low-dose treatments reduce the risk of endometrial hyperplasia [18] and the rate of side effects, such as bleeding [19]. Our study found that the mean endometrial thickness of postmenopausal women at baseline and final evaluation was <5 mm. Endometrial biopsies did not report endometrial hyperplasia and there were no cases of spotting. This finding suggests that the use of microspheres may be safe as it does not induce hyperplasia; however, this result should be interpreted with caution because this study was a short-term safety evaluation.

The inclusion of natural P was taken into account to provide endometrial protection and better effects over vessels and the brain than the use of synthetic progestins. As an added value, the monthly dose of P used in our study is lower than the one provided by oral micronized P. Indeed, P has poor oral bioavailability and presentations currently available on the market require high doses to achieve adequate plasma concentrations. Using a lower monthly dose could help to reduce the appearance of progesterone-related side effects.

Finally, our study has strengths and weaknesses. The use of microspheres that provides a monthly continuous delivery of a low E dose and natural P is indeed a potential strength. Our preliminary data contribute at exploring suitable and innovative low-dose alternatives that can minimize HT-related risks [20]. Prevalence of overweight/obesity is increasing in the world and is considered a problem in aging women [21]. Moreover, an important proportion of women still present hot flushes 5 years after menopause onset and related to impaired quality of life. These women definitely need to be treated [22]. Symptomatic high risk women could be a potential target for treatment using our novel low dose presentation. In this sense, it has been reported that low-dose HT may in fact help to reduce many of the parameters of the metabolic syndrome [23].

Not comparing with another hormonal route and the short-term follow-up period are potential weaknesses of our study. It is recommended that studies evaluating safety should complete follow-up at least 12 months and endometrial hyperplasia should not exceed a 1% [24]. Our initiative aimed at testing the efficacy and adverse events of E/P microspheres at different doses in order to gather evidence that would help to define optimal doses for the monthly administration of the microspheres. The efficacy of E and P is already well known, but the optimal and innovative form of administration is not. Thus, our results are useful for the designing of a randomized clinical trial where the microspheres would be compared with a product having similar pharmacokinetic characteristics, such as transdermal patches.

To the best of our knowledge reports using this form of novel hormonal delivery is lacking in the literature; however a longer period of follow-up is warranted. Despite this, our preliminary data have an interesting potential and require more investigation.

In conclusion, the three low-dose continuous sequential intramuscular monthly E/P treatments using novel microsphere technology were effective at reducing menopausal symptoms at short-term with a low rate of adverse events. More long-term and comparative research is warranted to support our positive findings.

Acknowledgements

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Declaration of interest

The authors declare no conflicts of interest.

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