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Efficacy of Low-Dose (0.3 mg) Conjugated Estrogen Cream for Managing Atrophic Vaginitis

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ABSTRACT

Objectives: To evaluate efficacy and safety of low-dose conjugated estrogen cream (0.3 mg) for treatment of atrophic vaginitis in postmenopausal women.

Methods and Methods: A double-blind, placebo-controlled, randomized trial was conducted during November 2012 and September 2013, involving 73 postmenopausal women with symptomatic atrophic vaginitis and vaginal maturation index (VMI) ≤ 55. Participants were randomly assigned to receive conjugated estrogen cream 0.3 mg or placebo twice a week for 12 weeks. The primary outcome was the change in the mean of VMI from baseline. Endometrial thickness was assessed by transvaginal sonography.

Results: 73 women were randomized into two group: 36 women in study group and 37 women in control group. All participants were completely follow up. Mean change of VMI in intervention group was significant higher than placebo group (34.5 ± 19.7 versus -0.6 ± 14.4, p<0.001). The mean change of VMI at 4 weeks was significantly higher in study group (21.2 ± 18.9 versus 1.3 ± 12.6, < 0.001). A significant greater reduction from baseline in vaginal pH at 12 weeks was shown in study group (-1.4 ± 1.0 versus -0.1 ± 0.9, p<0.001).

Conclusions: Low-dose estrogen cream was superior to placebo in the mean change of VMI, decrease in vaginal pH and improved vaginal symptoms after 12 weeks of administration without increasing of endometrial thickness.

Keywords: conjugated estrogens cream, atrophic vaginitis, postmenopausal, vaginal maturation index

Introduction

Menopause is the period of life after complete cessation of ovarian function[1]. Estrogen-deficient environment leads to clinically relevant changes in the vagina, cervix, urethra, and bladder. Approximately 10% to 40% of postmenopausal women will experience symptoms related to urogenital atrophy, but only 20% to 25% of symptomatic women seek medical help, despite the availability of safe and effective options to treat vaginal and urological symptoms related to estrogen deficiency[2].

To improve the vaginal atrophic symptoms and

to reverse atrophic anatomic changes, conjugated estrogens (Premarin vaginal cream) 0.5-2.0 g/d (0.625 mg active ingredient/g) was suggested[3]. Estrogen cream applied vaginally can be administered with dose high enough to relieve vasomotor symptoms and are effective in producing vaginal maturation[2]. Additionally, The previous studies reported low dose of conjugated estrogen 0.3 mg can relief symptom of vaginal atrophy in menopausal woman better than placebo[2-7].

Sexual activity is an important factor to maintain a healthy vaginal epithelium[8-10]. Chompootweep S et al., reported that the most striking effect of menopause was a dramatic loss of sexual desire in 86.9% of Thai postmenopausal women who living in Bangkok area[11]. In the same way the study in Khon Kaen province showed 85.4% and 88.5% of the subjects had either less or absent sexual desire and less sexual activity, respectively[12]. A multinational survey reported the reasons for seeking treatment in Asian menopausal are higher than Europeans, which indicated reduce sex drive and vaginal pain (17%, 13% versus 7%, 8%)[13]. Peeyananjarassri K, et al.[14], reveal higher reporting of vaginal dryness in Thai menopausal women 55.3% compare to European population (29%)[13].

The aim of our study was to know the efficacy of low dose estrogen cream compared to placebo in our population with more atrophic vaginal symptoms than the western world. We hypothesized that low dose estrogen cream could improve the mean change of VMI, vaginal pH, and vaginal symptoms.

Materials and Methods

This was a double-blind, randomized, placebo-controlled study. The study was performed between November 2012 and September 2013 at the Khon Kaen Hospital, Khon Kaen, Thailand. The protocol was approved by the Khon Kaen Hospital Ethics Committee. All women gave written, informed consent. Subjects were healthy 45-60 years old postmenopausal women, both surgical and natural menopause (natural menopause was defined as the women who had cessation of mense for at least 1 year. Surgical menopause was defined as menopause after bilateral oophorectomy with or without hysterectomy), Eligible patients also had to have a VMI (vaginal maturation index) ≤ 55 at screening, with symptomatic atrophic vaginitis and vaginal examination confirmed postmenopausal status (pallor, dryness, and diminished rugosity of the vaginal mucosa). The subjects were excluded from this study if they had an existing or suspected estrogen-dependent neoplastic diseases or breast cancer, vaginal bleeding of unknown origin, hypersensitivity to study medication, previous hormonal treatment within 6 months, a current diagnosis of vaginal infection.

Participants were randomly assigned to one of two treatment regimens: conjugated estrogen 0.3 mg cream or placebo cream applied twice weekly for a 12 weeks period after screened at first visit and 2 weeks later. Placebo in our study is the lubricating cream base which is pharmaceutical preparation of Department of Phamacy, Khon Kaen Hospital. Subjects and all medical personnel were blinded to study treatment assignment. During the treatment period, all of the patients were scheduled visits on 4 and 12 weeks. A lateral wall smear to calculate the vaginal pH (using standardized pH paper) and vaginal maturation index (VMI scored under light microscopy by the cytopathologist who was blinded with our treatment) were obtained at each visit. Vaginal maturation index was calculated using the following formula:

$$VMI = (\%\ \text{Intermediate Cells} \times 0.5) + \%\ \text{Superficial Cells}$$

Safety and tolerability was assessed by physical examinations (general, including breast and pelvic examinations) at screening and follow up visit. A transvaginal ultrasound was performed at the baseline and 12 weeks visits in the case who remained had a uterus. Compliance assessment was performed on each visit in all subjects.

The change of baseline in VMI and vaginal pH from baseline were collected. The sample size was calculated by using results from a previous Study[3]. A 5% level of significance and a power of 80%. A sample size of 29 women per group was required. Considering a 10% drop-out rate, 33 women per group, was recruited.

RESULTS

The baseline characteristics were presents in Table 1. Total 92 postmenopausal women were screened, and 73 women were eligible to the study. These 73 women were randomized into two groups: 36 women in study group and 37 women in control group. All participants had completed follow up.

The study and the control groups were not statistically significant, (Table 1) with mean age 54.3 ± 3.2 years and 53 ± 3.3 years (p = 0.96), median duration time of menopause was 60 (12-168) and 36 (3-192) months (p = 0.13), respectively. The number of hysterectomized women in both groups were not significant difference (47% versus 38%,). Most of them were housewives (63%), undergraduate (84.9%), and no underlying disease (75.3%). Most of them (61.6%) had sexual activity less than once a week. Almost 40% of women were hysterectomized with bilateral salpingo-oophorectomy (TAH with BSO). The study group had more improve in VMI from baseline than the control group (34.5 ± 19.7 versus -0.6 ± 14.4, p<0.001). The mean change of VMI from baseline at 4 weeks was significantly higher in study group (21.2 ± 18.9 versus 1.3 ± 12.6, < 0.001). A significant greater reduction from baseline in vaginal pH at 12 weeks was shown in study group (-1.4 ± 1.0 versus -0.1 ± 0.9, p<0.001).

At baseline, the atrophic vaginitis symptoms those disturbed the participants were comparable in both groups, there were 53 (70.7%) vaginal dryness, 62 (82.7%) dysparunia, 37 (49.3%) vaginal soreness and 34 (45.3%) pruritus. The predominant vaginal symptoms at screening were vaginal dryness and dyspareunia, and our prevalence of vaginal dryness reporting was higher than findings from previous study[14]. A significantly decrease of dyspareunia at 12 weeks in study group (86.1% to 19.4%, p=0.001) (Table 3).

Abnormal pap smear was reported in five participants in study group during follow up period (ASCUS:5), all of them had normal colposcopic findings and returned to normal after 4 and 12 weeks of follow up. After completion of the 12 weeks treatment period, there were no significantly increase of endometrial thickness in both groups. No serious adverse event was reported in all women.

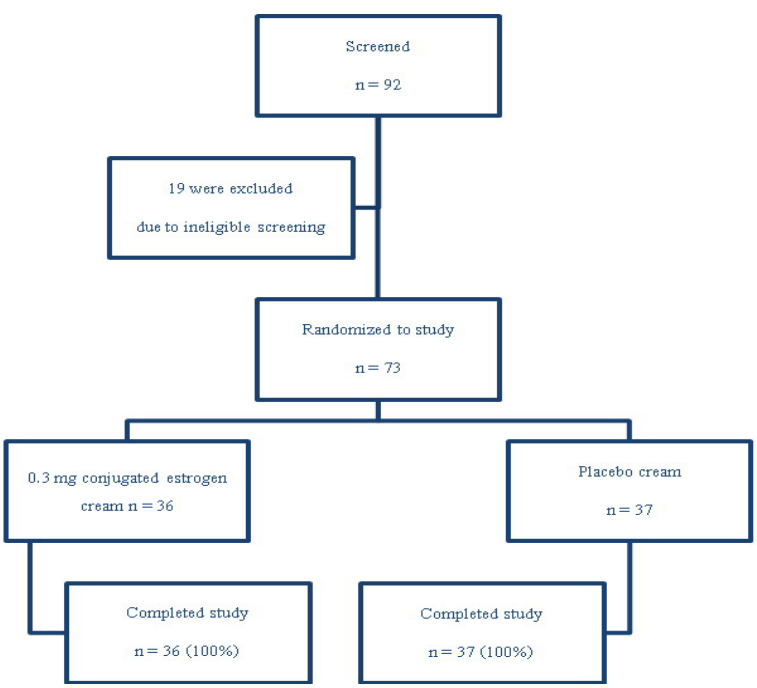

Fig. 1. Participants flow

Table 1. Baseline characteristics.

Characteristrics	0.3 mg CE cream (n=36)	Placebo (n=37)	p
Age -y, mean (SD)	54.3 (3.2)	53.0 (3.3)	0.96
Menopause - month, median (interquartile range)	60 (12-168)	36 (3-192)	0.13
BMI -kg/m^2,mean (SD)	24.5 (3.2)	24.0 (2.8)	0.46
Weight -kg, mean (SD)	57.6 (6.8)	58.5 (7.8)	0.60
Height -cm, mean (SD)	153.6 (5.2)	156.0 (5.9)	0.07
Uterus present -n (%)	153.6 (5.2)	156.0 (5.9)	0.07
Uterus present -n (%)	19 (52.8%)	23.0 (62.2%)	0.86
Systolic blood pressure - mmHg, mean (SD)	118.7 (17.4)	121.2 (13.4)	0.49
Diastolic blood pressure - mmHg, mean (SD)	71.6 (12.2)	74 (10.4)	0.39
MAP – mmHg, mean (SD)	86.5 (11.9)	89.7 (10.1)	0.21
Sexual activity - n (%)			
• no	14 (38.9%)	12 (32.4%)	0.85
• < 1 times / week	21 (58.3%)	24 (64.9%)	0.84
• 1-3 times / week	1 (2.8%)	1 (2.7%)	0.93
Occupations – n (%)			
• Employee	5 (13.9%)	3 (8.1%)	0.63
• Housewife	23 (63.9%)	23 (66.2%)	0.61
• Agriculturist	3 (8.3%)	4 (10.8%)	0.88
• Government officer	4 (11.1%)	3 (8.1%)	0.91
• Freelance	1 (2.8%)	4 (10.8%)	0.52
Educations – n (%)			
• none	1 (2.3%)	1 (2.7%)	0.95
• under graduate	31 (86.1%)	31 (83.8%)	0.94
• bachelor degree	4 (11.1%)	5 (13.5%)	0.78
history of gynecological surgery, n (%)			
• none	19 (52.8%)	23 (62.2%)	0.80
• TAH	1 (2.8%)	1 (2.7%)	0.86
• TAH + BSO	16 (44.4%)	13 (35.1%)	0.63
Underlying diseases, n (%)			
• none	26 (72.2%)	35 (94.6%)	0.23
• DM	3 (8.3%)	2 (5.4%)	0.18
• HT	7 (19.4%)	0	0.53

BMI=body mass index; MAP=Mean arterial pressure; TAH= total abdominal hysterectomy;
BSO= bilateral salpingo oophorectomy; DM= diabetes mellitus; HT= hypertension

Table 2. Vaginal maturation index (VMI) and vaginal pH changes.

parameters	Study week	0.3mg CE cream (n = 36) Mean ± SD	Placebo (n = 37) Mean ± SD	p
VMI (%)	• Screening	25.1 ± 16.9	30.4 ± 16.5	0.185
	• 4 weeks	46.3 ± 19.4	29.0 ± 17.7	<0.001
	• 12 weeks	59.6 ± 16.9	29.8 ± 18.8	<0.001
Vaginal pH	• Screening	7.2 ± 0.6	7.0 ± 0.9	0.406
	• 4 weeks	6.2 ± 1.2	6.6 ± 0.8	0.051
	• 12 weeks	5.8 ± 1.0	7.0 ± 0.8	<0.001

Table 3. Vaginal symptoms.

symptoms	Study week	0.3mg CE cream (n = 36) n (%)	Placebo (n = 37) n (%)	p
Vaginal dryness	• Screening	26 (72.2)	27 (73.0)	
	• 12 weeks	8 (22.2)	22 (59.5)	0.06
Dyspareunia	• Screening	31 (86.1)	31 (83.8)	
	• 12 weeks	7 (19.4)	22 (59.5)	0.001
Vaginal soreness	• Screening	19 (52.8)	18 (48.6)	
	• 12 weeks	11 (30.6)	25 (67.6)	0.10
Pruritus	• Screening	15 (41.7)	19 (51.4)	
	• 12 weeks	13 (36.1)	11 (29.7)	0.81

Table 4: Endometrial thickness by transvaginal sonography at screening and 12 weeks.

Endometrial thickness	Screening-mm, mean ± SD	12 weeks-mm, mean ± SD	Mean change-mm, mean ± SD	p
0.3 mg conjugated estrogen cream (n = 19)	2.17 ± 0.5	2.12 ± 0.5	-0.05 ± 0.5	0.23
Placebo (n = 23)	2.36 ± 0.5	2.48 ± 0.8	0.13 ± 0.7	0.40

DISCUSSION

Vaginal symptoms are usually found in postmenopausal women such as vaginal dryness, dyspareunia, vaginal soreness and pruritus, especially vaginal dryness which higher when compare with previous reported in European survey (70.7% versus 29%)[13]. To relief these symptoms, vaginal estrogen formulations (cream, tablet and ring) are widely used. (2) Thai women preferred vaginal estrogen cream rather than vaginal tablet or ring[15], therefore, vaginal estrogen cream was commonly prescribed by gynecologists. The dosage of vaginal estrogen cream was studied and found that low dose vaginal estrogen cream showed improvement in VMI and vaginal symptoms[16-18]. The results of the current study shown that low dose estrogen cream was superior to placebo in mean change of VMI at 4 and 12 weeks, vaginal pH and vaginal symptoms at the end of treatment. These findings were compatible with Bachmann et al[4]. The proportion of women who had vaginal dryness, dyspareunia, vaginal soreness and puritus were significantly decrease after 12 weeks of vaginal estrogen cream application. Estrogen is known to has an effect on integrity of the vaginal wall[10,19]. Improvement of vaginal symptoms was not surprisingly improve their sexual life. In our study, we found that 24 of 31 women in study group who suffered from dyspareunia at screening period have got better after treatment. Nevertheless, some women in placebo group get better dyspareunia symptoms but lesser proportion than study group. It might be explained by placebo effects. Sexual activity plays an important role in VMI because of increasing of vaginal elasticity and genital blood flow[8-10]. The more frequent sexual activity, the more increase in VMI. Approximately two third (61.6%) of women in this study had sexual activity less than once a week (usually once or twice a month). However, mean VMI change was also observed despite infrequent sexual activity. In cases of vaginal soreness and puritus, we found that study group had more reduction in these symptoms than placebo but with lesser proportion. There were as high as 20% of placebo group those vaginal soreness were worsen. Moisturizing and lubrication effects of estrogen cream might have an impact on vaginal moisture. A meta analysis of estrogen therapy reported that estrogen therapy was efficacious in treatment of vaginal atrophy when compared to placebo[20]. Vaginal pH in study group was more significantly decrease than in placebo group which was consistent to Marx et al[5]. Estrogen level in blood circulation maintain the glycogen content of epithelial cell, which stimulate the production of lactic acid by lactobacilli. Normal vaginal pH is helpful in protecting vaginal mucosa against infection, especially urogenital infection[21].

One of the benefit of estrogen cream is to elucidate the diagnosis of abnormal Pap smear, particularly in equivocal Pap smear (ASCUS). Because cytologic feature of atrophy may include nuclear enlargement, hyperchromasia, abnormalities of the nuclear envelope or chromatin distribution, pleomorphism, and keratinized cytoplasm which could be diagnosed as ASCUS. But after administration of estrogen cream, these features would be eliminated[22]. In our study, there were five women who had ASCUS cytology on screening. After four weeks of estrogen cream administration, all of these five returned normal cytology. The improvements in vaginal cytology were observed as early as four weeks after treatment[5].

All women had no adverse effect. The advantages of estrogen cream include localized effects, lower bypass first-pass hepatic effect, limits systemic exposure, and had lesser adverse effect when compared to oral estrogen. This study also evaluated endometrial thickness by vaginal sonography as a safety factor of estrogen treatment. We found no significant change in endometrial thickness in both groups. We did not performed endometrial biopsy because of it invasiveness for postmenopausal women without abnormal uterine bleeding and our study determined the effect of estrogen cream in only 12 weeks, which was too short to evaluated histologic abnormality of endometrium.

The strength of the study was randomized control trial with planned allocation concealment, adequate sample size and completely follow-up. The limitation of this study was a lack of determination of severity of

vaginal symptoms which might affect the efficacy of treatment.

Duration of action and maintenance of efficacy of estrogen cream and comparison of standard dose (0.625 mg) with low dose (0.3 mg) of conjugated estrogen cream should be taken into account for the future research.

In conclusion, low-dose estrogen cream was superior to placebo in mean change of VMI, decrease in vaginal pH and improved vaginal symptoms after 12 weeks of administration without increasing of endometrial thickness.

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ประสิทธิภาพการรักษาภาวะช่องคลอดแห้งในสตรีวัยหมดระดู ด้วยยาคอนจูเกท เอสโตรเจนครีม ขนาด 0.3 มิลลิกรัม

หนึ่งฤทัย สินนิธิถาวร, หลิงหลิง สาลัง, สมศักดิ์ ประฏิภาณวัตร

วัตถุประสงค์ *: เพื่อศึกษาประสิทธิภาพในการรักษาภาวะช่องคลอดแห้งในสตรีวัยหมดระดูของยาคอนจูเกทเอสโตรเจนครีม (conjugated estrogen cream) ขนาด 0.3 มิลลิกรัม*

รูปแบบการวิจัย *: การวิจัยเชิงทดลองแบบสุ่ม และมีกลุ่มควบคุม*

สถานที่ทำวิจัย *: คลินิกสตรีวัยหมดระดู แผนกผู้ป่วยนอก กลุ่มงานสูติศาสตร์-นรีเวชวิทยา โรงพยาบาลศูนย์ขอนแก่น*

กลุ่มตัวอย่าง *: สตรีวัยหมดระดูที่มีภาวะช่องคลอดแห้ง ที่ติดตามการรักษาคลินิกสตรีวัยหมดระดู โรงพยาบาลศูนย์ขอนแก่น*

วัสดุและวิธีการ *: สตรีวัยหมดระดูที่มีภาวะช่องคลอดแห้ง 73 คน สุ่มเป็น 2 กลุ่มโดยใช้คอมพิวเตอร์ กลุ่มทดลองจำนวน 36 คนได้รับการรักษาด้วยยาคอนจูเกท เอสโตรเจนครีม (conjugated estrogen cream) ขนาด 0.3 มิลลิกรัม และกลุ่มควบคุมจำนวน 37 คน ได้รับการรักษาด้วยครีม placebo ทาช่องคลอด 2 ครั้งต่อสัปดาห์ (วันจันทร์และพฤหัสบดี) นาน 12 สัปดาห์ โดยทำการประเมินผล ด้วยการวัดค่า vaginal maturation index (VMI) ก่อนเข้ารับการรักษาและหลังการรักษา ที่ 4 และ 12 สัปดาห์ ทั้งนี้ขณะติดตามการรักษาจะมีการวัดค่าความเป็นกรด-ด่างของช่องคลอด, ประเมินอาการช่องคลอดแห้ง, การตรวจร่างกาย, ตรวจภายใน และอัลตราซาวน์ทางช่องคลอด (วัดความหนาของเยื่อบุโพรงมดลูก) ร่วมด้วย*

ตัววัดที่สำคัญ *: ผลการศึกษาหลักของการทดลองนี้คือค่าความเปลี่ยนแปลงของ VMI โดยพยาธิแพทย์ หลังได้รับการรักษาภาวะช่องคลอดแห้ง 12 สัปดาห์ ผลการศึกษารอง ได้แก่ ค่าความเปลี่ยนแปลงของค่าความเป็นกรด-ด่างของช่องคลอด, การเปลี่ยนแปลงของอาการของภาวะช่องคลอดแห้ง เมื่อจบการศึกษา*

ผลการวิจัย *: สตรีวัยหมดระดูที่เข้าร่วมการศึกษาได้มีการติดตามการรักษาครบตลอดระยะเวลา 12 สัปดาห์ และทั้งสองกลุ่มไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติในแง่ของข้อมูลพื้นฐาน พบว่ามีค่าความเปลี่ยนแปลงของ VMIในกลุ่มทดลองมากกว่ากลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติ ที่ 4, 12 สัปดาห์ (21.2 ± 18.9 versus 1.3 ± 12.6, < 0.05, 34.5 ± 19.7 versus -0.6 ± 14.4, p<0.001) และการลดลงของค่าความเป็นกรด-ด่าง ของช่องคลอด ที่ 12 สัปดาห์ (-1.4 ± 1.0 versus -0.1 ± 0.9, p<0.001) ร่วมกับมีอาการของภาวะช่องคลอดแห้งที่ลดลงในกลุ่มทดลอง โดยเฉพาะอาการเจ็บขณะมีเพศสัมพันธ์(dyspareunia) อย่างมีนัยสำคัญทางสถิติเมื่อเปรียบเทียบกับกลุ่มควบคุม (86.1% to 19.4%, p<0.001) และไม่พบอาการข้างเคียงจากยาตลอดการทดลอง*

สรุป *: การศึกษานี้แสดงให้เห็นว่าการรักษาภาวะช่องคลอดแห้งด้วย 0.3 มิลลิกรัม conjugated estrogen cream มีประสิทธิภาพเหนือกว่าเมื่อเปรียบเทียบกับ placebo โดยวัดจากการเปลี่ยนแปลงของ VMI, ภาวะความเป็นกรด-ด่างของช่องคลอดที่ลดลง และอาการทางช่องคลอดที่ดีขึ้น โดยไม่พบว่ามีอาการข้างเคียงที่เกิดจากจากการรักษา*