

ประสิทธิภาพยาเอสโตรเจนครีมที่ผลิตขึ้นเองในการรักษาภาวะช่องคลอดแห้ง ในสตรีวัยหมดระดู การทดลองแบบสุ่ม ปกปิดทั้งสองทาง

พองผน ผลจันทร์¹, สนธยา พิริยะกิจไพบูลย์¹, ปิยวดี วุฒิกรลัมมากิจ¹

บทคัดย่อ

หลักการและเหตุผล: ช่องคลอดแห้งเป็นอาการที่พบบ่อยของสตรีวัยหมดระดู ซึ่งยาเอสโตรเจนครีมทางช่องคลอดขณะนี้ไม่มีขายในท้องตลาด การศึกษานี้ทำเพื่อศึกษาประสิทธิภาพการรักษาภาวะช่องคลอดแห้งในสตรีวัยหมดระดูด้วยยาเอสโตรเจนครีมที่ผลิตขึ้นเองขนาด 0.625 มิลลิกรัมเทียบกับกลุ่มยาหลอก

วัสดุและวิธีการทำ: การวิจัยเชิงทดลองแบบสุ่ม มีกลุ่มควบคุม ปกปิดทั้งสองทาง สตรีวัยหมดระดูที่มีอาการช่องคลอดแห้งที่มารับการรักษาแผนกผู้ป่วยนอกกลุ่มงานสูติศาสตร์-นรีเวชวิทยาโรงพยาบาลสรรพสิทธิประสงค์ จังหวัดอุบลราชธานี จำนวน 20 ราย แบ่งเป็น 2 กลุ่มกลุ่มละ 10 รายโดยวิธีสุ่ม 1) กลุ่มยาหลอก จะได้รับยาครีมซึ่งมีส่วนประกอบคือ cetyl alcohol, stearyl alcohol, spermaceti, methyl paraben, propyl paraben, glycerin, sodium lauryl sulfate และน้ำ 2) กลุ่มทดลอง ได้รับยาเอสโตรเจนครีมที่ผลิตขึ้นขนาด 0.625 มิลลิกรัมในครีมเบส 1 กรัม โดยทาช่องคลอดทุกวันเป็นเวลา 1 สัปดาห์จากนั้นทาสัปดาห์ละสองครั้งเป็นเวลาทั้งหมด 12 สัปดาห์ วัดค่าเปลี่ยนแปลงดัชนีความสมบูรณ์ของเยื่อบุช่องคลอด การเปลี่ยนแปลงอาการของภาวะช่องคลอดแห้งโดยใช้แบบสอบถามและค่าความเปลี่ยนแปลงของความเป็นกรดต่างของช่องคลอด ในวันแรกที่เข้าโครงการ สัปดาห์ที่ 4 และ 12 สัปดาห์หลังได้รับยา

ผลการศึกษา: สตรีวัยหมดระดูจำนวนทั้งหมด 20 ราย มาตามนัดตรวจติดตามครบทุกราย พบว่าดัชนีความสมบูรณ์ของเยื่อบุช่องคลอดในกลุ่มที่ได้รับยาเอสโตรเจนดีขึ้นกว่ากลุ่มยาหลอกอย่างมีนัยสำคัญหลังจากได้รับยา 4 สัปดาห์และ 12 สัปดาห์ ($p=0.045$, 0.005 ตามลำดับ) โดยค่ามัธยฐานดัชนีความสมบูรณ์ของเยื่อบุช่องคลอดในกลุ่มที่ได้รับยาเอสโตรเจนเท่ากับ 8.75, 61.50, 68.75 เมื่อเทียบกับกลุ่มยาหลอก 15.09, 27.50, 15.00 ในวันแรกที่เข้าโครงการ สัปดาห์ที่ 4 และสัปดาห์ที่ 12 หลังได้รับยาตามลำดับ ส่วนอาการแสดงของช่องคลอดแห้งความเป็นกรดต่างของช่องคลอด และความหนาของเยื่อบุโพรงมดลูกไม่แตกต่างกัน

สรุป: ยาเอสโตรเจนครีมที่ผลิตในโรงพยาบาลสรรพสิทธิประสงค์มีประสิทธิภาพในการรักษาภาวะช่องคลอดแห้งในสตรีวัยหมดระดู ทำให้ค่าดัชนีความสมบูรณ์ของเยื่อบุช่องคลอดเพิ่มขึ้น โดยไม่พบความหนาตัวของเยื่อบุโพรงมดลูกหลังได้รับยา

คำสำคัญ: ยาเอสโตรเจนครีมที่ผลิตเอง ภาวะช่องคลอดแห้งในสตรีวัยหมดระดู ดัชนีความสมบูรณ์ของเยื่อบุช่องคลอด อาการแสดงของภาวะช่องคลอดแห้ง

¹ กลุ่มงานสูตินรีเวชกรรม โรงพยาบาลสรรพสิทธิประสงค์ อุบลราชธานี

Introduction

Menopause is that point in time when permanent cessation of menstruation occurs following the loss of ovarian activity. A woman is said to have reached menopause if she has remained amenorrheic for a consecutive of 12 month interval⁽¹⁾. Thinned endometrium, increased vaginal pH level and clinical consequences are related to estrogen deficiency. Normal vaginal pH (pH 3.5–4.5) is helpful in protecting vaginal mucosa infection. Vaginal symptoms such as vaginal dryness, vaginal itching/irritation, vaginal soreness, dyspareunia, bleeding after sexual intercourse and urological symptoms may occur after menopause⁽²⁾. Atrophic vaginitis is commonly found 4-5 years after menopause⁽³⁾. Vulvovaginal atrophy (VVA) is affecting at least 50% of menopausal women and significant adverse impact on quality of life⁽⁴⁾. Vulvovaginal atrophy typically worsens in the absence of treatment.

The previous studies⁽⁵⁻⁷⁾ showed varied doses of topical conjugated estrogen cream administered were effective for the treatment of moderate to severe vulvovaginal atrophy (VVA) in symptomatic postmenopausal women for the three measures of vaginal maturation index (VMI), pH, and severity of the most bothersome symptoms (MBS). Estrogen therapy is approved for the treatment of atrophic vaginitis. Several formulations are available, including vaginal estradiol tablets and creams, and a ring. Topical conjugated estrogen vaginal cream 0.5-2.0 g/d is suggested⁽⁸⁾.

In Thailand, the previous study⁽⁹⁾ showed 0.3 mg conjugated estrogen cream applied twice a week is effective to improve VMI, vaginal pH and vaginal symptoms after 12 weeks. At present, the commonly used-commercial product containing conjugated estrogen 0.625 mg/g (Premarin™) is not available in Thailand. The author interests in generate a new in-house estrogen containing cream (0.625 mg of conjugated estrogen/ 1 gm of cream) under the supervision of Pharmaceutical Group at Sanpasitthiprasong Hospital to use instead of the original commercial cream. The objective of this study is to assess the efficacy of in-house estrogen-containing cream compared with placebo for treatment of atrophic vaginitis in postmenopausal women at Sanpasitthiprasong Hospital. We hypothesized that the in-house estrogen-containing cream could improve the change of vaginal maturation index, vaginal pH, and most bothersome symptoms (MBS) in 12 weeks after treatment without adverse effect.

Materials and Methods

A randomized, double blind, placebo-controlled trial study was conducted at the department of Obstetrics and Gynecology, Sanpasitthiprasong Hospital, Ubon Ratchathani, Thailand from July 2018 to July 2019. The protocol was approved by the Sanpasitthiprasong Hospital Ethics Committee and was registered in Thai Clinical Trial Registry website (TCTR20190309004). The study started after ethical committee approval.

Postmenopausal women aged 45-75 year-old who had at least one of five MBS of atrophic vaginitis including vaginal dryness, vaginal itching/irritation, vaginal soreness, dyspareunia and bleeding after sexual intercourse were screened to participate. The women who had previous hormonal treatment within 3 months, vaginal bleeding of unknown origin, suspected estrogen-dependent neoplastic diseases or breast cancer, coagulopathy, ischemic stroke, ischemic heart disease, venous thromboembolism, and endometrial thickness >4 mm measured by transvaginal sonography were excluded from this study. All participants must give written informed consents. Postmenopausal women defined as a woman who had natural menopause by 12 months of amenorrhea or a woman who had surgical menopause at least 6 months after bilateral oophorectomy with or without hysterectomy.

Twenty participants included into study were randomized into two groups: 1) control group which received cream base containing cetyl alcohol, stearyl alcohol, spermaceti, methyl paraben, propyl paraben, glycerin, sodium lauryl sulfate and water 2) intervention group which received in-house estrogen-containing cream (grounded 0.625 mg conjugated estrogen tablet mix together with cream base 1 gm) applied daily for 1 week then twice weekly for a 11 weeks (total 12 weeks period). Both placebo and estrogen containing cream were prepared and tested about stability of products including physical, color, odor, pH and microbial culture test at room

temperature (25°C) for 4 months under the supervision of Pharmaceutical Group at Sanpasitthiprasong Hospital. All products were white-colored, physical stable, pH 9.9 and sterile.

At first visit, the baseline characteristic data were collected included age, occupation, duration of menopause, weight, height, obstetric history, underlying disease, current medication, history of gynecologic surgery, and sexual activity. All participants were interviewed to evaluate most bothersome symptoms including vaginal dryness, vaginal itching/irritation, vaginal soreness, dyspareunia and bleeding after sexual intercourse) and categorized these symptoms into scores 0-3 (0=absent, 1=mild, 2=moderate, or 3=severe). The pelvic examination was performed to observe appearance of vaginal discharge, vaginal mucosa, anatomy of cervix, uterus, adnexa and recorded. Collecting vaginal epithelial cells for VMI and evaluating vaginal pH were performed only by one physician (F.P.) who was blind whether treatment or placebo group. To measure vaginal pH, piece of litmus paper is placed on lateral vaginal wall after a vaginal speculum was inserted without lubrication for 5-10 second then pH value was determined by comparing the color with colorimetric scale on enclosed card. To evaluate VMI, vaginal epithelial cells were collected from junction of upper and middle third of lateral vaginal wall using by Ayre's spatula and cells were smear on slide then fixed in 95% alcohol after measuring vaginal pH. The slides were sent to the

cytopathologist (N.L.) who was blinded to evaluate VMI under microscope. All participants did not use medication or have sexual intercourse within 24 hours before evaluating VMI and pH.

Vaginal maturation index (VMI) is criterion standard for vulvovaginal atrophy (VVA) confirmation, this test assesses relative proportion of parabasal, intermediated and superficial vaginal epithelial cell type. Vaginal maturation index (VMI) scored = $(\% \text{ intermediate cells} \times 0.5) + \% \text{ superficial cells}^{(10,11)}$. The most bothersome symptoms (MBS) score calculated from addition scores of those severity of five parameters.

The primary outcome was the change of vaginal maturation index from baseline which was evaluated at first visit, 4 weeks and 12 weeks after treatment. The secondary outcomes were vaginal pH, most bothersome vaginal symptoms, and most bothersome symptoms (MBS) score, which were also evaluated at first visit, 4 weeks and 12 weeks after treatment

For safety of all participants, we assessed participants' underlying diseases by asking history accompanied by physical examinations (general examination, including breasts examination and pelvic examination) at screening and during the follow up visit at 4 weeks and 12 weeks after treatment. Transvaginal ultrasonography to evaluate endometrial thickness and endometrial biopsy were performed at screening and the end of study in all participants who had uterus.

Sample size was calculated by N4Studies program using result from

previous study⁽⁵⁾ that showed VMI in study group and control group cream of 31.46 and 5.16, with standard deviation (SD) in study group and control group cream of 25.16 and 3.11, respectively. Considering a 10% drop-out rate, ten postmenopausal women per group were required. Randomization number was generated by computer program, then all codes were stored in enveloped. The pharmacist (J.A.) who prepared cream for both intervention and placebo group were blinded-prepack those cream for 12 week applying and gave to participants according to the codes.

Statistical analysis

Statistics analyses were performed using SPSS version 21, p-value of < 0.05 was considered statistically significance. Categorical, normally and non-normally distributed continuous variables were described as number (%) and mean (standard deviation, SD) or median (interquartile range, IQR). Comparison of baseline characteristics between groups were performed using Chi-square test for categorical variables and independent sample t-test, Fisher exact test for normally and non-normally distributed continuous variables. Comparison of vaginal maturation index (VMI), MBS score, vaginal pH and endometrial thickness between intervention group and placebo control were done using Kruskal-Wallis test. Comparison of moderate to severe most bothersome symptoms (MBS) between intervention group and placebo control were done using Fisher exact test

Results

During study period, there were 23 postmenopausal women who had vaginal symptoms whether vaginal dryness, vaginal itching/irritation, vaginal soreness, dyspareunia and bleeding after sexual intercourse. Three women were not eligible to the study due to difficult to follow up. The total twenty women were enrolled and randomized into two groups (ten women in each group) to received treatment or placebo. All participants were completely

followed up to evaluate VMI, vaginal pH, most bothersome vaginal symptoms, MBS score at screening, 4 weeks and 12 weeks after treatment. Among the participants, there were three women who had history of total abdominal hysterectomy for benign condition, therefore, the endometrial evaluation was completed in 17 cases. Two cases in treatment group and one case in placebo group had no uterus (as shown in Figure 1).

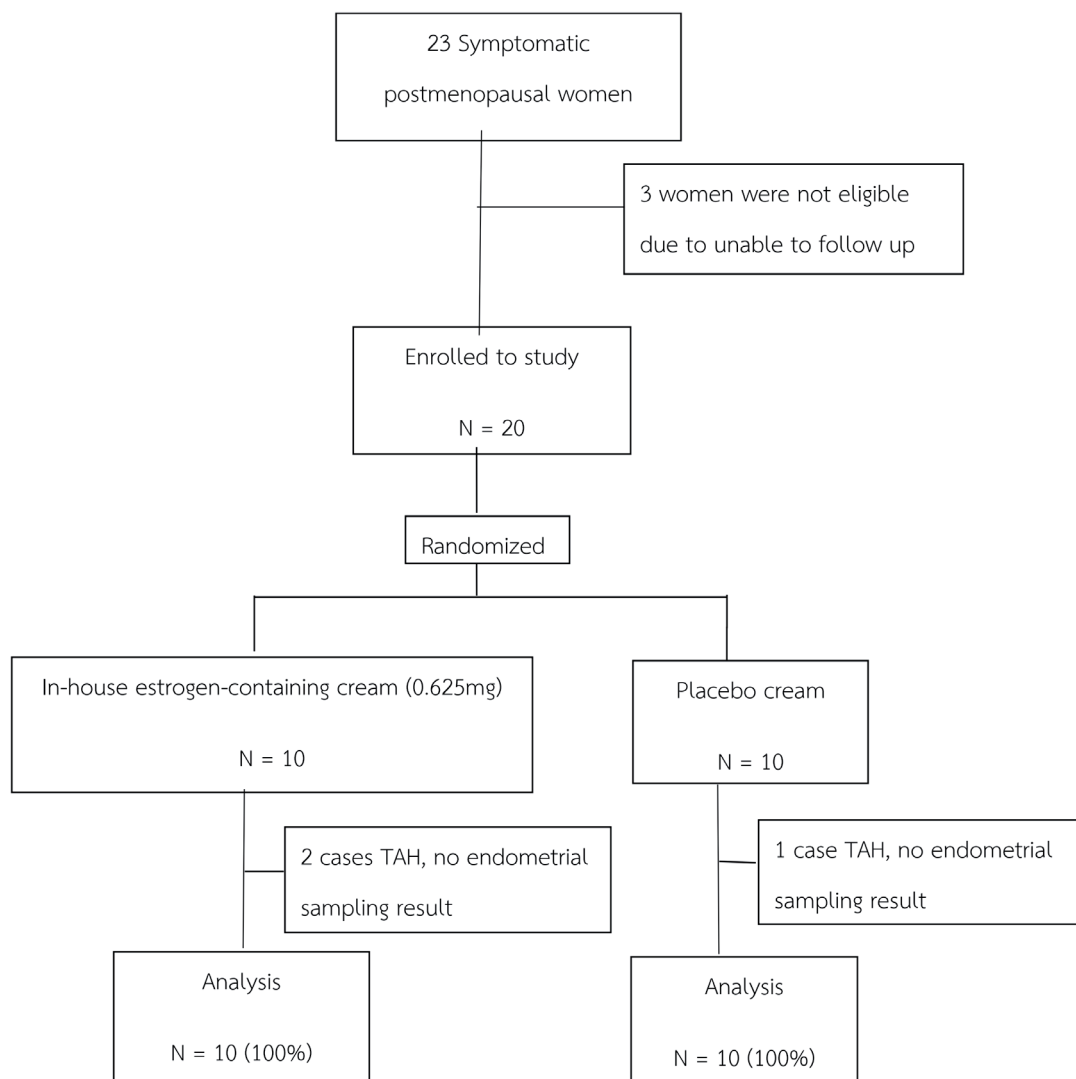


Figure 1 Flowchart of participants

ประสิทธิภาพยาเอสโตรเจนที่ผลิตขึ้นเองในการรักษาภาวะช่องคลอดแห้ง
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There were no significant differences in baseline characteristics among groups such as age, occupation, duration of menopause,

sexual activity, weight, height, history of gynecologic surgery, and underlying disease (as shown in Table 1).

Table1 Participants baseline characteristic* (n=20)

Characteristics	Intervention group (n=10)	Placebo group (n=10)	p-value
Age, years	63.70 (55.00,73.00)	62.90 (58.00,72.00)	0.940
Duration of menopause,years	15.70 (5.00,25.00)	14.70 (6.00,17.0)	0.792
Weight, kilogram	54.90 ($\pm$ 7.30)	50.80 ($\pm$ 9.40)	0.292
Height, centimeter	153.80 (150.00,160.00)	154.30 (151.00,155.00)	0.676
Body mass index, kilogram/ meter ²	23.20 (21.30,25.20)	21.30 (19.90,24.10)	0.187
Sexual activity			0.639
No	7 (70)	7 (70)	
<1 times/week	3 (30)	3 (30)	
1-3 times/week	0 (0)	0 (0)	
Occupations			0.315
None	3 (30)	4 (40)	
Merchant	0 (0)	1 (10)	
Agriculturist	7 (70)	3 (30)	
Government officer	0 (0)	1 (10)	
History of Obstetrics and Gynecological surgery			0.531
None	8 (80)	9 (90)	
Total abdominal hysterectomy	2 (20)	1 (10)	
Underlying disease			0.369
None	4 (40)	8 (80)	
Diabetic mellitus	3 (30)	1 (10)	
Hypertension	2 (20)	1 (10)	
Other	1 (10)	0 (0)	

*Values are given as mean $\pm$ standard deviation, median (interquartile range), or number (%)

Comparison of the main outcomes between groups was shown in Table 2. There were significantly increased vaginal maturation index (VMI) in treatment group when compared with control group ($p=0.045$ at 4 weeks, and $p=0.005$ at 12 weeks of treatment). The median of VMI increased from baseline, 4 weeks and 12 weeks after treatment 8.75, 61.50, and 68.75 in treatment group compared with 15.09, 27.09,

and 15.00 in placebo group (as shown in Table 2). The change occurred as early as 4 weeks of treatment and also continuously increased at 12 weeks after treatment (as shown in Figure 2). Even vaginal pH took more time to change, but also significantly changed to be better. The median pH changed from 6.0 at screening to 5.0 at 12 weeks after topical hormonal treatment ($p<0.05$).

Table2 Vaginal maturation index (VMI) and vaginal pH at screening, 4 weeks and 12 weeks after treatment (n=20)

Parameters	Intervention group (n=10)	Placebo group (n=10)	p-value
Vaginal maturation index (VMI)			
Screening	8.75 (7.50,52.50)	15.09 (7.50,50.00)	0.789
4 weeks	61.50 (20.50,80.00)	27.50 (6.50,52.50)	0.045
12 weeks	68.75 (36.00,98.00)	15.00 (2.50,45.50)	0.005
Vaginal pH			
Screening	6.00 (6.00,6.00)	6.00 (6.00,7.00)	0.403
4 weeks	6.00 (5.00,6.00)	6.00 (6.00,6.00)	0.226
12 weeks	5.00 (5.00,5.00)	6.00 (6.00,6.00)	0.000

Note: Values in the table are given as median (interquartile range) and Kruskal-Wallis test was used for comparison across intervention group and placebo group.

Vaginal maturation index

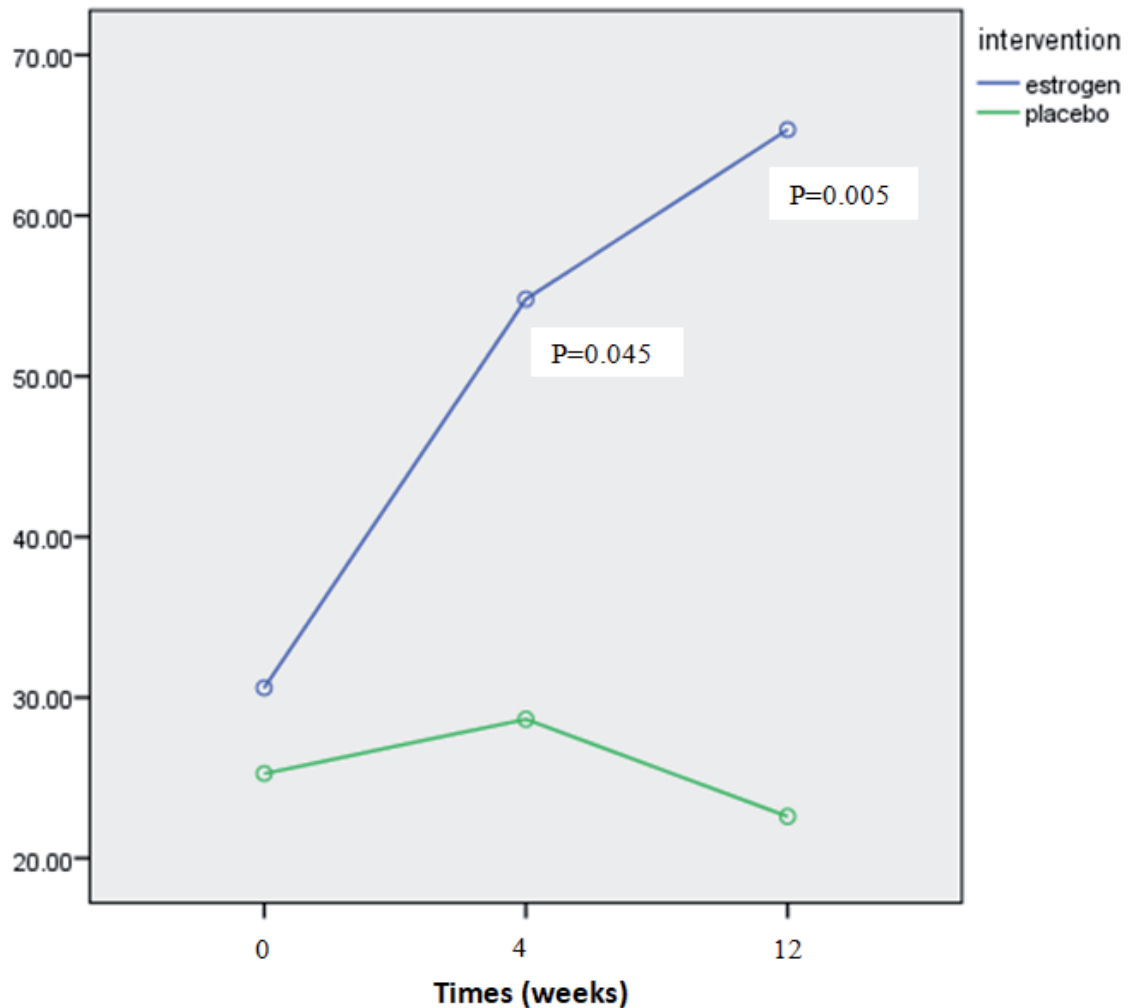


Figure 2 Change of vaginal maturation index (VMI) at screening, 4 weeks and 12 weeks after treatment (n=20)

The most bothersome vaginal symptoms especially moderate to severe symptoms including vaginal dryness, vaginal itching/irritation, vaginal soreness, dyspareunia and

bleeding after sexual intercourse had no significant improvement (as shown in Table 3). There was also no significant change of the MBS score between groups.

Table3 Moderate to severe vaginal symptoms and most bothersome symptoms (MBS) score at screening, 4 weeks and 12 weeks after treatment (n=20)

Symptoms	Intervention group (n=10)	Placebo group (n=10)	p-value
Vaginal dryness			
Screening	6 (60)	8 (80)	0.628
4 weeks	0 (0)	1 (10)	1.00
12 weeks	0 (0)	0 (0)	NA
Vaginal itching/irritation			
Screening	7 (70)	6 (60)	1.000
4 weeks	2 (20)	2 (20)	1.000
12 weeks	0 (0)	0 (0)	NA
Vaginal soreness			
Screening	5 (50)	2 (20)	0.350
4 weeks	0 (0)	0 (0)	NA
12 weeks	0 (0)	0 (0)	NA
Dyspareunia			
Screening	2 (20)	1 (10)	1.000
4 weeks	0 (0)	0 (0)	NA
12 weeks	0 (0)	0 (0)	NA
Bleeding after intercourse			
Screening	0 (0)	0 (0)	NA
4 weeks	0 (0)	0 (0)	NA
12 weeks	0 (0)	0 (0)	NA
Most bothersome symptoms (MBS) score			
Screening	5.50 (3.75,6.25)	5.00 (3.75,6.00)	0.589
4 weeks	3.00 (1.00,3.25)	2.00 (1.00,3.25)	0.612
12 weeks	1.50 (0.00,2.00)	1.00 (0.75,2.00)	1.000

Note: Values in the table are given as number (%), median (interquartile range) and Fisher exact test was used for comparison across intervention group and placebo group.

NA; not applicable

For safety aspect of all participants who had uterus, there were significant difference of endometrial thickness (ET) evaluated by transvaginal ultrasonography between group at screening. However, all participants had endometrial thickness less than 4.0 mm. The median (IQR) of ET was 2.00 (2.00, 2.70) in treatment group compared with 1.30 (1.20, 1.95) in placebo

group (p=0.008). But there was no significant change of endometrial thickness at the end of treatment. The median (IQR) of ET was 1.80 (1.33, 2.00) in treatment group compared with 1.30 (1.10, 1.75) millimeters in placebo group (p=0.159) (as shown in Table 4). All seventeen endometrial biopsy pathologic results showed no evidence of endometrial hyperplasia.

Table4 Endometrial thickness by transvaginal sonography (n=17)

Parameters	Intervention (n=8)	Placebo (n=9)	p-value
Endometrium thickness, millimeter			
Screening	2.00 (2.00,2.70)	1.30 (1.20,1.95)	0.008
12 weeks	1.80 (1.33,2.00)	1.30 (1.10,1.75)	0.159

Note: Values in the table are given as median (interquartile range) and Kruskal-Wallis test was used for comparison across intervention group and placebo group.

Discussion

Atrophic vaginitis is a common problem that women encountered after menopause. Estrogen therapy is effective treatment for atrophic vaginitis. There was no significant difference in factors affecting atrophic vaginitis and endogenous estrogen level such as duration of menopause, body mass index, underlying diabetic mellitus and hypertension. This study showed significant improvement in VMI change as early as 4 weeks after treatment and maintain its effect through 12 weeks after treatment when compared with placebo group. However,

the clinical symptoms especially moderate to severe most bothersome symptoms, and MBS score did not show significant change. This in-house estrogen containing cream is effective in treating atrophic vaginitis in postmenopausal women without any harm. Local estrogen therapy is effective treating vulvovaginal atrophy (VVA) and its effect is achieved after 1-3 months of therapy⁽¹²⁾. Absorption of low-dose vaginal estrogen preparations into the systemic blood stream is minimal and serum estradiol level does not exceed the physiological

value for the postmenopausal period ⁽¹³⁾. Such a route of administration of drugs allows to avoid hepatic metabolism, which minimizes the risk of side effects inherent in systemic estrogen therapy and excludes the effects on the endometrium and breast tissue, and thus, there is no need to prescribe progesterone preparations for the prevention of endometrial hyperplasia and adenocarcinoma. This study aimed to validate the possibility of using the in-house estrogen containing cream instead of the traditional commercial conjugated estrogen cream (Premarin™) containing estrogen 0.625 mg/1 gm, which is recommended in treatment of atrophic vaginitis in postmenopausal women.

The main outcome of this study is the change of VMI is significantly improved which correlate with previous studies ^(5-7,9) despite unequal dosage of topical estrogen. This cytological change is demonstrated earlier as 4 weeks after treatment and this cellular change happened before clinical improvement. This change can be explained by estrogen change epithelial cells of vagina. Increased proportion of superficial cells resulted increased glycogen for lactobacilli, which produced lactic acid and reduced in vaginal pH. This mechanism was proved in previous study ⁽¹⁴⁾. The significant change of vaginal pH in this study also supported the findings in previous studies ^(5-7,9), that vaginal pH changed after 12 weeks of hormonal treatment.

Prevalence of vaginal dryness in European survey ⁽¹⁵⁾ was 29%, varying from 19-40%, but 42% of women did not seek treatment as it was not important. In Thailand, prevalence of vaginal dryness in our population is slightly higher than previous study ⁽¹⁶⁾. In our study, the majority of vaginal symptoms were vaginal dryness, and vaginal irritation 70% and 65%. Both hormonal and placebo groups had improvement of all symptoms. This finding is not surprising because vaginal cream base is a kind of vaginal moisturizer which could help alleviate dryness and irritative symptoms. This finding also supported the findings of non-hormonal moisturizer for treatment of atrophic vaginitis in previous studies ^(6, 17). The result in our study showed insignificantly alleviate vaginal symptoms which was different from previous studies ⁽⁵⁻⁷⁾ because of much less in sample size. Because most of our participants (70%) had no sexual activity, so symptom of dyspareunia could hardly evaluate.

Although topical estrogen cream is safe to use in atrophic vaginitis without increasing endometrial stimulation as been proved in previous studies ^(7, 18), our in-house estrogen containing cream (0.625 mg/1gm) had no proven data of its bioavailability and systemic absorption. For safety concern, further investigation of pharmacokinetics is required. After the improvement of symptoms, this product should be discontinued. In case that is necessary to use for longer than 12 weeks, the endometrial surveillance is suggested.

The strength of this study is randomized, double-blind, placebo-controlled trial, and complete follow up of all participants. Even this study had randomization error, resulting in selection bias, the baseline characteristics of participants showed no significant difference. The significant difference in endometrial thickness at screening may be explained by this error. However, at the end of study, there was no significant difference in endometrial thickness and no evidence of endometrial hyperplasia. Limitation of this study was a small sample size, which make this trial can proved only the primary outcome of cellular change. This trial could not demonstrate the significant improvement of clinical atrophic vaginitis such as vaginal symptoms or MBS score.

Conclusion

In-house estrogen-containing cream is effective in increasing VMI, and decreasing vaginal pH after 12 weeks of administration without increasing risk of endometrial stimulation.

Acknowledgments

The author would like to thank Jirana Anansushatgul (J.A.), pharmacist at department of pharmacology, Sanpasitthiprasong hospital, Nopphanant Lathulee (N.L.) cytopathologist at department of pathology, Sanpasitthiprasong hospital, Parinya Chamnan, epidemiologist at Cardio-metabolic Research Group, Department of Social Medicine, Sanpasitthiprasong hospital,

Ubonratchathani, Thailand for statistic consultant of this study.

Potential conflicts of interest

The authors declare no conflicts of interest.

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Efficacy of in-house estrogen-containing cream for treatment of atrophic vaginitis in postmenopausal women, a randomized, double-blind, placebo-controlled trial

Fongfon Phonjan ¹, Sonthaya Piriyaikitphaiboon ¹, Piyawadee Wuttikonsammakit ¹

ABSTRACT

Background: Atrophic vaginitis is the common symptoms encountered during postmenopausal period caused by estrogen deficiency. The traditional treatment with vaginal Premarin cream® is not available, now. This study aimed to evaluate efficacy of in-house estrogen-containing cream for treatment of atrophic vaginitis in postmenopausal women compare with placebo.

Materials and Methods: A randomized, double blinded, placebo-controlled study was conducted at department of Obstetrics and Gynecology, Sanpasitthiprasong Hospital, involving twenty postmenopausal women with symptomatic atrophic vaginitis. All participants were randomized into two groups: 1) control group which received cream base containing cetyl alcohol, stearyl alcohol, spermaceti, methyl paraben, propyl paraben, glycerin, sodium lauryl sulfate and water 2) intervention group which received in-house estrogen-containing cream (0.625 mg/tab mix together with cream base) apply daily for 1 week then twice weekly for a 11 weeks (total 12 weeks period). The change of vaginal maturation index (VMI), most bothersome symptoms (MBS) and vaginal pH were evaluated at randomized time, 4 weeks and 12 weeks after treatment.

Results: Twenty postmenopausal women had completely followed up. The study group had significant increased vaginal maturation index at 4 weeks and 12 weeks compared with control group ($p= 0.045, 0.005$), median VMI 8.75, 61.50, 68.75 VS 15.09, 27.50, 15.00 at 0, 4, and 12 weeks, respectively. There is no significant improvement in all vaginal symptoms, MBS score, vaginal pH. No significant endometrial thickness change was observed.

Conclusion: In-house estrogen-containing cream was superior to placebo in increased vaginal maturation index after 4 weeks of administration with no evidence of endometrial stimulatory effect.

Keywords: estrogen-containing cream, postmenopausal atrophic vaginitis, vaginal maturation index, most bothersome symptoms

¹ Department of Obstetrics and Gynecology, Sanpasitthiprasong Hospital, Ubon Ratchathani