EFFECTIVENESS OF ESTORGEN CREAM IN THE TREATMENT OF VAGINAL ATROPHY USING CLASSICAL VAGINAL APLICATOR COMPARED TO EXTENSION TUBE

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ประสิทธิผลของเอสโตรเจนครีมในการรักษาอาการช่องคลอดฝ่อลีบ ในสตรีวัยหมดระดูเปรียบเทียบระหว่างเครื่องมือสำหรับใส่ครีม ในช่องคลอดชนิดดั้งเดิมและชนิด Extension tube

นายกระเษียร ปัญญาคำเลิศ

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
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Thesis Title	Effectiveness of estrogen cream in the treatment of vaginal atrophy using classical vaginal applicator compared to extension tube
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กระเชียร ปัญญาคำเลิศ : ประสิทธิผลของเอสโตรเจนครีมในการรักษาอาการช่องคลอดฝ่อลีบในสตรีวัยหมดระดู เปรียบเทียบระหว่างเครื่องมือสำหรับใส่ครีมในช่องคลอดชนิดดั้งเดิมและชนิด EXTENSION TUBE. (EFFECTIVENESS OF ESTORGEN CREAM IN THE TREATMENT OF VAGINAL ATROPHY USING CLASSICAL VAGINAL APLICATOR COMPARED TO EXTENSION TUBE.) อ. ที่ปรึกษา : ศ.นพ.สมภพ ลิ้มพงศานุรักษ์, M.D., M.P.H., 46 หน้า. ISBN 974-14-1780-2

วัตถุประสงค์: เพื่อเปรียบเทียบประสิทธิผลของเอสโตรเจนครีมโดยใช้เครื่องมือสำหรับใส่ครีมในช่องคลอดชนิดดั้งเดิมและชนิด EXTENSION TUBE ในการรักษาอาการช่องคลอดฝ่อลีบ

รูปแบบการศึกษา: การศึกษาแบบสุ่มเปรียบเทียบ

สถานที่ทำการวิจัย: โรงพยาบาลจุฬาลงกรณ์ สภากาชาดไทย

วิธีการศึกษา: สตรีวัยหมดระดูที่มีอาการช่องคลอดฝ่อลีบจำนวน 120 รายเข้าร่วมการศึกษาโดยถูกสุ่มออกเป็น 2 กลุ่ม กลุ่มแรกใช้เครื่องมือใส่ช่องคลอดชนิดดั้งเดิม (60 ราย) กลุ่มที่สองใช้เครื่องมือชนิด EXTENSION TUBE (60 ราย) ผู้ป่วยกลุ่มแรกและกลุ่มที่สองได้รับคอนจูเกตเอสโตรเจนครีม 1 กรัมและ 1.1 กรัมตามลำดับ ใส่ช่องคลอดวันละ 1 ครั้ง เป็นเวลา 4 สัปดาห์ และบันทึกการใช้ครีมลงในแบบบันทึกทุกครั้งที่ใช้ ประเมินประสิทธิผลของการรักษาโดยเปรียบเทียบคะแนนเฉลี่ยของ Vaginal maturation index (VMI) คะแนน Vaginal atrophy score (VAS) ประเมินอัตราการคงใช้ครีม การยอมรับการใช้เครื่องมือ และผลข้างเคียงเปรียบเทียบระหว่างผู้ป่วยทั้งสองกลุ่มเมื่อสิ้นสุดการศึกษา

ผลการศึกษา: ผู้ป่วยกลุ่มแรก 57 ราย กลุ่มที่สอง 58 ราย ติดตามการรักษาจนครบ คะแนนเฉลี่ยของ VMI ในผู้ป่วยกลุ่มที่สองสูงกว่ากลุ่มแรกอย่างมีนัยสำคัญทางสถิติ (p=0.007) คะแนน VAS ให้ผลทำนองเดียวกัน (p=0.009) อัตราการคงใช้ครีมของผู้ป่วยกลุ่มที่สองสูงกว่ากลุ่มแรกอย่างมีนัยสำคัญทางสถิติ (p=0.008) เมื่อเปรียบเทียบสัดส่วนของผู้ป่วยต่อการยอมรับเครื่องมือที่ใช้และต่อผลข้างเคียงที่เกิดขึ้น พบว่ามีความแตกต่างกันอย่างไม่มีนัยสำคัญทางสถิติ

สรุป: การใส่เอสโตรเจนครีมในช่องคลอดโดยใช้เครื่องมือ ชนิด EXTENSION TUBE มีประสิทธิผลในการรักษาอาการช่องคลอดฝ่อลีบดีกว่าการใช้เครื่องมือชนิดดั้งเดิม และมีอัตราการคงใช้ที่สูงกว่า

สาขาวิชา การพัฒนาสุขภาพ ลายมือชื่อนิสิต.....

ปีการศึกษา 2548 ลายมือชื่ออาจารย์ที่ปรึกษา.....

4775001830 : MAJOR HEALTH DEVELOPMENT

KEY WORD : VAGINAL APPLICATOR / ESTROGEN CREAM / VAGINAL ATROPHY

KRASEAN PANYAKHAMLERD: EFFECTIVENESS OF ESTROGEN CREAM IN THE TREATMENT OF VAGINAL ATROPHY USING CLASSICAL VAGINAL APPLICATOR COMPARED TO EXTENSION TUBE. THESIS ADVISOR: PROF. SOMPOP LIMPONGSANURAK, M.D., M.P.H., 46 pages. ISBN 974-14-1780-2

Objective: To compare the effectiveness of estrogen cream using classical vaginal applicator versus extension tube vaginal applicator for the treatment of vaginal atrophy.

Design: Randomized controlled trail

Setting: King Chulalongkorn Memorial Hospital, Thai Red Cross Society

Methods: A total of 120 postmenopausal women with vaginal atrophy were recruited. Patients were randomized into two groups: classical group (n=60) who used classical vaginal applicator and extension group (n=60) who used extension tube applicator. Patients in classical group received 1 gram of conjugated estrogen cream daily for 4 weeks and the other group received 1.1 grams of the same medication and period. Vaginal maturation index (VMI), vaginal atrophy score (VAS) were assessed. Number of days of use and patients' acceptability were recorded. Adverse events were also monitored.

Results: Fifty seven patients in classical group and 58 in extension group completed the study. The mean of VMI was significantly increased in extension group more than classical group (p=0.007). The VAS was significantly improved in extension group more than classical group (p=0.009). The compliance with extension tube was significantly higher than classical vaginal applicator (p=0.008). Considering the acceptability and the occurrence of adverse events, there were no statistically significant differences between two groups.

Conclusion: The effectiveness in the treatment of vaginal atrophy with estrogen cream was significantly higher when using extension tube than classical vaginal applicator. The compliance with extension tube was also higher than with classical vaginal applicator.

Field of study Health Development Student's signature.....

Academic year 2005 Advisor's signature.....

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CHAPTER I

RATIONALE AND BACKGROUND

Vaginal epithelium is an estrogen dependent tissue, begins to undergo atrophic changes when endogenous estrogen concentration declines after menopause. Vaginal atrophy is a frequent complaint of postmenopausal women. The symptoms of vaginal atrophy include vaginal dryness, itching, burning and painful intercourse. Some patients may have foul smell vaginal discharge from atrophic vaginitis (1). It was reported that 35-55% of Thai postmenopausal women attending a menopause clinic experienced some urogenital problems (2). In addition over 40% of postmenopausal women experienced lack of vaginal lubrication and frequent vaginal infection (3).

Atrophic vaginitis can compromise a women's quality of life and bring about sexual problems, however, a few women receive appropriate treatment as a result of patient embarrassment, underdiagnosis and the greater attention towards other postmenopausal health problems such as osteoporosis (4). A previous study reported that, only a small percentage of women who experienced atrophic vaginitis received estrogen treatment (5). Systemic treatment for these symptoms in the form of oral administration of estrogens is effectively restore the vaginal tissue, resulting in an improvement of these symptoms (6). However, 40-50% of women on oral hormonal therapy have persistent complaints of vaginal dryness (7). Another concern is that systemic hormone replacement therapy may carry some risks of cardiovascular disease, stroke, venous thromboembolism, breast cancer and endometrial cancer (8). The recent publication of the results of the Women's Health Initiative (WHI), reporting the early termination of oral hormone replacement therapy for healthy postmenopausal women was due to the excess of incidence of breast cancers in estrogen-progestogen arm compared to placebo (9). Thus the benefit of any hormonal replacement therapy must be balanced against possible harm before making any decision to use.

At present, local therapy by administration of estrogens in the form of vaginal cream has been found to be more appropriate in the treatment of vaginal atrophy than oral or parenteral administration forms, thereby avoiding enterohepatic circulation, inactivation by hepatic metabolism and unwanted systemic effects (10). Also the topical estrogen

therapy has been approved by the United State Food and Drug Administration (US-FDA) for the treatment of moderate to severe symptoms of vulva and vaginal atrophy (11). The most common use of topical estrogen therapy is in the form of conjugated estrogen cream which composes of conjugated estrogen 0.729 mg/g (sodium estrone sulfate 55.5%, sodium equilin sulfate 29.9%) and phenylethyl alcohol 9.51 mg/g.

As a matter of fact, women in oriental countries differ from those in occidental countries in attitude, concern and social acceptance in expression of privacy sexual and genital complaints. In Thailand, postmenopausal women who suffer from vaginal atrophy may try to avoid sexual activity with painful intercourse. They may loss of sexual desire and as a consequence worsening the sexual relationship. These conflicts may create family's problems. For those who need treatment, poor compliance and inadequate treatment are commonly found. In clinical practice, a large number of Thai postmenopausal women face the problems of applying the available vaginal applicator. The current classical vaginal applicator is rather rigid and the diameter of the barrel is as wide as 1.5 cm. Trying to insert this applicator may cause pain, discomfort, ulcer or bleeding. Some women decide to put estrogen cream on her index finger and insert it into the vaginal canal. This method of estrogen administration may pose the problems of inadequacy of dosage and depth of estrogen insertion.

Data collection from Menopause Research Unit, Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University demonstrated that the compliance with estrogen vaginal cream for the treatment of postmenopausal vaginal atrophy was only 50% (Menopause Research Unit data, unpublished). We introduce the extension tube as a new vaginal applicator which is softer and has a smaller diameter (only 1/3 compared to the classical vaginal applicator). Women who use this new applicator may improve their compliance, leading to an increase in the effectiveness of this medication. Therefore, this study is conducted to evaluate the effectiveness and the compliance of estrogen cream using the new vaginal applicator compared to the classical applicator for the treatment of postmenopausal vaginal atrophy.

CHAPTER II

LITERATURE REVIEW

The search strategy was performed by searching PubMed database through December 2004 to find studies that assessed the effectiveness or the compliance with conjugated equine estrogen cream for the treatment of vaginal atrophy. The medical subject heading terms used for the search strategy were conjugated estrogen cream, efficacy, compliance and vaginal atrophy.

The information was largely from Cochrane Review about the local estrogen for vaginal atrophy in postmenopausal women (12). The search strategy in this review came from the Cochrane Menstrual Disorders and Subfertility Group register of trials, The Cochrane Library, MEDLINE (1966-2003), EMBASE (1980-2003), Current Contents (1993-2003), Biological Abstracts (1969-2002), Social Sciences Index (1980-2003), PsycINFO (1972-2003), CINAHL (1982-2003) and reference list of articles. This review used the selection criteria as "randomized comparison of estrogenic preparations administered intravaginally in postmenopausal women for the treatment of symptoms resulting from vaginal atrophy or vaginitis". The outcome analysis was performed under the headings of efficacy, safety and acceptability. The results from this review included 16 trials with 2,129 women showed that there was significant difference in efficacy for women using vaginal cream as opposed to moisturizing gel. There was an improvement in vaginal dryness, vaginal moisture, vaginal fluid volume and vaginal elasticity in vaginal cream group more than in moisturizing gel group. For safety analysis, there were no significant differences between groups (cream versus tablets, cream versus ring and cream versus gel) for the following outcomes: hyperplasia, endometrial thickness and proportion of women with separate adverse events. For the acceptability, there were no significant differences between groups (cream versus ring and ring versus tablet) for adherence to treatment and withdrawal from study due to adverse events. In this 16 trials, there were 4 studies measured the efficacy by assessment of vaginal maturation index, but only 2 studies focused on conjugated equine estrogen cream. The first study demonstrated that the mean vaginal maturation index (VMI) increased from 25 to 59 in

conjugated estrogen cream users after 3 weeks of treatment (13). The second study revealed an improvement of the vaginal mucosa in women who received conjugated estrogen cream (the mean VMI = 32.92 at baseline and 69.27 at week 4 of treatment) (2).

Vaginal atrophy is a consequence of aging which occurs after menopause and affects a significant number of women. It has been suggested that about 50% of healthy women over 60 years of age have symptoms related to vaginal atrophy (5). The estrogen deprivation from the loss of ovarian function causes the vaginal epithelium to become thinner, drier, less elastic and more easily irritated. A decrease in blood flow in the vagina leads to fewer secretions and more dryness, as a consequence intercourse can become uncomfortable and painful (3). Cytologic examination of the vaginal mucosa shows a decreased proportion of superficial cells, increased parabasal cells and decreased vaginal maturation index (14,15). The vaginal mucosa atrophies until its glycogen content and acidity decrease. Vaginal pH increases from the normal range of 3.5-4.0 to 6.0-8.0. With this alkaline milieu, doderlein bacilli disappear and replaced by a flora of various pathologic organisms causing atrophic vaginitis (15,16).

A meta-analysis reviewing randomized, placebo-controlled trials published between 1969 and 1995 determined that estrogen therapy, as compared to placebo, was more efficacious in treatment of vaginal atrophy (17). Various forms of estrogen-based therapies have been shown to effectively manage signs and symptoms of vaginal atrophy (3,14,18), by decreasing vaginal pH and increasing the number of superficial cells, on the other words increasing the vaginal maturation index (15). The improvements in vaginal cytology were demonstrated as early as 4 weeks following initiation of estrogen therapy (17).

Bachman et al (7) studied about the efficacy of systemic estrogen for the treatment of vaginal atrophy and reported that 40-50% of women on oral estrogen therapy had persistent complaint of vaginal dryness. Concerns about the safety, the potential harmful effects of oral estrogen therapy have been reported, then, hindered its use by postmenopausal women (9,19). Attention has recently been focused on a local administration of estrogen to the affected vaginal tissue. Topical estrogen in form of vagina cream is highly effective in the treatment of vaginal atrophy (20).

Although vaginal estrogen preparations are prescribed for their local effects, a variety of systemic actions have been observed, including significant rises in serum estradiol levels and causes uterine bleeding due to endometrial proliferation and hyperplasia (21). Widholm et al (22) reported that two subjects had endometrial hyperplasia during the first 10 days of high-dose conjugated estrogen cream (more than 3 mg/day) therapy. However, Manoni et al (2) reported that no endometrial hyperplasia found with conjugated estrogen cream treatment with the dosage of 0.625 mg/day for 2 weeks, then 0.625 mg/day twice a week for 10 weeks. Also Ayton et al (13) found no endometrial hyperplasia or malignancy after 12 weeks of treatment of postmenopausal vaginal atrophy. Subsequently, Marx et al (23) reported three cases of endometrial thickness > 4 mm. performed by transvaginal ultrasonogram at week 16 of 0.3 g/day of conjugated estrogens treatment but none of the endometrial biopsy demonstrated hyperplasia. In addition, Willhite et al (18) performed a study and found that progestin treatment is not needed for short-term (6 months) local estrogen treatment in women with an intact uterus.

Although local treatment appears to have fewer adverse effects, many women consider cream to be messy and might be technically difficult to apply for the elderly (13). From this reason, patients may have poor compliance and ineffective symptom control. Regarding the acceptability, there were 9 studies from Cochrane Review about the local estrogen for vaginal atrophy in postmenopausal women (12). There were significant differences in adherence to treatment in the ring versus cream group favoring the ring due to the comfort of product and ease to use. When compared the tablets to cream group, the former was more preferable in ease of administration and more comfortable to use. Rioux et al (1) investigated the efficacy of conjugated estrogen cream for relieving atrophic vaginitis and reported 13% of the participants discontinued prematurely because of noncompliance or cumbersome application of the cream.

CHAPTER III

RESEARCH METHODOLOGY

3.1 Research question

Does the treatment of vaginal atrophy with estrogen cream using extension tube as a vaginal applicator have ≥ 20% higher in the effectiveness than using classical vaginal applicator?

3.2 Objective

3.2.1 Primary objective

To compare the effectiveness of estrogen vaginal cream using classical vaginal applicator versus extension tube for the treatment of postmenopausal vaginal atrophy.

3.2.2 Secondary objective

To assess the compliance and acceptability with estrogen vaginal cream using classical vaginal applicator compared to extension tube for the treatment of postmenopausal vaginal atrophy.

3.3 Hypothesis

Null hypothesis

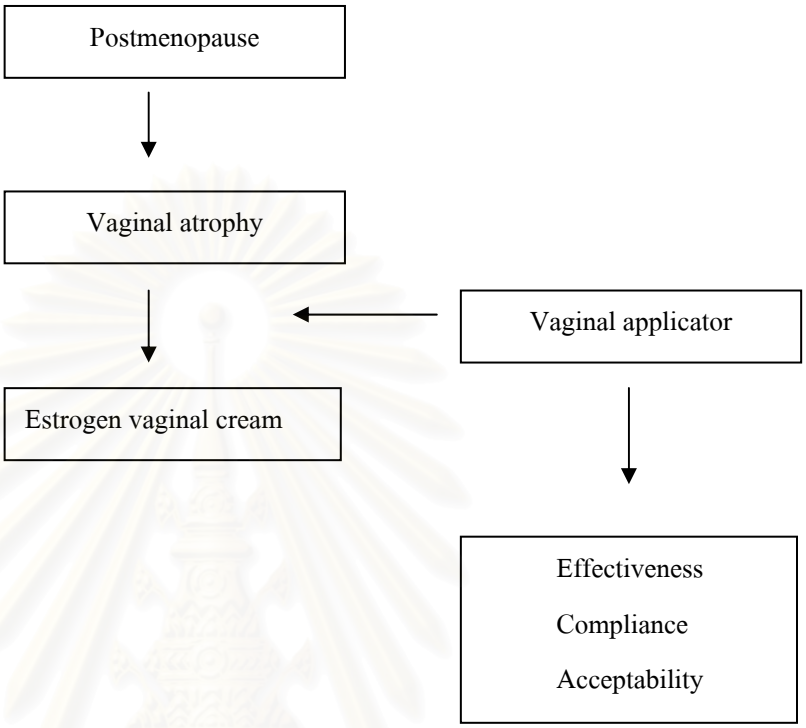
There is no statistically significant difference in the effectiveness between two methods of applying estrogen vaginal cream (classical vaginal applicator versus extension tube).

Alternative hypothesis

There is a statistically significant difference in the effectiveness between two methods of applying estrogen vaginal cream (classical vaginal applicator versus extension tube).

3.4 Conceptual framework

Figure 1 : Proposed conceptual framework



3.5 Operational definitions

Vaginal atrophy : an inflammation of the lubricated inner lining of the vagina that is caused by thinning and decreased vaginal lubrication

Estrogen vaginal cream : cream used vaginally composed of conjugated equine estrogens (CEE) for treating vaginal atrophy (1 gram of cream contains 0.625 mg of CEE)

Applicator : a plastic device used for inserting cream into the vaginal lumen

Vaginal maturation index (18) : obtained by cytologic examination of a smear from the upper lateral vaginal wall. The number of parabasal, intermediate and superficial cells out of 100 cells were counted. These percentage were utilized in the following equation to determined the maturation index of the vaginal mucosa

Vaginal maturation index = (% intermediate cells x 0.5) + (% superficial cells x 1)

Vaginal atrophy score (24) : the score for the assessment of signs of vaginal atrophy by pelvic examination with 5 measures as shown in the table 1. Each sign

was graded using a description assessment of vaginal mucosa (table 1) with 4-point ordinal scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). The sum of these 5 scores provides a vaginal atrophy score.

Table 1 : Descriptive assessment of vaginal mucosa

Signs of atrophy	Vaginal atrophy score			
	None	Mild	Moderate	Severe
Rugae	Normal number and depth	Reduced rugae	Rare rugae	Smooth vagina
Pallor	Normal pink	Light pink	Very pale	White or deep red
Petechiae	None	Clearly seen	Bleeds on scraping	Bleeds on contact
Mucosal thinning (elasticity)	Normal	Decreased	None	Stenosis
Dryness	Normal lubrication	Slightly decreased	Minimal lubrication	Dry

Compliance : rate of use of vaginal applicator contained estrogen cream

Acceptability : patient acceptability with the vaginal applicator

3.6 Research design

Randomized controlled trial

3.7 Research methodology

3.7.1 Population and sample

Target population

Postmenopausal women with signs of vaginal atrophy

Sample population

Postmenopausal women with vaginal atrophy who were in eligible criteria and attended menopause clinic, King Chulalongkorn Memorial Hospital

3.7.2 Inclusion criteria

- General healthy postmenopausal women between 45-70 years of age
- Last natural menstrual cycle completed at least 12 consecutive months before screening, or have documented bilateral oophorectomy, with or without hysterectomy, at least 12 weeks before screening
- Patients who have experience of sexual intercourse
- Patients must have symptoms of vaginal dryness and have at least two signs of vaginal atrophy (decreased vaginal rugae, pallor color, petechiae on vaginal wall, vaginal mucosa thinning or decreased vaginal lubrication) (24).
- Patients must provide a signed and dated informed consent.

3.7.3 Exclusion criteria

- Patients with known sensitivity or contraindications to estrogen therapy
- Patients who used any estrogen within the previous 3 months
- Patients with abnormal Papanicolaou smear (class 3 or higher)
- Patients with a history of breast cancer or estrogen dependent neoplasia e.g. endometrial carcinoma
- Patients who have any disorder of the vulva or vagina that would preclude proper assessment of drug effects
- Patients with a history of major diseases of cardiovascular, hepatic, renal or endocrine systems
- Patients with known or suspected pregnancy

3.7.4 Sample size calculation

The sample size was calculated from the formula for 2 independent means as the following:

$$n = \frac{(Z_{\alpha} + Z_{\beta})^2 \, 2 \, \sigma^2}{D^2}$$

n = sample size in each group

μ_1 = mean of vaginal maturation index in week 4^{th} in the group who used classical vaginal applicator

μ_2 = mean of vaginal maturation index in week 4^{th} in the group who used extension tube

D = 20% of μ_1

σ^2 = pooled variance

Z_{α} = 1.96 for α of 0.05 (two-tailed)

Z_{β} = 0.84 for β of 0.2 (power 80%)

From pilot study (10 patients in each group), we calculated the sample size as below:

μ_1 = 52.2, μ_2 = 65.0, σ = 19.33

Following the research question, 20% of μ_1 = 10.44

$$n = \frac{(1.96+0.84)^2 \text{ x2x } (19.33)^2}{(10.44)^2}$$

$$= 54$$

The number of sample in each group calculated from the formula was 54.

With the assumption that there is 10% drop out rate, then the adjust sample size in each group was 60.

3.7.5 Randomization and allocation concealment

- Patients who met the eligible criteria were randomly allocated into two treatment groups: classical group (using classical vaginal applicator) and extension group (using extension tube).
- The randomization list was computer-generated random sequence. The third digit of each number was used to generate treatment code: even number for classical group and odd number for extension group.
- The allocation was concealed and kept in separate opaque envelops, which was sequentially numbered.
- The secretary opened the next in a series of envelops when a new patient was enrolled.

3.7.6 Intervention

Patients in classical group received 1 gram of the conjugated estrogen cream (equivalent to 0.625 milligrams of conjugated estrogen) daily for 4 weeks and extension group received 1.1 grams of the same medication and period. The amount of estrogen cream used in extension group was 1.1 grams because there was 0.1 gram of cream remained in the extension tube after use. The classical group used classical vaginal applicator (figure 2) and the extension group used extension tube connected to 10 milliliters plastic syringe (figure 3). The extension tube is a non-pyrogenic sterile tube connected with intravenous fluid set as a line transferring fluid to the patient. This tube has 0.5 cm. in diameter and 18 inches long and we shortened it to 4.5 inches (the same length as classical vaginal applicator). The extension tube used in this study is manufactured by M.E.MEDITEK Company Limited.

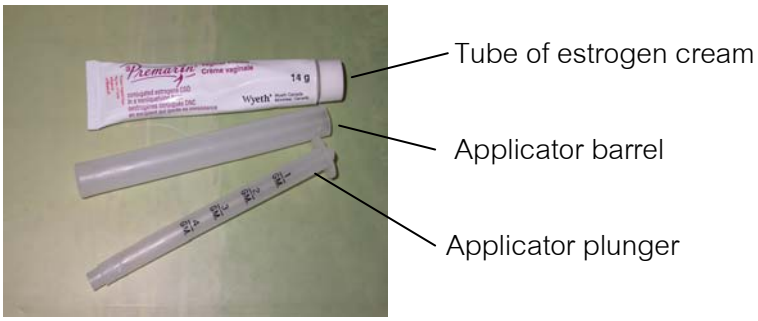


Figure 2 : Classical vaginal applicator

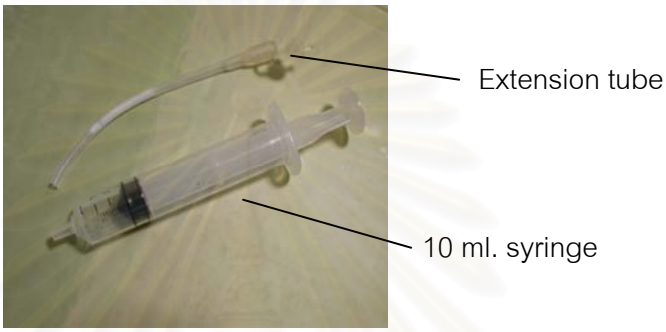


Figure 3 : Extension tube and syringe

Visit 0 (screening)

1. A complete medical history including demographic information was performed.
2. Physical examination, including breast examination was performed.
3. Gynecologic examination and Papanicolaou smear were performed and vaginal atrophy score was assessed by the investigator.

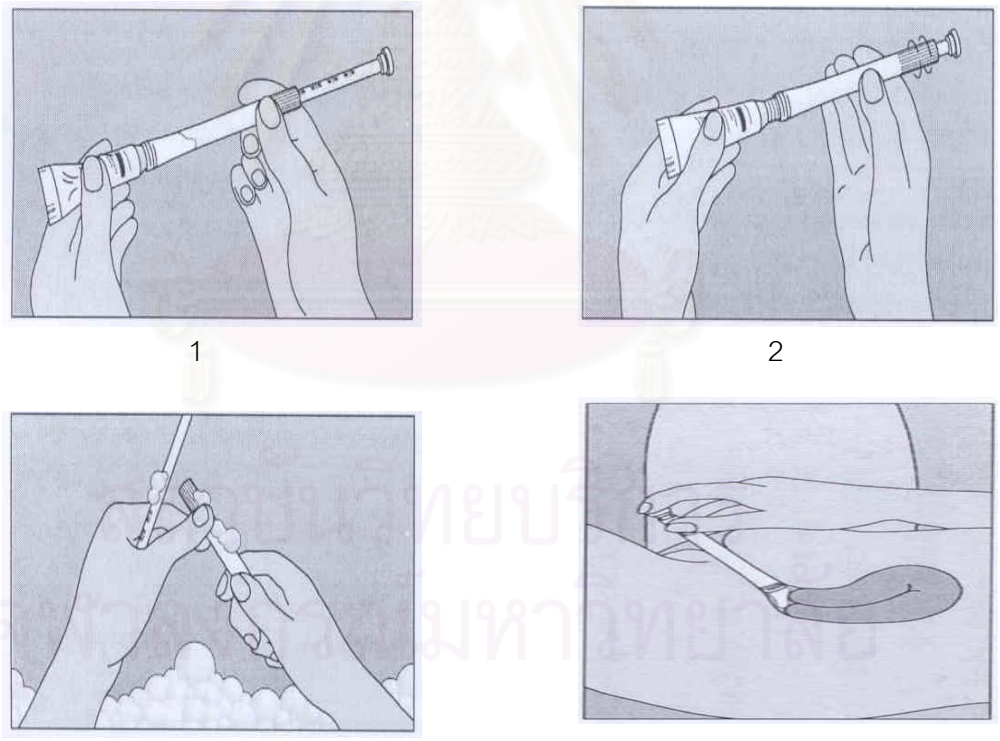
Visit 1

Visit 1 took one week after visit 0. Patients who met the eligible criteria were randomly allocated into 2 groups according the type of vaginal applicator.

1. Cytologic smear was obtained from the upper lateral vaginal wall for vaginal maturation index. Samples were analyzed by the same cytopathologist.
2. Patients were instructed about steps in applying estrogen vaginal cream.
3. Steps in applying estrogen vaginal cream

Classical group : steps in applying vaginal cream using classical vaginal applicator (figure 4)

- Insert the applicator plunger into the smooth end of the applicator barrel.
- Remove cap from the tube of estrogen cream and screw the tube onto the grooved end of the applicator barrel.
- Gently squeeze the tube until cream fills the applicator up to the measurement mark (1gram).
- Unscrew and remove the applicator from the tube.
- The patient lies down on her back with knees drawn up.
- Insert the applicator deep into the vagina and push the plunger in the way to fully dispense the cream.
- Remove the applicator from the vagina.



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3 4

Figure 4 : Steps in applying classical vaginal applicator

Extension group : steps in applying vaginal cream using extension tube vaginal applicator (figure 5)

- Insert the applicator plunger into the smooth end of the applicator barrel.
- Remove cap from the tube of estrogen cream and screw the tube onto the grooved end of the applicator barrel.
- Gently squeeze the tube until cream fills the applicator up to the measurement mark (1.1 grams).
- Unscrew and remove the applicator from the tube.
- Remove the syringe plunger from the syringe tube.
- Put the applicator with 1.1 grams of cream into the syringe tube, and push the applicator plunger down to dispense the cream into the syringe.
- Remove the applicator and insert the syringe plunger into syringe tube ~ 2 cm depth.
- Connect the extension tube to the small opening end of the syringe tube.
- The patient lies down on her back with knees drawn up.
- Insert the extension tube deep into the vagina and push the syringe plunger down until it reaches the bottom of syringe tube.
- Disconnect the syringe from the extension tube, draw air into the syringe tube ~ 3 milliliters volume, then reconnect the syringe to the extension tube again and push the syringe plunger down to the bottom of syringe tube, this will push the remaining cream out of the extension tube into the vagina.
- Remove the extension tube from the vagina.

After using vaginal applicator, wash all instruments in soapy water to remove all traces of cream. Allow it to dry and store it in a convenient place.

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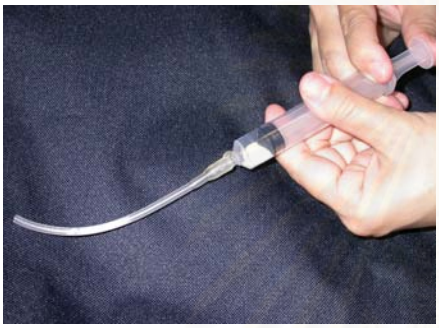

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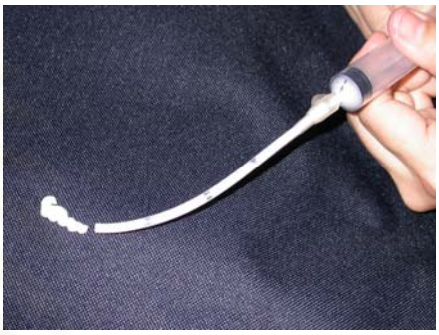

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Figure 5 : Demonstration of the use of extension tube with syringe

3. Patients were instructed to apply estrogen vaginal cream daily for 4 weeks and were informed to strictly follow the method of applying cream.
4. Patients received diary card and were informed that she had to record the use of cream every time in this diary card for compliance checking and record any adverse events (if occurred).

5. Patients were instructed to return to the investigative site after 4 weeks (visit 2) and brought their unused study medication with them.

Visit 2

Visit 2 took place 4 weeks after visit 1.

1. The investigator reviewed the diary card and the study medication to ensure patient compliance and reviewed all of the adverse events recorded by the patients.
2. The secretary called a group of 3 patients to have pelvic examination. Each patient lied down on lithotomy position and the investigator performed pelvic examination and assessed for vaginal atrophy score, then the secretary recorded the score. The investigator did not know the type of vaginal applicator that each patient used because there was a curtain between patient's face and the investigator. Then the investigator was blinded for vaginal atrophy score assessment.
3. Vaginal smear was performed for vaginal maturation index calculation.
4. Patients were asked to rate of her overall opinion on the vaginal applicator they used during 4 weeks as excellent, good, acceptable, bad or unacceptable.

Contamination

The substance that had potential effects on vaginal tissue was withheld during the study period such as nonhormonal vaginal gel and herbal products.

Safety measures

Adverse events at each clinic visit were recorded.

3.7.7 Outcome measurement

Primary outcome measure:

- Vaginal maturation index taken on visit 1 and visit 2 for both groups

Secondary outcome measures:

- Rate of use of vaginal applicator in each subject in 28 days taken on visit 2 for both groups.
- Vaginal atrophy score taken on visit 0 and visit 2 for both groups.
- Acceptability grading taken on visit 2 for both groups.

All of the data being measured are summarized in table 2

Table 2 : Summary of measurements

Variables	Type of data	Description of data
Baseline characteristics		
Age	Continuous	Mean, SD
Parity	Discrete	Mean, SD
Body mass index (BMI)	Continuous	Mean, SD
Years since menopause	Continuous	Mean, SD
Primary outcome variable		
Vaginal maturation index	Continuous	Mean, SD
Secondary outcome variables		
Vaginal atrophy score	Discrete	Mean, SD Median, IQR
Compliance (rate of use of vaginal applicator)	Continuous	Mean, SD Median, IQR
Acceptability	Discrete	Frequency
Safety variables		
Adverse events	Discrete	Frequency

SD = standard deviation

IQR = interquartile range

3.7.8 Data collection

The following data were recorded

1. Demographic data, baseline characteristics :
   - Age (years)
   - Parity
   - Body weight (kg), height (cm) and body mass index (kg/m^2)
   - Years since menopause (years)
2. Outcomes :

   These following data were obtained
   - Vaginal maturation index
   - Vaginal atrophy score
   - Compliance
   - Acceptability
   - Adverse events

3.7.9 Data analysis

- All data were collected and analyzed by computer program (SPSS version 11.0). The statistical analysis focused on the detection of significant differences between two groups with respect to vaginal maturation index measured at the endpoint of the study.

- The data were analyzed on a per-protocol (PP) basis, an intention-to-treat (ITT) basis and a worst-case-analysis. Per-protocol analysis included randomized patients who completed the study. Intention-to-treat analysis included all randomized patients who started treatment and who lost to follow up. A worst-case-analysis was carried out assuming that the values for drop-outs were least favorable in extension group and most favorable in classical group. Tests of hypotheses were conducted at the two-sided, 0.05 level of significance and confidence intervals of 95%.

Baseline characteristics

The baseline variables include age, parity, body mass index and years since menopause were presented using mean and standard deviation.

Outcome analysis

Primary outcome: vaginal maturation index was treated as continuous variables. The distribution of the data was normal, then the analysis of co-variance (ANCOVA) with the baseline values as covariates was used primarily in the analysis.

Secondary outcomes:

- compliance (rate of use of the vaginal applicator) is continuous variable. The data did not normally distribute, then we used Mann–Whitney U test for the analysis.

- Vaginal atrophy score was ordinal scale and the data did not normally distribute, then Mann–Whitney U test was used to analyze this data.

- Acceptability: Chi–square test was used to analyze the differences between two groups to be related to the ordering (compared 5 grades of the acceptability).

Safety analysis

The frequency of adverse events in both groups was tabulated. Fisher's exact test was used to analyze the differences in the occurrence of adverse events of two techniques.

All of the data being analyzed are summarized in table 3

Table 3 : Summary of statistical analysis

Dependent variables	Type of data	Statistics
Primary outcome variable		
Vaginal maturation index	Continuous	Analysis of co-variance
Secondary outcome variables		
Compliance (rate of use of vaginal applicator)	Continuous	Mann- Whitney U test
Vaginal atrophy score	Discrete	Mann – Whitney U test
Acceptability	Discrete	Chi–square test
Safety variables		
Adverse events	Discrete	Fisher's exact test

3.7.10 Ethical consideration

The researchers submitted the documents required by the regulations according to Ethics Committee and obtained their opinion in writing. This study protocol had already approved by the Ethics Committee. Patients could not be included until the approval of the Ethics Committee had been received.

The trial was conducted in accordance with ICH guidelines for Good Clinical Practice. All eligible patients received detail of the study protocol and the researcher explained the protocol thoroughly to the patients. All patients gave written informed consent before enrollment. The patient's right to confidentiality was maintained during data collection and processing.

The extension tube used in this study is softer and has a smaller diameter than the classical vaginal applicator. Therefore, the new device will not be harmful to the vaginal tissue greater than the classical vaginal applicator. However, if the patients feel uncomfortable or have any adverse effects, they can contact the investigator immediately for the problems.

3.7.11 Limitation

A major limitation of this study was the method of use for measuring compliance. In this study the investigator checked the diary card and the unused study medication at the second visit for compliance checking. It is still the most frequently recommended and most widely used method for measuring compliance, particularly for clinical trials, because it is cheap, not complicated, fast and does not require sophisticated equipment.

3.7.12 Implication

If the results of this study demonstrate that the treatment of postmenopausal vaginal atrophy using extension tube vaginal applicator for insertion of estrogen cream is more effective than using the classical applicator, then we can apply to young women who have an indication to use some types of vaginal cream for the treatment of any vaginal disease such as applying antibiotic cream for treating bacterial vaginitis.

CHAPTER IV

RESULTS

4.1 Basic characteristics of patients

One hundred and twenty women were enrolled in the study, 60 were randomly allocated into classical group and 60 into extension group. The mean age of the patients was 57.0 years, the mean parity was 2.2, the mean body mass index (BMI) was 24.1 kg/m^2 and the mean duration since menopause was 8.4 years. At baseline, there were no statistically significant differences between two groups regarding the mean age, parity, BMI and years since menopause (Unpaired student's t test) (Table 4).

A total of 115 women completed the study. Five patients (4.2%) withdrew from the study, 3 from classical group and 2 from extension group. The reasons for discontinuation were personal for 4 subjects and one subject in extension group was admitted in the hospital because of acute pyelonephritis before starting the medication.

Table 4 : Patients' characteristics

	Classical group (N=60)	Extension group (N=60)
Age (years)	56.6 $\pm$ 5.2	57.4 $\pm$ 4.8
Parity	2.3 $\pm$ 1.3	2.1 $\pm$ 1.2
Weight (kg)	57.9 $\pm$ 8.1	56.6 $\pm$ 5.8
Height (cm)	154.6 $\pm$ 4.6	153.9 $\pm$ 4.8
Body mass index (kg/m^2)	24.3 $\pm$ 3.6	23.9 $\pm$ 2.8
Years since menopause (years)	8.3 $\pm$ 6.2	8.5 $\pm$ 5.1

Value are expressed as mean $\pm$ SD (standard deviation)

4.2 Primary outcome analysis

Vaginal maturation index (VMI)

There was no statistically significant difference between two groups for the mean of vaginal maturation index at baseline (p=0.083). Before treatment, the mean of VMI was 27.83 ± 22.54 in classical group and 26.99 ± 19.93 in extension group. After 4 weeks of treatment, the mean of VMI in extension group was superior to the mean of VMI in classical group (p<0.001, per-protocol, ANCOVA, table 5). Missing data were analyzed by worst-case analysis (favored classical group) by assuming the lowest and highest value of VMI at the end of the study in extension group and classical group respectively. The analysis showed that the mean of VMI in extension group was higher than the mean of VMI in classical group (p<0.01, intention-to-treat, ANCOVA, table 6).

Table 5 : Assessment of vaginal maturation index (VMI) by per-protocol analysis

	Classical group	Extension group	p-value
VMI at week 0	27.83 ± 22.54	26.99 ± 19.93	0.829*
VMI at week 4	61.58 ± 17.29	74.66 ± 12.26	0.000009*

Values are expressed as mean ± SD

* ANCOVA

Table 6 : Assessment of vaginal maturation index (VMI) by intention-to-treat analysis

	Classical group	Extension group	p-value
VMI at week 0	27.83 ± 22.54	26.99 ± 19.93	0.083*
VMI at week 4	63.38 ± 18.61	72.25 ± 17.77	0.007*

Values are expressed as mean ± SD

* ANCOVA

4.3 Secondary outcome analysis

Vaginal atrophy score (VAS)

The analysis of the vaginal atrophy score showed no statistically significant difference between two groups at baseline (p=0.120). At the end of the study, the VAS was significantly improved in extension group more than in classical group from both per-protocol and intention-to-treat using worst-case analysis (p<0.001, per-protocol, Mann-Whitney U test, table 7) (p<0.01, intention-to-treat, Mann-Whitney U test, table 8).

Table 7 : Assessment of vaginal atrophy score (VAS) by per-protocol analysis

		Classical group	Extension group	p-value
VAS at week 0	mean ± SD	9.55 ± 2.38	10.2 ± 2.34	0.120*
	median (IQR)	10 (8, 11)	11 (8.25, 12)	
VAS at week 4	mean ± SD	4.72 ± 1.91	3.57 ± 1.19	0.0003*
	median (IQR)	4 (4, 5)	4 (3, 4)	

IQR = interquartile range

* Mann-Whitney U test

Table 8 : Assessment of vaginal atrophy score (VAS) by intention-to-treat analysis

		Classical group	Extension group	p-value
VAS at week 0	mean ± SD	9.55 ± 2.38	10.2 ± 2.34	0.120*
	median (IQR)	10 (8, 11)	11 (8.25, 12)	
VAS at week 4	mean ± SD	4.53 ± 2.03	3.85 ± 1.92	0.009*
	median (IQR)	4 (4, 5)	4 (3, 4.75)	

IQR = interquartile range

* Mann-Whitney U test

Compliance

The extension group showed a statistically higher rate of use of cream than the classical group during 4 weeks of the study ($p<0.001$, per-protocol, Mann-Whitney U test, table 9) ($p<0.01$, intention-to-treat, Mann-Whitney U test, table 10).

Table 9 : Rate of use of vaginal applicator (compliance) by per-protocol analysis

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		Classical group	Extension group	p-value
Rate of use	mean $\pm$ SD	0.79 $\pm$ 0.24	0.91 $\pm$ 0.14	0.0007*
	median (IQR)	0.86 (0.71, 0.96)	0.96 (0.86, 1.00)	

IQR = interquartile range

* Mann-Whitney U test

Table 10 : Rate of use of vaginal applicator (compliance) by intention-to-treat analysis

		Classical group	Extension group	p-value
Rate of use	mean $\pm$ SD	0.80 $\pm$ 0.24	0.88 $\pm$ 0.21	0.008*
	median (IQR)	0.89 (0.72, 0.96)	0.96 (0.86, 1.00)	

IQR = interquartile range

* Mann-Whitney U test

Acceptability

The frequency of each grade of the acceptability is shown in figure 6 (the drop-outs are not included in this figure).

The frequency of the reported acceptability “bad” or “unacceptable” was very low, then we collapsed the grades of the acceptability from 5 to 3 grades as the following: “excellent + good”, “acceptable” and “bad + unacceptable”. The missing data were analyzed by worst-case analysis (favored classical group) by assuming the

grade “excellent + good” for the drop-outs (3 subjects) in classical group and assuming the grade “bad + unacceptable” for the drop-outs (2 subjects) in extension group.

At the 4-week visit, the proportion of patients reporting about 3 –graded scale of the acceptability was no statistically significant difference between two groups (p=0.207, per-protocol, Pearson chi-square test, table 11) (p=0.393, intention-to-treat, Pearson chi-square test, table 12). When evaluating the opinion only “excellent” or “good”, 58.3% of patients in extension group answered “excellent” or “good” as compared with 46.7% in classical group. In addition, only 10% in each group reported “unacceptable” or “bad” opinion at the end of the study (intention-to-treat analysis).

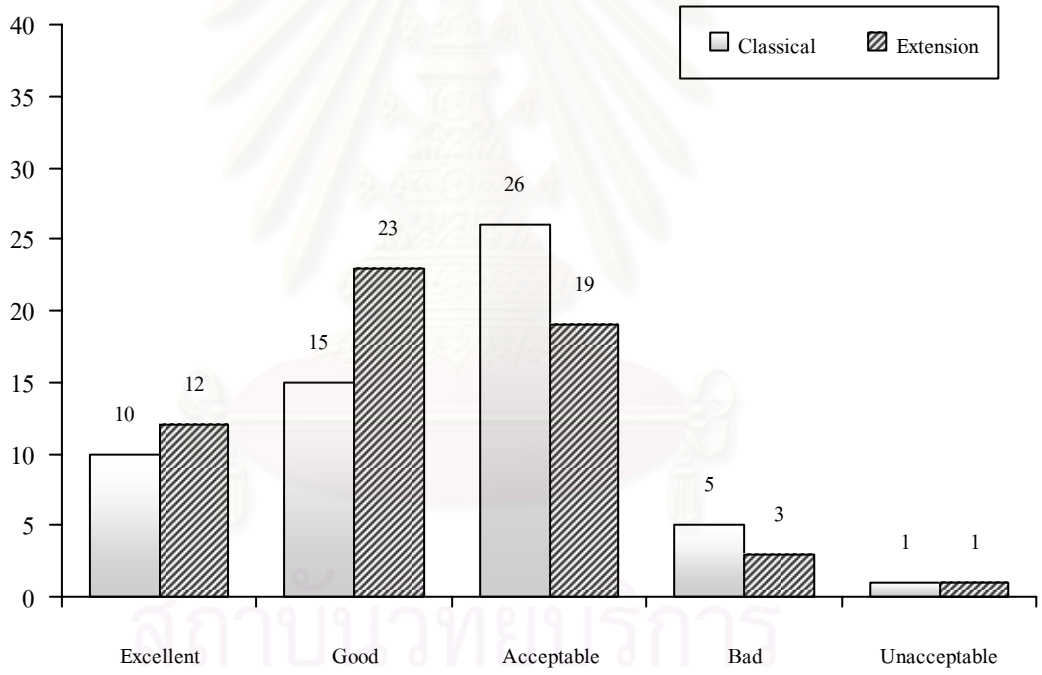

Figure 6 : Frequency of each grade of acceptability

Table 11 : Assessment of the acceptability by per-protocol analysis

	Acceptability			
	Excellent + Good	Acceptable	Bad +Unacceptable	p-value
Classical group	25	26	6	0.207*
Extension group	35	19	4	

* Pearson chi-square test

Table 12 : Assessment of the acceptability by intention-to-treat analysis

	Acceptability			
	Excellent + Good	Acceptable	Bad +Unacceptable	p-value
Classical group	28	26	6	0.393*
Extension group	35	19	6	

* Pearson chi-square test

4.4 Safety analysis

After 4 weeks of treatment, a total of 23 from 115 patients who completed the study reported the occurrence of adverse events. When using a worst-case-analysis by assuming that the drop-outs in extension group developed all adverse events and those in classical group had no adverse event. Vaginal irritation was the most common adverse event in both groups (8.3% in classical group and 11.7% in extension group). Breast pain is the second most common adverse event (6.7% in classical group and 8.3% in extension group). About 3.3% of women in classical group and 5% in extension group reported pelvic discomfort. The incidence of vaginal edema was the same as pelvic discomfort in both groups. All of the adverse events were mild and there were no statistically different in the proportion of patients with adverse events between both

groups (p>0.05, per-protocol, Fisher's exact test, table 13) (p>0.05, intention-to-treat, Fisher's exact test, table 14).

Table 13 : Adverse events during follow up by per-protocol analysis

	Classical group (%)	Extension group (%)	p-value
Vaginal itching	5 (8.8%)	5 (8.6%)	1.000*
Breast pain	4 (7.0%)	3 (5.2%)	0.717*
Pelvic discomfort	2 (3.5%)	1 (1.7%)	0.618*
Vaginal edema	2 (3.5%)	1 (1.7%)	0.618*

* Fisher's exact test

Table 14 : Adverse events during follow up by intention-to-treat analysis

	Classical group (%)	Extension group (%)	p-value
Vaginal itching	5 (8.3%)	7 (11.7%)	0.762*
Breast pain	4 (6.7%)	5 (8.3%)	1.000*
Pelvic discomfort	2 (3.3%)	3 (5.0%)	1.000*
Vaginal edema	2 (3.3%)	3 (5.0%)	1.000*

* Fisher's exact test

CHAPTER V

DISCUSSION

Vaginal atrophy is a common problem of postmenopausal women. Systemic hormone therapy is not always necessary and alternative choice is estrogenic preparation administered vaginally in the form of cream (12). The efficacy of topical estrogens in relieving the symptoms of vaginal atrophy was confirmed by Cochrane Review and the results indicated significant differences favoring the cream when compared to placebo (12). There also has been increasing interest in the development of new delivery systems for sex steroids which improved compliance and demonstrated high rate of acceptability. The vaginal applicator has been used to administer topical estrogen cream in the treatment of postmenopausal vaginal atrophy for several decades. However, the classical vaginal applicator has many disadvantages due to a big and rigid barrel. This applicator may cause pain or discomfort in the vagina during insertion and lead to have a low compliance especially in Thai women. The extension tube is applied from the extension tube set that we commonly use to connect with sterile solution bag for intravenous fluid administration. It contains a diameter of 5 mm. and has a soft consistency. It's interesting to study about the effectiveness and compliance of estrogen cream comparing between these two vaginal applicators.

Due to the different nature of the delivery systems, the study can not be blinded, Regarding the dosage of conjugated equine estrogens cream, the amount of cream used in this study was the starting dose as recommended in the Australian registered product information (13). Generally, a less frequent dosage schedule is in common use for long term maintenance therapy, but as this was a short term study of initiation therapy, the recommended starting dose (1 gram per day for 4 weeks) was considered to constitute a valid comparison.

Considering the duration of the study, the 4 weeks period of treatment is adequate for demonstrating the improvements in vaginal epithelial cells as reported by the study of Cardozo et al (17). The mean increase in vaginal cytology changed rapidly within 2-4 weeks and improved very little after 4 weeks (23). Therefore, we decided to

conduct the study of 4 weeks duration to assess the effectiveness of estrogen vaginal cream using an innovative extension tube. Willhite et al (18) reported that progestogen treatment is not needed for short term (6 months) local estrogen therapy in women with an intact uterus, then progestogen was not used in this 4 week comparative trial.

The primary outcome analysis was evaluated objectively by the blinded assessment of vaginal smears from single cytopathologist. The vaginal maturation index (VMI) is a standardized scale utilized to express the proportion of the various vaginal cell types. The typical VMI of premenopausal women is comprised of 30-60% superficial cells, 40-70% intermediate cells, and 0% parabasal cell depending on phase of menstrual cycle (18). During early menopause, parabasal cells increase to approximately 65% and intermediate and superficial cells increase to about 30% and 5% respectively (18). In some elderly women, all cells may be parabasal (18). In the present study, treatment with conjugated estrogen cream resulted in a significant estrogenic improvement in the distribution of the vaginal cell types. The mean of VMI increased in both groups when compared to the baseline. The data collected in the group who used classical vaginal applicator agree closely with results of previous studies which have demonstrated estrogen's effectiveness for restoring vaginal epithelial cells (3,15,17,18,25-27). When comparing between groups at the end of this study, the mean of VMI in extension group was statistically significantly higher than in classical group from per-protocol analysis ($p<0.001$).

Regarding an intention-to-treat analysis, we used worst-case-analysis for the missing values of patients who discontinued treatment. The values of VMI for drop-outs in the extension group was 2.5% which was the minimum of all of VMI values in this group at the end of the study and we put the maximal VMI value (97.5%) for drop-outs in the classical group. The mean of VMI in extension group was still statistically significantly higher than in classical group ($p<0.01$). The reasons for this finding will be discussed later.

For the secondary outcome analysis, the vaginal atrophy score was blinded assessment from the investigator as previously mentioned in the intervention of the study. At baseline there was no statistically significant difference between the two groups for vaginal atrophy score. After 4 weeks, the calculated global score was

decreased in both groups, which indicated improvement of vaginal tissue. However, from both per-protocol and intention-to-treat using worst-case-analysis the score was significantly lower in extension group than in classical group ($p<0.01$).

From data analysis about the effectiveness of treatment, the results of this study supported using extension tube vaginal applicator was superior to classical vaginal applicator as demonstrated by the assessment of vaginal maturation index from cytologic smears and vaginal atrophy score from pelvic examination. The type and amount of estrogen cream delivered into vaginal lumen were the same in both groups, therefore, the rate of use (compliance) of the cream should be taken into account. The result of this study showed high compliance rates in both groups. Comparing between groups, however, the compliance with the extension tube was significantly higher than with the classical vaginal applicator at the end of the study from both per-protocol and intention-to-treat using worst-case-analysis. The compliance with each type of the vaginal applicator is probably the obvious factor which we could use to explain why the means of vaginal maturation index and vaginal atrophy score were better in extension group than classical group. In the present study, all of the patients received diary cards for recording the number of use of vaginal applicator every time and returned the cards and unused medication to the investigator after 4 weeks. The investigator reviewed the diary card and weighted unused estrogen cream to assess the compliance. The weight of the remaining cream in the tube mostly corresponded to the number of days of unused estrogen cream. Then this method of determining the compliance is reliable.

. The means of VMI at the end of the study were 72.25% in extension group and 63.38% in classical group (intention-to-treat). From the calculation, the mean of VMI in extension group was 13.95% higher than the mean of VMI in classical group. Regarding our research question “Does the treatment of vaginal atrophy with estrogen cream using extension tube as a vaginal applicator have $\geq$ 20% higher in the effectiveness than using classical vaginal applicator?.” the answer for this research question is **“No”**. However, if we analyzed by per-protocol basis, the means of VMI were 74.66% in extension group and 61.58% in classical group at the end of the study, the mean of VMI in extension group was 21.2% higher than the mean of VMI in classical group. This finding is responsible to our research question. The explanation about the

difference of these findings should be from the data we put for the drop-outs. In this study we put the worst values for drop-outs in extension group and the best values for drop-outs in classical group, but in the real situation the drop-outs in extension group might produce high VMI whereas in classical group produced low VMI. However, this study showed that the extension tube vaginal applicator exhibited statistically significantly superior to classical vaginal applicator regarding patient compliance, leading to an increase in the effectiveness of treatment as we have seen from the compared means of vaginal maturation index.

Acceptability is a highly important parameter for local vaginal treatment forms, not least due to the fact that the symptoms of vaginal atrophy, in contrast to vasomotor symptoms, may continue throughout life and some patients may need long term treatment. It is very interesting from our findings that both delivery systems were highly acceptable at the end of the study. When comparing three grades of acceptability, there was no statistically significant difference between two groups. The patients in extension group reported more “excellent” or “good” than in classical group but the difference did not reach statistical significance.

Considering the safety of medication and type of the applicator used in this study, the incidence of adverse events in the current study was low and these were no statistically significant differences in the occurrence of adverse events between two groups. The most common adverse event was vaginal itching. Other adverse events were breast pain, vaginal edema and pelvic discomfort. All of the adverse events described by the patients were mild and required no treatment. The evidence of systemic toxicity in the women in both groups was not found. The adverse events might be related mostly to the medication itself rather than the vaginal applicator. After 4 weeks, a less frequent dosage is required for long term maintenance therapy (1 g twice a week), therefore, the reported adverse events may be ablated.

During recruitment for this study, it became apparent that many women had suffered from atrophic vaginitis for several years, but had been either unhappy to discuss this with their doctors or afraid of using classical vaginal applicator. To make the patients feel comfortable in using this device is an important issue. This study is responsible to this question and we found that extension tube vagina applicator can be

used as an alternative of vaginal applicator for delivering estrogen cream in the treatment of vaginal atrophy. In addition, we may apply to use the extension tube vaginal applicator in a single or unmarried woman in various conditions which requires vaginal treatment such as atrophic vaginitis or local vaginal infection. For further research, it is very interesting to study about the qualitative aspect especially the satisfaction of use of this new vaginal applicator.

CHAPTER VI

CONCLUSION

The treatment of vaginal atrophy with estrogen cream using extension tube as a vaginal applicator produced significantly higher effectiveness and compliance than using classical vaginal applicator. It has also been shown in our study that both groups demonstrated high rate of acceptability. There was no statistically significant differences in the proportion of patients related to the grades of the acceptability and the occurrence of the adverse events. The extension tube can be used as an alternative vaginal applicator for postmenopausal women who suffer from vaginal atrophy and need vaginal estrogen therapy.

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APPENDICES

APPENDIX A

หนังสือยินยอมเข้าร่วมโครงการ

ข้าพเจ้า.....ได้รับทราบเกี่ยวกับโครงการวิจัยเรื่อง ประสิทธิผลของการเอสโตรเจนครีมในการรักษาอาการช่องคลอดฝ่อลีบในสตรีวัยหมดระดู เปรียบเทียบระหว่างเครื่องมือสำหรับใส่ครีมเอสโตรเจนในช่องคลอดชนิดดั้งเดิมและชนิด Extension tube โดยข้าพเจ้าจะได้รับการซักประวัติ ตรวจร่างกาย ตรวจภายใน ตรวจเช็คมะเร็งปากมดลูกและตรวจเยื่อบุผิวช่องคลอด

ข้าพเจ้าจะได้รับครีมทาช่องคลอด PREMARIN® และได้รับเครื่องมือสำหรับใส่ครีมในช่องคลอด ชนิดดั้งเดิมหรือชนิด Extension tube โดยการสุ่ม พร้อมคำอธิบายวิธีการใช้โดยละเอียด หลังจากนั้นจะได้รับการตรวจติดตามที่ระยะเวลา 4 สัปดาห์

ข้าพเจ้าได้รับการชี้แจงถึงวัตถุประสงค์ของโครงการวิจัย วิธีการศึกษา ประโยชน์ที่จะได้รับ และ ผลข้างเคียงที่อาจเกิดขึ้น พร้อมทั้งซักถามถึงสิ่งที่สงสัย ซึ่งในกรณีที่มีผลแทรกซ้อนเกิดขึ้น ข้าพเจ้าจะได้รับการดูแลรักษาอย่างเหมาะสมโดยแพทย์ผู้ทำการวิจัย และข้าพเจ้าได้รับทราบว่าข้อมูลส่วนตัวของข้าพเจ้าจะได้รับการเก็บไว้เป็นความลับ

ข้าพเจ้าได้พิจารณาแล้วว่าการศึกษาวิจัยนี้จะเป็นประโยชน์ต่อตนเอง สังคม และการสาธารณสุขของประเทศไทย ข้าพเจ้าจึงมีความยินดีและเต็มใจที่จะเข้าร่วมการศึกษาวิจัยนี้ ในระหว่างการศึกษานี้ข้าพเจ้ามีสิทธิ์ที่จะเลิกการศึกษาวิจัยนี้เวลาใดก็ได้ และการเลิกการศึกษาวิจัยนี้ จะไม่มีผลกระทบต่อการให้การรักษาของแพทย์ผู้ทำการวิจัยต่อข้าพเจ้าแต่อย่างใด

ข้าพเจ้าได้อ่าน และทำความเข้าใจในหนังสือยินยอมเข้าร่วมโครงการวิจัยนี้โดยตลอดแล้ว จึงลงลายมือชื่อไว้เป็นหลักฐานต่อหน้าพยาน

วันที่.....เดือน.....พ.ศ. .....

ลงชื่อ.....ผู้เข้าร่วมการวิจัย
(.....)

ลงชื่อ.....แพทย์ผู้ดำเนินการวิจัย
(นพ.กระเษียร ปัญญาคำเลิศ)

ลงชื่อ.....พยาน
(.....)

ลงชื่อ.....พยาน
(.....)

APPENDIX B

ข้อมูลสำหรับผู้ป่วย (Patient Information)

การศึกษาทางคลินิก : ประสิทธิผลของเอสโตรเจนครีมในการรักษาอาการช่องคลอดฝ่อลีบในสตรีวัยหมดระดู เปรียบเทียบระหว่างเครื่องมือสำหรับใส่ ครีมในช่องคลอดชนิดดั้งเดิมและชนิด Extension tube (Effectiveness of estrogen cream in the treatment of vaginal atrophy using classical vaginal applicator compared to extension tube)

เรียน ผู้ป่วยทุกท่าน

ท่านเป็นผู้ได้รับเชิญจากแพทย์ให้เข้าร่วมการศึกษาทางคลินิกเพื่อประเมินประสิทธิผลของเอสโตรเจนครีมในการรักษาอาการช่องคลอดฝ่อลีบ โดยมีการเปรียบเทียบการใช้เครื่องมือสำหรับใส่ครีมในช่องคลอดชนิดดั้งเดิมและชนิดใหม่ (Extension tube) ก่อนที่ท่านตกลงเข้าร่วมการศึกษาดังกล่าว ขอเรียนให้ท่านทราบถึงเหตุผลและรายละเอียดของการศึกษาวิจัย ในครั้งนี้

สตรีไทยวัยหมดระดูเป็นจำนวนมากต้องประสบกับปัญหาช่องคลอดฝ่อลีบ แห้ง ทำให้มีปัญหาช่องคลอดอักเสบ หรือเจ็บเวลามีเพศสัมพันธ์ สาเหตุของช่องคลอดฝ่อลีบเกิดจากการขาดฮอร์โมนเอสโตรเจนในวัยหมดระดู ร่วมกับการเสื่อมตามอายุ อาการช่องคลอดฝ่อลีบจะเป็นมากขึ้น ถ้าหมดระดูเป็นระยะเวลานาน มีรายงานพบว่าสตรีมากกว่าร้อยละ 40 ประสบปัญหานี้ แต่กลับพบว่ามีสตรีเพียงจำนวนน้อยที่มาพบแพทย์เพื่อรับการรักษา อาจเนื่องจากสตรีไทยมีความอายที่จะบอกอาการทางช่องคลอดหรือปัญหาทางเทศสัมพันธ์กับแพทย์ และสตรีบางท่านมีความกลัวเรื่องการใช้ฮอร์โมนทดแทน โดยเฉพาะความเสี่ยงต่อการเกิดมะเร็งเต้านม รวมทั้งปัญหาของการใช้ครีมเอสโตรเจนทางช่องคลอด เนื่องจากเครื่องมือสำหรับใส่ครีมเข้าไปในช่องคลอด อาจทำให้เจ็บช่องคลอด ทำให้อัตราการคงใช้ต่ำและส่งผลให้ประสิทธิผลของการรักษาไม่ดี สำหรับการศึกษานี้จะใช้ครีมเอสโตรเจนชนิด Premarin วันละ 1 กรัม ก่อนนอน เป็นเวลา 4 สัปดาห์ ฮอร์โมนชนิดนี้มีส่วนประกอบของตัวยา Conjugated equine estrogen 0.625 มิลิกรัม ในครีม 1 กรัม ซึ่งเป็นฮอร์โมนที่ใช้กันทั่วไปในการรักษาอาการช่องคลอดฝ่อลีบในสตรีวัยหมดระดู การศึกษานี้จะแบ่งสตรีออกเป็น 2 กลุ่มๆ ละ 60 คน โดยกลุ่มแรกจะได้รับเครื่องมือสำหรับใส่เอสโตรเจนครีมในช่องคลอดชนิดดั้งเดิม กลุ่มที่สองจะได้รับเครื่องมือชนิดใหม่ ชนิด Extension tube ท่านจะได้รับกระดาษบันทึกจำนวนครั้งของการใช้เครื่องมือ และเมื่อครบ 4 สัปดาห์ แพทย์จะนัดท่านมาเพื่อสอบถามอาการของช่องคลอด และตรวจภายในเพื่อประเมินอาการแสดงทางช่องคลอด

หากท่านตกลงที่จะเข้าร่วมการศึกษาวิจัยนี้ จะมีข้อปฏิบัติดังต่อไปนี้

- ท่านไม่ต้องเสียค่าใช้จ่ายในการรักษา ดังนั้นท่านจะต้องกลับไปพบแพทย์ตามนัดเพื่อติดตามการรักษา โดยไม่เสียค่าใช้จ่ายใด ๆ
- ก่อนเริ่มต้นการศึกษาและการพบแพทย์แต่ละครั้ง แพทย์จะตรวจร่างกายตามปรกติ (ตรวจร่างกายทั่วไป, ตรวจภายใน) และตรวจมะเร็งปากมดลูก คัดเลือกผู้ที่มีพยาธิสภาพอื่นๆ ออก
- ระหว่าง 4 สัปดาห์ที่ศึกษา ขอความร่วมมือจากท่านให้บันทึก การใช้เครื่องมือสำหรับใส่ เอสโตรเจนครีม ในช่องคลอดในแต่ละครั้งลงในแบบบันทึก
- ในการมาพบแพทย์หลังจาก 4 สัปดาห์ ท่านจะได้รับการตรวจจากแพทย์ดังนี้
  - ตรวจวัดความดันโลหิต, ชีพจร และน้ำหนัก
  - ส่งปฏิทินบันทึกการใช้เอสโตรเจนครีม
  - ประเมินอาการของช่องคลอดฝ่อลีบ
  - ตรวจภายในเพื่อประเมินอาการแสดงของช่องคลอดฝ่อลีบ

การเข้าร่วมการศึกษานี้ เป็นไปโดยสมัครใจ ท่านอาจจะปฏิเสธที่จะเข้าร่วม หรือถอนตัวจากการศึกษานี้ได้ทุกเมื่อ โดยไม่กระทบต่อการดูแลรักษาที่ท่านจะได้รับจากแพทย์

ประการสำคัญที่ท่านควรทราบคือ

ผลการศึกษานี้ จะใช้สำหรับวัตถุประสงค์ทางวิชาการเท่านั้น โดยข้อมูลต่าง ๆ จะถูกเก็บไว้ในคอมพิวเตอร์ และไม่มีการแพร่งพรายสู่สาธารณชน ขอรับรองว่าจะไม่มีการเปิดเผยชื่อของท่านตามกฎหมาย

หากท่านมีปัญหา หรือข้อสงสัยประการใด กรุณาติดต่อ นพ.กระเษียร ปัญญาคำเลิศ หน่วยวิจัยสตรีวัยหมดระดู ตึก ภ.ป.ร. ชั้น 7 โรงพยาบาลจุฬาลงกรณ์ โทร. 02-2565304 ซึ่งยินดีให้คำตอบแก่ท่านทุกเมื่อ

ขอขอบคุณในความร่วมมือของท่านมา ณ ที่นี้

APPENDIX C

CASE RECORD FORM

Center No. Pat initials ..... Pat No. | | |

Effectiveness of estrogen cream in the treatment of vaginal atrophy using classical vaginal applicator compared to extension tube

Principal investigator

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Center No. Pat initials ..... Pat No. [ ][ ][ ]

Assessment data [ ][ ] [ ][ ] [ ][ ]
dd mm yy

Eligibility criteria

Inclusion criteria	No	Yes
■ Written informed consent	[ ]	[ ]
■ Age 45-70 years	[ ]	[ ]
■ Spontaneous amenorrhea at lest 12 months or had bilateral oophorectomy, with or without hysterectomy, at least 12 weeks before screening	[ ]	[ ]
■ Married	[ ]	[ ]
■ Have symptoms of vaginal dryness and $\geq$ 2 signs of vaginal atrophy	[ ]	[ ]
Exclusion criteria		
■ known sensitivity or contraindications to estrogen therapy	[ ]	[ ]
■ Known or suspected pregnancy	[ ]	[ ]
■ Use of any estrogen within the previous 3 months		
■ Abnormal Papanicolaou smear (class 3 or higher)	[ ]	[ ]
■ History of breast cancer or estrogen dependent neoplasia e.g. endometrial carcinoma	[ ]	[ ]
■ Any disorder of the vulva or vaginal that would preclude proper assessment of drug effects	[ ]	[ ]
■ History of major diseases of cardiovascular, hepatic, renal or endocrine systems	[ ]	[ ]
Conclusion		
Patient fulfils all inclusion criteria and none of the exclusion criteria	[ ]	[ ]

Withdraw Patient _____

Center No. Pat initials ..... Pat No. ___

Assessment data ___ (dd mm yy)

Patient description

Date of birth ___ (dd mm yy)

Month and year at menopause ___ (mm yy)

Parity ___

Year since menopause (yr) ___

Any history of allergy No [ ] Yes [ ] If yes, please specify.....

Physical examination and Papanicolaou smear

Weight (kg) ___

Height (cm) ___

Pulse (beats/min) ___

Blood pressure (mmHg) ___/___

	Normal	Abnormal	Specification of abnormalities
General appearance	[ ]	[ ]	
Heart	[ ]	[ ]	
Lungs	[ ]	[ ]	
Breasts	[ ]	[ ]	
Abdomen	[ ]	[ ]	
Pelvic exam	[ ]	[ ]	
Papanicolaou smear	[ ]	[ ]	

Center No. Pat initials ..... Pat No. ___ ___ ___

Assessment data ___ ___ ___ ___ ___ ___
dd mm yy

Medical history

Do patient have any current or past medical disease or have taken any medication

No [ ] Yes [ ] If you please specify below

	Past	Current		Current medication		
.....	[ ]	[ ]		[ ]	[ ]	.....
.....	[ ]	[ ]		[ ]	[ ]	.....
.....	[ ]	[ ]		[ ]	[ ]	.....

Effectiveness

	Screening	Visit 2
Vaginal maturation index	[ ]	[ ]
Vaginal atrophy score	[ ]	[ ]

Compliance

Number of use of vaginal application in 28 days [ ]

Acceptability

Excellent	Good	Acceptable	Bad	Unacceptable
[ ]	[ ]	[ ]	[ ]	[ ]

Adverse effect

1. _____
2. _____
3. _____
4. _____

VITAE

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