Efficacy, Safety and Acceptability of a Seven-Day, Transdermal Estradiol Patch for Estrogen Replacement Therapy

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Abstract

Objectives : To evaluate the efficacy, safety and acceptability of a seven-day, transdermal estradiol patch, in the treatment of menopausal symptoms.

Design : Open-label trial.

Setting : Hat Yai Regional Hospital, Thailand.

Subjects : Hysterectomized women with surgical or natural menopause.

Method : The clients received a 12.5 cm^2 matrix patch®, containing 3.9 mg of estradiol delivering 0.05 mg/day, once a week for six months. The efficacy, safety, and acceptability were evaluated at the end of 1-, 3- and 6-months.

Results : Six-month responses were analyzed among 50 enrolled patients. The mean estradiol level/Follicle Stimulating Hormone/Lutienizing Hormone were 27.88/70.03/31.19, 44.08/53.37/26.86, and 42.43/48.53/24.39 pg/ml, mIU/L, mIU/L at admission, 1- and 3-months, respectively. The average climacteric score was 27.18, 16.60, 12.78, and 12.18 at admission, 1-, 3- and 6-month, respectively. At least 94 per cent of patches were not dislodged more than one quarter. The most common skin irritation was itching, followed by erythema, vesicle, and burning sensation. The patches were generally well tolerated, and acceptability was satisfactory.

Conclusion : Transdermal estradiol patch effectively reduced the severity of menopausal symptoms, measured by modified climacteric score. Adhesion was found to be excellent. In actual clinical practice, the transdermal patch should be appropriately introduced to tolerant users.

Key word : Transdermal Estradiol, Estrogen Replacement Therapy, Efficacy, Safety, Acceptability

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We live in a society that is slowly getting older. Two hundred years ago, only 30 per cent of women lived long enough to reach menopause, whereas 90 per cent of today's women will experience the climacteric[1]. Although menopause is not a disease, it is an estrogen-deficient state. There are many consequences of a relative lack of estrogen that may adversely affect health. Estrogen replacement therapy (ERT) and combination of estrogen and progesterone therapy, also known as hormonal replacement therapy (HRT), will ameliorate many of these adverse effects but may in turn increase other risks.

The risks and benefits of estrogen and progestin in healthy postmenopausal women have been a subject of considerable debate for the last 25 years. Recently, meta-analyses of observational studies indicated benefits of HRT included prevention of osteoporotic fractures and colorectal cancer, while prevention of dementia is uncertain. While, harms include coronary heart disease (CHD), stroke, thromboembolic events, breast cancer, and cholecystitis[2]. An earlier study also reported the overall health risks exceeded benefits from use of combined estrogen plus progestin for an average 5.2-year follow-up among healthy postmenopausal women, and the results indicate that this regimen should not be initiated or continued for primary prevention of CHD, the risk of placebo/HRT was 30/37 women per 10,000 per year, 29 per cent increase. The same was true of breast cancer, the risk of placebo/HRT was 30/38 women per 10,000 per year, 26 per cent increase. There were some decreases; a 37 per cent decrease in the risk of colorectal cancer, and a 34 per cent decrease in the risk for hip fracture. However, in the present study there was no subanalyses of other risks factors were performed[3].

Relief of disruptive transitional symptoms has been and continues to be the main indication for using systemic HRT. In terms of vasomotor symptoms, the American College of Obstetricians and Gynecologists (ACOG) recommendations are that nonhormonal alternatives may be helpful, but long-term use of HRT should be discontinued in asymptomatic patients as soon as possible, and the lowest effective dose should be entertained. When considering the use of HRT for longer than 5 years, the clinician and individual patient should weigh the benefits *versus* the potential side effects and risks for that particular patient[4]. In addition, transdermal ERT is an alternative to oral ERT that has been associated with good compliance rate[5], and positive efficacy on climacteric symptoms[6-10].

The present study investigated the efficacy, safety, and acceptability, of continuous low-dose transdermal estradiol in the treatment of climacteric symptoms in hysterectomized menopause women.

METHOD

This was an open-label, simple clinical trial, conducted in Hat Yai Regional Hospital. Patients were recruited from the menopause clinic, outpatient department, beginning on January 9, 2000. The last patient completed the intended 24-week follow-up on September 16, 2001. Hysterectomized females, legal age, experiencing vasomotor symptoms, including one or more of the following; hot flushes, urogenital or psychological symptoms, night sweats with or without other unpleasant symptoms, were enrolled. The modified Greene climacteric score was used, evaluating of the treatment efficacy[11], 20 indicators were adapted and each had scored from 0 to 3: 0 = none, 1 = mild, 2 = moderate, and 3 = severe. At screening, the eligible subjects were recruited if the climacteric score was at least 15.

Exclusion criteria included allergy to estrogens, having taken an ERT within 1 week prior to screening, no willingness to continuously take the trial product for 6 months of the study, and those with chronic illnesses. The Institutional Review Board (IRB), Hat Yai Regional Hospital, approved the protocol. All subjects gave their informed consent before entering the trial.

The subjects received the transdermal patch, a 12.5-cm^2 matrix patch, containing 3.9 mg of 17β-estradiol®[12]. The patch was to be applied to a dry location on the abdomen or upper buttock. One patch was worn for 7 days (1 patch per week), and patches were applied on the same day of the week for the duration of 6 months. Subjects were allowed to have showers, but not to directly rub on the patch. Patches were not to be removed except for scheduled weekly replacement. If a patch fell off prematurely, or more than one quarter of the patch area was dislodged, a new patch was applied for the remainder of the week. The regular weekly cycle of patch replacement was then to be resumed. If another patch fell off during the same cycle, it was not to be replaced; a new patch was to be applied at the end of the week, and the weekly cycle of patch was resumed. If a patch was partially lifted from the skin, it was to be pressed back into place.

The primary end point of the study was to consider the positive effects of the product on climac-

teric score, including from the point of screening; admission and follow-up visit at week 1-, 3- and 6-months. The secondary end points were hormonal assays; serum estradiol, serum follicle-stimulating hormone (FSH) and serum lutienizing hormone (LH), and lipoprotein analyses; cholesterol, low-density lipoprotein (LDL) plus very low-density lipoprotein (VLDL), high-density lipoprotein (HDL), and triglycerides (TG). The local adverse events and acceptability were assessed by the subjects' responses to the questions.

Descriptive statistics for mean, standard deviation, minimum, and maximum, were present for the absolute data and change from baseline. The Chi square test was used to compare differences between visits and baseline within each group, performed using EpiInfo version 6.

RESULTS

A total of 62 hysterectomized women were screened for the study; 6-month full follow-up of 50 of 62 cases (80.6%), 3-month partial follow-up of 1 case (1.6%), 1-month partial follow-up of 7 cases (11.2%), and voluntary withdrawal before admission of 4 cases (6.4%). Among those of the incomplete continuation group, the reasons included inconvenient drug administration, adverse events, adherence with the schedule, and lost to follow-up.

Full six-month evaluation was analyzed, among 50 subjects for measurement outcomes. The mean age of the study subjects was 45.7 years, standard deviation of 5.6, and the range was from 28 to 57 years old. The majority of the women, 38 from 50 (76%) were married, and 6 from 50 (12%) were single, 6 from 50 (12%) were widowed. The variety of surgical menopause was 44 cases from 50 cases (88%) of hysterectomy, 5 from 50 cases (10%) of hysterectomy and unilateral oophorectomy, and 1 of 50 cases (2%) of hysterectomy and without oophorectomy. Mean of baseline characteristics is presented in Table 1.

The modified climacteric score confined in 20 indicators; hot flushes, night sweats, headaches, mood instability, nervous, feeling neglected, excitable, insomnia, feeling tired, back pain, joint pain, muscle pain, dry skin, dry vagina, dyspareunia, loss of sexual satisfaction, loss of interest in sex, dysuria, urinary frequency, and urinary incontinence. Each indicator was weighted by the subjects as; 0 = none, 1 = mild, 2 = moderate, 3 = severe. Overall, only one case reported no improvement after the therapy, by self assessment.

Table 1. Mean of baseline characteristics.

	Total n = 50
Weight (kg)	58.6
Modified climacteric scale (0-60)	27.1
Hot flushes scale (0-3)	2.1
Night sweats (0-3)	2.08
Estradiol (pg/ml)	27.8
FSH (mIU/ml)	70.0
LH (mIU/ml)	31.1
Cholesterol (mg/dl)	207.0
HDL (mg/dl)	60.8
LDL + VLDL (mg/dl)	146.2
TG (mg/dl)	125.0

After medication, the mean of modified climacteric score had decreased from the baseline of 27.18 to 16.60, 12.78, and 12.18 at 1-, 3- and 6-months respectively. The mean climacteric score was significantly decreased, $p < 0.01$, after medicating at 1-, 3- and 6-months visits. The distribution of all indicators is shown in Table 2. The majority of indicators showed significant changes except, hot flushes and muscle pain.

Mean of hormonal and lipoprotein profiles are shown in Fig. 1 and Fig. 2. The mean serum estradiol slightly fluctuated from the baseline of 27.88 to 44.08 and 42.43 pg/ml at 1- and 3-month respectively. Whereas, the mean of FSH/LH was gradually decreased from the baseline of 70.03/31.19 to 53.37/26.86, and 48.53/24.39 mIU/ml at 1- and 3-months respectively. There were no statistical changes of hormonal profile.

The mean cholesterol level, was slightly changed from the baseline of 207.04 to 211.04 and 215.06 mg/dl at 1- and 3-month; as well as, the mean LDL plus VLDL level from the baseline of 146.22 to 149.76 and 154.02 mg/dl. While the mean HDL level varied from the baseline of 60.82 to 61.28 and 61.04 mg/dl, The mean triglyceride levels slightly fluctuated from the baseline of 125.04 to 126.34 and 109.58 mg/dl at 1- and 3-months. There were no statistical changes of lipoprotein profiles.

Blood pressure, pulse rate, and physical examination, including breast examination, were performed monthly, and no abnormal findings were detectable. The pelvic examination and Papanicolaou

Table 2. Comparison of mean scale of modified climacteric indicators at admission, 1-, 3- and 6-months.

Indicators	Admission	Month 1	Month 3	Month 6
Hot flushes	2.16	0.72	0.44	0.42
Night sweats	2.08	0.86*	0.60	0.58
Headaches	1.58	0.86**	0.74	0.82
Mood instability	1.52	0.70**	0.48**	0.64
Nervousness	1.66	0.90	0.58**	0.72
Feeling neglected	0.92	0.54**	0.30	0.38*
Excitable	1.26	0.78**	0.44	0.44
Insomnia	1.40	0.80**	0.56**	0.48*
Feeling tired	1.68	1.28**	0.94*	0.80
Back pain	1.66	1.08**	1.30	1.08
Joint pain	1.54	1.20**	1.12	1.08
Muscle pain	1.54	1.00	0.88	0.74
Dry skin	1.58	1.00*	0.80	0.68
Dry vagina	1.28	0.84**	0.58	0.52*
Dyspareunia	0.78	0.46	0.26*	0.34*
Loss of sex satisfaction	1.04	0.78	0.54**	0.52**
Loss of interest in sex	1.34	1.12	0.92**	0.90**
Dysuria	0.44	0.16	0.06	0.04*
Urinary frequency	1.06	0.80**	0.64	0.48
Urinary incontinence	0.92	0.80	0.66**	0.58*
Total mean scale	27.18	16.60**	12.78**	12.18**

* p-value < 0.05
** p-value < 0.01

smear were conducted at admission, and no abnormal features were noted. Estrogenic effects were encountered: 2 cases of headache (4%), 1 case of nausea (2%), and 1 case of mastodynia (2%).

All subjects adhered to patch application and it was well tolerated. The local adverse events, occurring at the site of application, included erythema, burning sensation, vesicle, and itching. The severity of events was classified into no, mild, moderate, and severe. The number of subjects and distribution by severity are shown in Table 3. Every patch did not always bring about the episode of adverse events, but some patches did. Erhythema and vesicle were significantly decreased at 3-months, while burning sensation was significantly decreased at 3- and 6-months but itching was not. The various kinds of skin irritations, mild to severe degree, varied from 25 to 76 per cent, and averaged 40.3 per cent. Of those, the most common event was itching (66%), followed by erythema (62%), vesicle (19.3%, and burning sensation (13.3%).

By the end of the study, 48 cases (96%) strictly complied with the weekly schedule, 46 cases (92%) reported easy application, while 2 cases (4%) felt it disrupted their lifestyle. Twenty seven cases prefered the transdermal estradiol patch, compared to the oral ERT (54%). The acceptability of the transdermal patch appeared to be satisfactory.

Patch adhesiveness was assessed, and at least 94 per cent of cases found it to be excellent, detachment less than one quarter, and at least 88 per cent were total adhesion plus total adhesion with slightly open edge. The description of adhesiveness revealed: 1) total adhesion with closed edge was 24 cases (48%), 19 cases (38%), and 22 cases (44%); 2) total adhesion with slightly open edge was 20 cases (40%), 28 cases (56%), and 26 cases (52%); 3) total adhesion with markedly open edge was 3 cases (6%), 1 case (2%), and 1 case (2%); and 4) detached less than one quarter was 3 cases (6%), 2 cases (4%), and 1 case (2%), at 1-, 3- and 6-months, respectively. Frequency of detachment were addressed: 1) always - 7 cases (14%), 3 cases (6%), and 2 cases (4%); 2) often - 8 cases (16%), 18 cases (36%), and 10 cases (20%); 3) sometimes - 13 cases (26%), 4 cases (8%), and 11 cases (22%); 4) seldom - 4 cases (8%), 6 cases

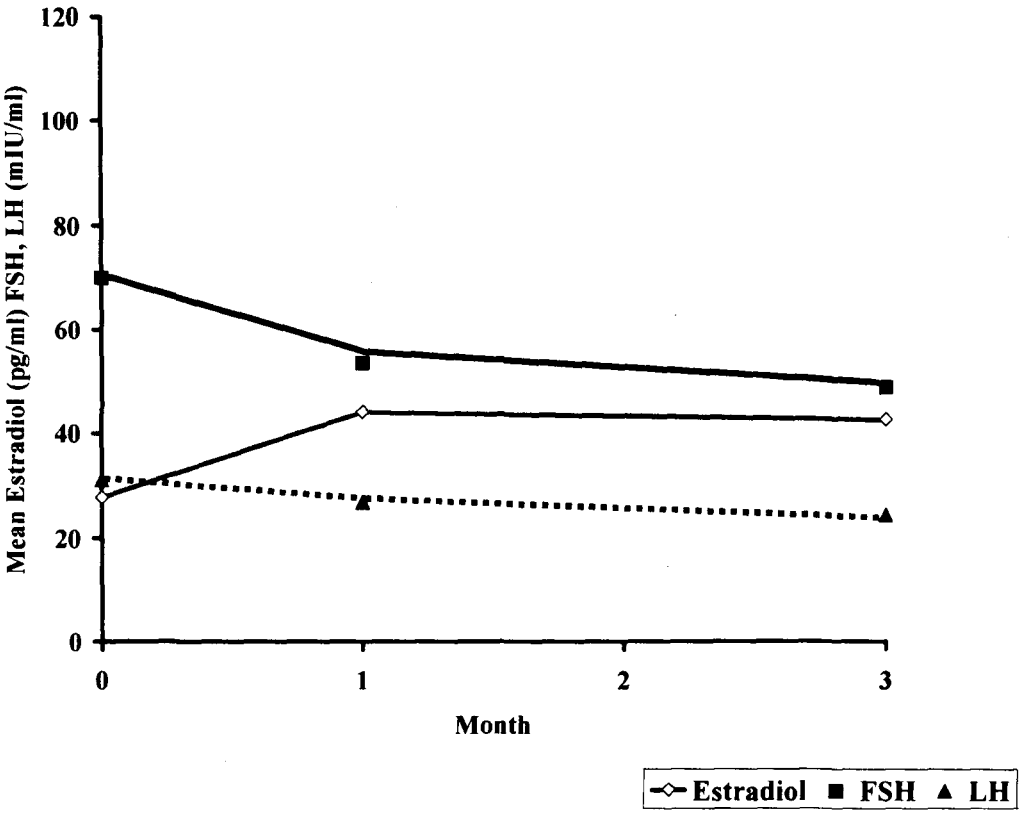

Fig. 1. Mean estradiol, FSH, and LH at admission, 1- and 3-months.

(12%), and 4 cases (8%), and 5) no answer or not sure - 18 cases (36%), 19 cases (38%), and 23 cases (46%), at 1-, 3- and 6-months, respectively. (Table 4)

DISCUSSION

The period of time, both before and after cessation of menses, is often termed the perimenopausal or the climacteric. The criteria women use to self-define their menopausal status have not been elucidated. The clinician is concerned not with what proportion of the climacteric population experiences symptoms, but rather with the individual who comes to the doctor seeking relief for her complaints. The clients may be premenopausal, perimenopausal, or postmenopausal or have had a hysterectomy with or without oophorectomy. Despite the advent of menopause treatment clinics, in many countries most women consult their own physician.

The first major step for the clinician is to establish the diagnosis of the symptoms presented. With regard to mood and sexual complaints, the doctor needs to have complete details of the presenting symptoms, their duration, and their association with the onset of the climacteric. The doctor should ask about other menopausal complaints. In taking the history, symptoms suggesting other major disorders should be sought. These include psychiatric disorders, especially major depression and generalized anxiety disorder; marital problems or sexual dysfunction; and midlife crisis. In the present study, the authors modified the Greene climacteric score, to be the clinical set criteria for the diagnosis of climacteric syndrome[11]. Other

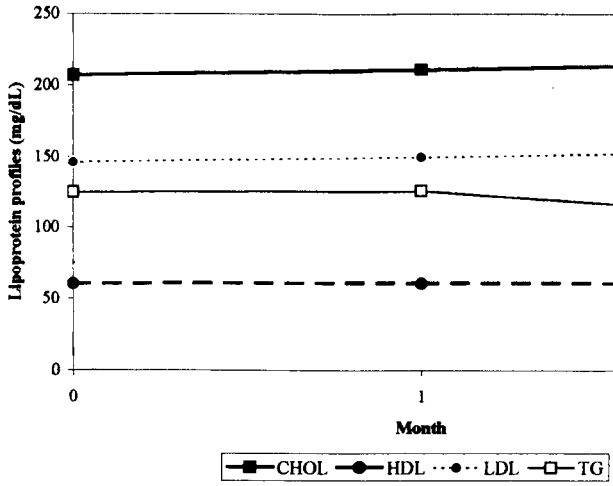

Fig. 2. Mean cholesterol, HDL, LDL and TG at admission, 1- and 3-months.

Table 3. Local adverse events, occurring at site of application.

Events	Month 1		Month 3		Month 6	
	No.	%	No.	%	No.	%
Erythema (n = 50)						
No	25	50	20	40	12	24
Mild	13	26	17	34	29	58
Moderate	7	14	8	16	6	12
Severe	5	10	5	10	3	6
Burning sensation (n = 50)						
No	41	82	45	90	44	88
Mild	7	14	5	10	5	10
Moderate	2	4	-	-	1	2
Vesicle (n = 50)						
No	43	86	41	82	37	74
Mild	4	8	4	8	10	20
Moderate	3	6	4	8	3	6
Severe	-	-	1	2	-	-
Itching (n = 50)						
No	17	34	17	34	16	32
Mild	23	46	24	48	26	52
Moderate	7	14	6	12	4	8
Severe	3	6	3	6	4	8

unpleasant symptoms such as, urogenital and psychological symptoms were also evaluated. The score of 15 or more was considered as clinical climacteric syndrome.

Transdermal therapy will be beneficial if blood levels of biologically active estrogen, estradiol, are at least equivalent to those found in premenopausal women. The goal is to have blood levels between 60 and 150 pg/100 ml[13]. The subjects received 12.5-cm^2 patches containing 3.9 mg of 17β-estradiol® which delivered 0.05-mg estradiol per day, and the peak blood levels averaged approximately 50 pg/ml, over the 7-day period of the first week. After patch removal, blood level fell to near

Table 4. Adhesiveness of the patches, and frequency of detachment.

Item	Month 1		Month 3		Month 6	
	No.	%	No.	%	No.	%
Adhesiveness (n = 50)						
TA with close edge	24	48	19	38	22	44
TA with slightly open edge	20	40	28	56	26	52
TA with markedly open edge	3	6	1	2	1	2
Detachment less than one quarter	3	6	2	4	1	2
Frequency of detachment (n = 50)						
Always	7	14	3	6	2	4
Often	8	16	18	36	10	20
Sometime	13	26	4	8	11	22
Seldom	4	8	6	12	4	8
No answer or not sure	18	36	19	38	23	46

TA = total adhesion

baseline within 12 hours[14,15]. The pharmacokinetic analysis, over a 7-day period during the second week, of ®, a 12.5-cm^2 patch containing 3.9 mg of estradiol and delivering 0.05 mg estradiol/day when applied for 7 days, the difference in fluctuation reflected the difference in their maximal value of 67.7 pg/ml[16]. In the present study, the transdermal estradiol patch effectively reduced the severity of menopausal symptoms, measured by the modified climacteric score, with statistical significance. That means having good health-related quality of life. The use of well-known standard questionnaires for the evaluation will facilitate interpretation and comparison of results obtained in different timeframes and trials. Only a few indicators were not significantly reduced, in real practice those should be weighted against the clients' satisfaction. If not, a higher dose of ERT can be considered, case by case.

The usefulness of postmenopausal ERT in the management of hypercholesterolemia has been prescribed by Darling, et al[17]. Recent studies have shown that transdermal estradiol induces a statistically significant fall in the concentrations of serum triglycerides in healthy menopausal women[18,19]. This short-term study has shown significant initial reduction in the concentration of triglycerides. However, an obstacle to the use of transdermal hormone therapy has been the scarcity of data indicating a beneficial impact on the lipoprotein profile. There has been concern that delivery of estrogen through the skin yields a blood level that might be too low to provide protection against CHD, especially because after peak concentrations in the first day after application, there is a progressive decrease that can be relatively rapid. Furthermore, there is marked variation in levels among individuals and within the same individual. Also, the CHD is likely to have other risk factors such as smoking, family history, high blood pressure, or increased cholesterol.

The current generation of patches has the hormones dissolved and distributed throughout the adhesive matrix, less adverse events than an alcohol reservoir in which the estrogen was released through a semipermeable membrane attached to the skin with an adhesive[15]. In contrast to the reservoir patch, the matrix patch is well accepted in a hot, humid climate [20]. The use of the transdermal delivery system is an expanding area with an increased number of drugs becoming commercially available by this method. Future systems may include the use of iontophoresis to drive the active agent across the skin barrier [21]. Applying patches to varying sites should help reduce the incidence and severity of skin sensitivity reactions[22].

Advantages and disadvantages should be considered. The first advantage is only small amounts of estradiol need to be delivered through the skin, avoid the first-pass impact on the liver that occurs with oral estrogen and produces estradiol serum level adequate to relieve climacteric symptoms[5]. The other advantages are precise control of dosage, predictable absorption without major intermediary metabolism, less hepatic protein induction, and a more natural serum profile of estradiol and estrone. The ease and convenience of a weekly dose may motivate

the clients' compliance. The disadvantage is skin irritation at the application site. The literature review revealed adverse skin reactions have been reported from 2 per cent to > 25 per cent, depending on transdermal system, climate conditions, and individual sensitivity[23-26]. From the authors' experience, the overall degree of skin irritations was up to 40.3 per cent an average minimum of 2 per cent and maximum of 76 per cent.

In conclusion, the transdermal estradiol patch effectively reduced the severity of menopausal symptoms, measured by a modified climacteric score. Adhesion was found to be excellent. In actual clinical practice, the transdermal patch should be appropriately introduced to tolerant users.

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ประสิทธิผลความปลอดภัยและการยอมรับของเอสโตรเจนแผ่นแปะผิวหนัง ระยะการใช้ 7 วัน สำหรับการใช้ฮอร์โมนเอสโตรเจนทดแทน

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วัตถุประสงค์ : เพื่อประเมินประสิทธิผล ความปลอดภัย และการยอมรับเอสโตรเจนแผ่นแปะผิวหนัง ระยะการใช้ 7 วัน สำหรับการใช้ฮอร์โมนเอสโตรเจนทดแทน

การออกแบบ : การศึกษาแบบปลายเปิด

สถานที่ : โรงพยาบาลศูนย์หาดใหญ่

ผู้เข้าร่วมการศึกษา : สตรีที่ตัดมดลูกที่มีอาการของวัยหมดระดูตามธรรมชาติหรือการผ่าตัด

วัสดุและวิธีการ : ผู้เข้าร่วมการศึกษาได้รับแผ่นแปะขนาด 12.5 ตารางเซนติเมตร บรรจุ estradiol จำนวน 3.9 มิลลิกรัม® ซึ่งปล่อยยาออกวันละ 0.05 มิลลิกรัม ใช้สัปดาห์ละครั้ง นาน 6 เดือน การประเมินเกี่ยวกับประสิทธิผล ความปลอดภัย และการยอมรับ กระทำเมื่อสิ้นเดือนที่ 1, 3 และ 6

ผลการศึกษา : อาสาสมัครทั้งหมด 50 ราย ค่าเฉลี่ย serum estradiol/ follicle-stimulating hormone (FSH)/ luteinizing hormone (LH) เท่ากับ (27.88/70.03/31.19), (44.08/53.37/26.86) และ (42.43/48.53/24.39) pg/ml, mIU/L, mIU/L เมื่อแรกรับ เดือนที่ 1 และเดือนที่ 3 ตามลำดับ

ค่าเฉลี่ยของ modified Greene climacteric score เท่ากับ 27.18, 16.60, 12.78, และ 12.18 เมื่อแรกรับ เดือนที่ 1 เดือนที่ 3 และเดือนที่ 6 ตามลำดับ อย่างน้อยร้อยละ 94 ของแผ่นแปะที่ใช้ไม่หลุดออกเกิดกว่า 1 ใน 4 ของแผ่น อาการระคายผิวหนังที่พบบ่อยที่สุดคือ คัน ตามด้วยรอยแดง ถุงน้ำขนาดเล็กและปวดแสบปวดร้อน อาสาสมัครทนต่อแผ่นแปะได้ดีและการยอมรับเป็นที่น่าพอใจ

สรุป : เอสโตรเจนแผ่นแปะผิวหนังมีประสิทธิผลในการลดความรุนแรงของอาการวัยหมดระดูได้ดี โดยประเมินจาก modified climacteric score การติดของแผ่นปะดีเยี่ยม ในการใช้ทางคลินิกจริงการใช้แผ่นแปะผิวหนัง ควรแนะนำให้ใช้อย่างเหมาะสม เฉพาะผู้ที่ทนต่อแผ่นแปะได้ดี

คำสำคัญ : เอสโตรเจนแผ่นแปะ, การใช้ฮอร์โมนเอสโตรเจนทดแทน, ประสิทธิผล, ความปลอดภัย, การยอมรับ

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