Randomized Comparison of Lower and Standard Dosages of Transdermal Estradiol on Serum Estradiol Levels and Vaginal Maturation Index

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Objective: *To evaluate serum estradiol (E2) in postmenopausal women who received 0.025 mg/d or 0.05 mg/d transdermal estradiol, in an equivalent trial.*
Material and Method: *One hundred and eight postmenopausal women were randomized into 0.025 mg/d and 0.05 mg/d of transdermal E2 matrix patch. After 12 weeks, serum E2 and vaginal maturation index (VMI) were checked in both groups. Adverse effects, such as breast tenderness, application site reaction, weight gain, and headache, were also assessed.*
Results*: Serum E2 in 0.025 mg/d and 0.05 mg/d groups were 42.43 $\pm$ 35.11 and 48.41 $\pm$ 22.36 pg/mL, respectively. There was no statistically significant difference between the groups. Equivalence was found under CI of $\pm$ 14 pg/mL. Mean value of superficial cells and vaginal maturation index (VMI) were comparable between both groups. Adverse effects seem to be less in the lower dosage group compared to the standard dosage group.*
Conclusion*: The lower dosage (0.025 mg/d) of the transdermal E2 matrix system is probably an appropriate treatment option for postmenopausal women who need minimal effective and minimal adverse effects.*

Keywords: *Transdermal patch, Lower dosage, Serum estradiol, Menopause*

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Parenteral route of postmenopausal hormone therapy (HT) is the treatment option that can avoid first pass hepatic effects. Transdermal estradiol (E2) has been developed to minimize the effect of estrogen on hepatic metabolism. The reservoir system came first as the original transdermal patch that needs to be changed every 3-4 days. The failure of the system was due to its high incidence of skin irritation particularly when used in tropical regions with high temperature and humidity[1]. The side effect is probably caused by the skin sensitiveness to alcohol that is used as the vehicle for dermal absorption of E2[2].

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The more recent new matrix system has been introduced which demonstrates a lower incidence of skin irritation[3]. The new transdermal patch needs no particular vehicle. The dermal absorption of E2 depends on gradient concentration of hormone embedded in the matrix[4]. The doses comprise of daily 0.025, 0.5 and 0.1 mg of E2. The common recommended doses are 0.05-0.1 mg/day of E2 patch, which give E2 level approximately similar to that of daily 0.625 mg of oral conjugated equine estrogen (CEE). CEE of 0.625 mg is believed to raise serum E2 to the level that can prevent postmenopausal bone loss and relieve menopausal symptoms in most of the cases[5].

Actually, postmenopausal women in Asia have a smaller body build, less prevalence of menopausal symptoms and lower incidence of fractures

compared to their Caucasian counterparts[6-10]. Use of lower HT dosages may be appropriate to ensure drug safety while maintain its efficacy. With the global trend of HT towards lower dosages, the authors conducted a randomized comparison of daily dose of transdermal E2 0.025 and 0.05 mg matrix patch to assess the serum E2 level and its effect on vaginal epithelium in post-menopausal women. The authors hypothesized that the lower dose of transdermal E2 patch provided a comparable serum level of E2 and had a similar effect on vaginal epithelium when compared to the standard dose.

Material and Method

This randomized, placebo controlled trial was conducted at the menopause clinic of Chulalongkorn Hospital, Thailand. The present study included post-menopausal women 40-60 years of age, body mass index (BMI) between 19-29 kg/m^2 amenorrhea for more than 12 months with serum follicle stimulating hormone (FSH) level > 30 IU/L and serum estradiol < 30 pg/mL.

Exclusion criteria included users of HT within the past 3 months, having a previous history of breast cancer, endometrial cancer, venous thromboembolism, hepatitis, or regular smoking. The protocol and informed consent form were approved by the Ethical Review Board of the Faculty of Medicine, Chulalongkorn University, Thailand. Informed consent was obtained from all women before a screening visit.

Demographic data and medical history were obtained from all the participants. Screening visit assessment included general physical examination, manual breast examination, pelvic examination, vaginal maturation index (VMI) assessment and mammographic screening.

The participants were allocated into two groups using the block-of-four randomization. The first and second groups received a daily dose of transdermal E2 0.025 mg (Climara 6.5 cm^2) and transdermal E2 0.05 mg (Climara 12.5 cm^2) respectively. The patients were advised to apply the patch over the lower abdominal area. After 7 days, a new patch was replaced around 6-7 a.m. after taking a bath and letting the skin dry. The new patch was recommended to be placed at a new area of the lower abdomen. The participants were advised to apply the patch firmly over the skin to avoid an air bubble forming. A set of plaster micropore was provided to all the participants for use in case of partial patch detachment prior to the date due. For the incidence of complete premature detachment, a new patch was replaced by applying over a new area. Telephone interview was done every week for the first 4 weeks for the compliance check.

All the participants were followed up at 4, 8, and 12 weeks. At the last visit, a blood sample was collected approximately 24-26 hours after a new patch was applied for serum E2 assay. All samples were obtained by venipuncture at the antecubital fossa and collected into glass tubes without anticoagulant before centrifugation (3,000 rpm for 10 minutes at room temperature). The samples were then aliquoted into polypropylene test tubes and stored at -70 degree celcius unit analyzed. E2 concentration was quantified in duplicated samples by a method based on a modified Fluorescent Immunoassay (FIA) using commercial kits (DELFIA®, Wallac Oy, Finland). The level of FSH concentrations was determined in duplicate using semi-auto Fluorescent Immunoassay technique (DELFIA®, Wallac Oy, Finland).

The intra-assay and inter-assay precision of E2 assay was between 2.90-7.00% and 3.50-8.20% respectively. The analytical sensitivity of the DELFIA E2 assay was typically better than 13.60 pg/mL.

Vaginal maturation index (VMI) assessment was performed at baseline and 12 weeks visits. The validated cytologic assessment of vaginal mucosa was performed over the middle third of the lateral vaginal wall. VMI interpretation was done by one of the co-authors who is a gynecologic pathologist (ST) who was blinded of the treatment groups. As a standardized pattern, a hundred cells count was classified as superficial (S), intermediate (I) or parabasal (P) cell type. The VMI was calculated using the equation (1 x S) + (0.5 x I) + (0 x P)[11,12].

Assessment of treatment adverse effects such as breast tenderness, application site reaction (erythema and pruritus), weight gain and headache was done at each follow up visit.

The primary objective of the present study was to compare serum E2 level of women receiving either transdermal E2 daily 0.025 mg or 0.05 mg in equivalent trial. The authors conducted a pilot study and found that the two groups were considered equivalent of the 95% two sided confidence interval for the treatment difference falling within the interval of +/- 14 pg/mL. The authors accepted the variation of hormone assay at +/- 10%. The sample size under 95% confidence interval and the power of 0.80 is 51 cases per group.

The secondary objective was to compare the effect of transdermal E2 daily 0.025 and 0.05 mg on vaginal maturation index (VMI) after 12 weeks of treatment. The ANCOVA was used for analyzing the data.

Adverse effects of both groups were compared using Chi-square test. A p-value of less than 0.05 was considered statistically significant difference between groups.

Results

Of the 113 patients screened, 108 were randomized to receive transdermal E2 either 0.025 mg or 0.05 mg daily (n = 54 in each group). Twelve (11.1%) patients discontinued treatment before the schedule, nine due to adverse events, and three for nonmedical reasons (Fig. 1). Reasons for withdrawal due to adverse events included mastalgia (4, all receiving transdermal E2 0.05 mg daily), application site reaction (2 receiving transdermal E2 0.025 mg, whereas, 1 was receiving transdermal E2 0.05 mg daily) and excessive weight gain (2, all receiving transdermal E2 0.025 mg daily). At baseline, there were no significant differences between the two groups in terms of demographic and clinical characteristics (Table 1). Patient compliance was high with 96 (89%) using all 12 transdermal E2 patches, the remaining nine cases (11%) used at least 9 patches in the 12 weeks study period with no differences between the groups.

The basal and mean serum levels at 12 weeks of E2 were not significantly different between the groups (Table 2). Equivalence was found under CI of ± 14pg/mL (CI: -0.07 to +12.01). The basal and mean value at 12 weeks of superficial cells and vaginal maturation index are shown in Table 3. In each treatment group, subjects experienced significant increases in superficial cells and vaginal maturation index over the baseline value (P<.001 at week 12; two-tailed, paired t test). At all points, mean values at baseline and 12 weeks of superficial cells and vaginal maturation index were comparable between the groups (ANCOVA).

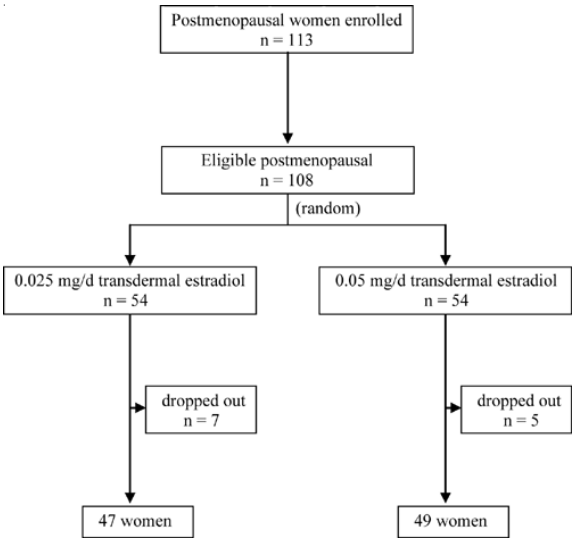

Fig. 1 Flow diagram of patient enrollment

Of the 108 randomized patients, 66 reported adverse experiences. The most frequent adverse events (56 patients) were weight gain (77.6% in transdermal E2 0.05 mg daily, 38.3% in transdermal E2 0.025 mg daily; P<0.001 between groups), application site reaction such as erythema and pruritus (36.7% in transdermal E2 0.05 mg daily, 31.9% in transdermal E2 0.025 mg daily). Most of these reactions were mild and not clinically significant. There were no significant differences between the two groups. The number of patients reporting moderate and severe mastalgia was significantly less with transdermal E2 0.025 mg than with 0.05 mg (32.7% versus 14.9% P = 0.04). Fourteen patients (14.6%) reported headache, with a similar incidence in both groups.

Table 1. Demographic data of studied participants between 0.025 mg and 0.05 mg transdermal estradiol groups at baseline (n = 108)

	0.025 mg transdermal E2 (mean ± SD) (n = 54)	0.05 mg transdermal E2 (mean ± SD) (n = 54)	p-value
Age (year)	51.19 ± 5.31	51.65 ± 5.54	0.65
Systolic blood pressure (mmHg)	111.29 ± 15.86	119.23 ± 11.88	0.94
Diastolic blood pressure (mmHg)	75.50 ± 10.13	74.93 ± 9.17	0.95
Duration of menopause (year)	4.88 ± 3.71	5.12 ± 3.01	0.76
BMI (kg/m^2)	22.92 ± 2.99	24.1 ± 2.39	0.94
Serum FSH (U/L)	88.10 ± 32.86	87.89 ± 29.91	0.97
Serum estradiol (pg/ml)	17.09 ± 7.99	14.27 ± 5.35	0.19
Vaginal maturation index (VMI)	15.45 ± 17.52	16.49 ± 16.11	0.75

BMI = Body Mass Index

Table 2. Serum estradiol level between both studied groups at 12th week (n = 96)

	0.025 mg/d transdermal E2 n = 47	0.05 mg transdermal E2 n = 49	p-value
	Estradiol level (pg/mL)	Estradiol level (pg/mL)	
Baseline	17.09 ± 7.99	14.27 ± 5.35	0.19
The 12th week	42.43 ± 35.11	48.41 ± 22.36	0.11

Table 3. Vaginal maturation index between both studied groups at screening and the visit in the following 12 weeks (n = 96)

	0.025 mg transdermal E2 n = 47		0.05 mg transdermal E2 n = 49		p-value
	Baseline	The 12th week	Baseline	The 12th week	
Percentage of superficial cells (Mean ± SD)	13.49 ± 14.40	32.81 ± 18.61	16.90 ± 16.82	38.82 ± 20.44	0.17
Vaginal maturation index (Mean ± SD)	48.26 ± 6.94	64.67 ± 10.23	48.38 ± 7.92	67.45 ± 11.51	0.22

Discussion

This randomized trial revealed that the lower dose of transdermal E2 (0.025 mg daily) gave a comparable serum E2 level compared with the standard dose (0.05 mg daily) in this equivalent trial. The effect on vaginal epithelium was comparable between the two groups when considering the improvements of vaginal maturation index. Subjects who used a lower dose of transdermal E2 reported fewer adverse effects compared to those who used the standard dose although there were no significant differences in application site reaction and headache.

The serial unveiling of Women's Health Initiative (WHI) study since 2002 has conveyed a message to the medical society that hormone therapy (HT) should not be prescribed to asymptomatic, healthy postmenopausal women. Long-term use of a daily dose 0.625 mg of conjugated equine estrogen (CEE) plus 2.5 mg of medroxyprogesterone acetate (MPA) was found to be associated with increased risks of coronary heart disease, stroke, dementia, thromboembolic phenomenon and breast cancer. The risks seem to outweigh the benefits of HT in terms of fractures and colo-rectal cancer risk reduction[13]. Nevertheless, the present study did not take into account the benefits of HT in relieving menopausal symptoms and improving menopausal symptom related quality of life (QOL).

The HT used in the WHI study is the most common regimen prescribed in the United States[11]. The results of the study have dramatically changed the daily clinical practice and given the menopause society a dilemma. However, the authors of the study cautiously remarked that the results should not be extrapolated to HT of lower dosage or different formulas.

In 1992, Barbieri made an interesting review showing that tissue from different organ systems or diseases responds differently to different levels of estrogen[14]. The review implies that there might be a window therapeutic level of estrogen that is beneficial without causing an adverse reaction. Recently, randomized trials looked into the efficacy and safety of lower dosages of HT and found them to have fewer side effects with comparable efficacy when compared to the conventional dose and regimen[15-20]. It is obvious that therapeutic trend of HT determines towards lower doses. Minimally effective dose is appropriate for treating postmenopausal women who used to have bad experience from side effects. However, a long-term study of side effects of this low dosage transdermal patch is suggested.

In the present study, the high incidence of skin irritation was probably caused by warm temperature and high humidity in this region. The patients may experience a higher incidence and severity of skin irritation during the summer resulting in poor treatment compliance. Therefore, it is more prudent to initiate the transdermal patch during the cool season and avoid prescribing the treatment on those who have a sensi-

tive skin ie., oily, perspiring, sweltering or those who are extremely obese.

In conclusion, the authors suggest that the lower dosage of 0.025 mg daily transdermal E2 matrix system is probably an appropriate treatment option for postmenopausal women who need a minimal effective dose to improve their menopausal condition with less concern on side effects.

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การศึกษาเปรียบเทียบผลของฮอร์โมนทดแทนแบบแผ่นแปะผิวหนังขนาดต่ำและขนาดมาตรฐาน ในสตรีไทยวัยหมดระดู

ทัศน์วรรณ รังรักษ์ศิริวร, กระเษียร ปัญญาคำเลิศ, สุรางค์ ตรีรัตนชาติ, นิมิต เตชไกรชนะ

วัตถุประสงค์: *ศึกษาระดับ Serum estradiol (E2) ในสตรีวัยหมดระดูที่ได้รับฮอร์โมนทดแทนชนิดแผ่นแปะผิวหนัง ขนาด 0.025 มิลลิกรัมต่อวัน และขนาด 0.05 มิลลิกรัมต่อวัน โดยใช้ Equivalent test*

วัสดุและวิธีการ: *สตรีวัยหมดระดูที่เข้าได้กับเกณฑ์การศึกษาจำนวน 108 คน แบ่งเป็น 2 กลุ่ม กลุ่มหนึ่งได้รับฮอร์โมนทดแทนชนิดแผ่นแปะผิวหนัง ขนาด 0.025 มิลลิกรัมต่อวัน และอีกกลุ่มได้ขนาด 0.05 มิลลิกรัมต่อวัน หลังจากใช้ยาไป 12 สัปดาห์ จึงได้ทำการตรวจระดับ Serum E2 และตรวจภายในและคำนวณหา Vaginal Maturation Index (VMI) และบันทึกผลข้างเคียงที่เกิดจากการใช้ยาซึ่งได้แก่ อาการเจ็บเต้านม, ผื่นแพ้บริเวณที่แปะยา, น้ำหนักที่เพิ่มขึ้น และอาการปวดศีรษะ*

ผลการศึกษา: *ระดับ Serum E2 ในกลุ่มที่ได้รับฮอร์โมนทดแทนชนิดแผ่นแปะผิวหนัง ขนาด 0.025มิลลิกรัมต่อวัน และขนาด 0.05 มิลลิกรัมต่อวันคือ 42.43 $\pm$ 35.11 พิโคกรัมต่อวันและ 48.41 $\pm$ 22.36 พิโคกรัมต่อวันตามลำดับ ซึ่งเมื่อวิเคราะห์โดยใช้ Equivalent test พบว่าทั้ง 2 กลุ่มแทนกันได้ ค่าเฉลี่ยของ VMI ในทั้ง 2 ลุ่มไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติ อาการข้างเคียงไม่แตกต่างในทั้ง 2 กลุ่ม โดยพบว่ากลุ่มที่ได้ฮอร์โมนขนาดต่ำมีอาการข้างเคียงน้อยกว่ากลุ่มที่ได้ขนาดมาตรฐาน*

สรุป: *ฮอร์โมนทดแทนชนิดแผ่นแปะผิวหนัง ขนาด 0.025 มิลลิกรัมต่อวันเป็นอีกทางเลือกหนึ่งที่จะมาใช้ในสตรีวัยหมดระดูที่ต้องการฮอร์โมนทดแทน โดยยังคงมีประสิทธิภาพในการป้องกันและรักษาอาการในวัยหมดระดู และในสตรีที่มีความกังวลในเรื่องผลข้างเคียงจากการใช้ยา*