Serum Estradiol Level in Thai Surgical Menopausal Women Receiving Oral Micronized 17 β-Estradiol 1mg

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Objective : *To compare serum estradiol (E_2) level in Thai surgical menopausal women before and after receiving a daily dose of 1 mg oral micronized 17 β-estradiol.*
Design : *Experimental study (before and after treatment).*
Setting : *Gynecological ward, Hatyai regional hospital.*
Patients : *40 premenopausal Thai women who had undergone total abdominal hysterectomy with bilateral salpingo-ooporectomy (Surgical menopause) for 1 week previously due to benign gynecologic conditions were recruited in the present study. These women had no contraindications for receiving hormonal replacement therapy and no history of any hormonal intake in the past.*
Intervention : *All women were assigned to receive a 1 mg micronized 17 β-estradiol (Estrofem , Novo Nordisk A/S, Denmark) orally applied at bedtime (08.00 p.m.) each day.*
Measurements : *Serum estradiol (E_2) levels were measured before and after treatment at 4, 8 and 12 weeks. The hormonal measurement was performed using the ELFA-technique (Enzyme Linked Fluorescent Assay).*
Results : *Four cases were excluded due to loss to follow up. Of the remaining 36 cases, the mean age (± SD) and the body mass index were 46.27 ± 5.74 years and 23.72 ± 2.92 kg/m^2, respectively. Serum E_2 level significantly increased from baseline value at 4, 8 and 12 weeks (mean (± SD) of E_2 level at 0, 4, 8 and 12 weeks : 3.82 ± 6.30 pg/ml, 117.11 ± 92.86 pg/ml, 135.28 ± 91.38 pg/ml and 164.48 ± 78.94 pg/ml, $p < 0.05$) respectively.*
Conclusion : *A daily dose of 1 mg oral micronized 17 β-estradiol for 12 weeks increased the serum E_2 level to the follicular phase level of the normal menstrual cycle.*

Keywords : *Micronized 17 β-estradiol, Serum estradiol, Surgical menopause*

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It is now agreed that premenopausal women on whom total abdominal hysterectomy and bilateral oophorectomy (surgical menopause) was performed had abrupt menopausal changes compared with several years for natural menopausal women[1]. The circulating level of estradiol in serum after surgical menopause can drop to ≤ 10 pg/ml[2,3]. Therefore, they constitute the predominant group for consideration of hormone replacement therapy. The benefits of hormone replacement are well documented and include reduction or elimination of vasomotor symptoms, protection against osteoporosis, prevention of urogenital atrophy and improvement in general well-being[4].

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There are many regimens of prescribing hormone replacement therapy. In the case of total abdominal hysterectomy and bilateral oophorectomy (surgical menopause), continuous oral estrogen is the most popular prescription in the form of oral conjugated equine estrogen (CEE) 0.625 mg per day[5]. The micronized 17 β-estradiol is another form of estrogen with good absorption and can be taken orally which gives a estradiol blood level comparable to conjugated equine estrogen (CEE)[6].

To date, there is no data of the blood level of estradiol in Thai women who receive oral 1 mg micronized 17 β-estradiol. In the present study, the authors aimed to study the estradiol level in Thai surgical menopausal women before and after receiving a daily dose of 1 mg micronized 17 β-estradiol in the oral form.

Material and Method

The study was conducted from July 2002 to April 2004. Forty premenopausal Thai women who underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy (surgical menopause) 1 week previously due to benign gynecologic conditions at Gynecological ward, Hatyai regional hospital were recruited in this study. These women had not received estrogen therapy or discontinued all steroid medications at least 4 weeks before the study initiation. In addition, they had no contraindications to hormonal replacement therapy ie., previous venous thrombosis, estrogen-dependent neoplasm or liver disease.

The surgical menopausal women were informed of the study protocol before enrollment and signed an informed consent. Baseline physical examination included pelvic examination and breast examination. Peripheral venous samples for estradiol (E_2) level were obtained from each patient before taking 1 mg micronized 17 β-estradiol (Estrofem , Novo Nordisk A/S, Denmark) and at week 4, 8 and 12 after taking the mediction at bedtime (08.00 pm) each day. The blood samples were drawn between 08.00 and 10.00 am (12-14 hours after oral ingestion). The hormonal measurement was performed using the ELFA-technique (Enzyme Linked Fluorescent Assay).

The patients were also monitored for side effects. The subjects would not be included in the analysis if they was lost to follow up or forgot to take more than 4 tablets of the medication per month.

Statistical analysis

Descriptive statistics such as mean, standard deviation were used to describe the summary measures. All data were analysed statistically, with continuous data compared using *t*-tests or ANOVA and categorical data using chi-square tests. For all analyses, $p < 0.05$ was considered to indicate statistical significance.

Results

The mean $\pm$ SD of age , BMI and parity are 46.27 $\pm$ 5.74 years, 23.72 $\pm$ 2.92 kg/m^2 , and 2.54 $\pm$ 1.68 respectively. There were forty surgical menopausal women enrolled into the present study. Four cases were excluded due to loss to follow up.

The most common indication for surgery was myoma uteri in 17 patients (47.22%) followed by endometriosis in 6 patients (16.67%) as shown in Table 1.

The mean $\pm$ SD of estradiol level before receiving 1 mg 17 β-estradiol was 3.82 $\pm$ 6.30 pg/ml. After administration of 17 β-estradiol, all women had an estradiol level significantly increased over their baseline values ($p < 0.05$), reaching a mean $\pm$ SD level of 117.11 $\pm$ 92.86 pg/ml, 135.28 $\pm$ 91.38 pg/ml and 164.48 $\pm$ 78.94 pg/ml at 4 , 8 and 12 weeks, respectively (Table 2).

Discussion

Whereas natural menopause causes a gradual decrease of estrogen after months to years of anovulation, surgical menopause is associated with a dramatic and precipitous decrease in estrogen. After total abdominal hysterectomy with bilateral salpingo-oophorectomy, circulating estrogen can drop to $\leq$ 10 pg/ml within 24 to 48 hours after the operation, compared with several years for natural menopause[1]. Therefore, these women are the predominant group for consideration of hormone replacement therapy.

Estradiol blood level of 40-100 pg/ml was associated with the standard doses of hormone therapy [7]. In addition, there is evidence that estrogen administration with average levels of estradiol in the early to mid-follicular range (60 pg/ml) is adequate to protect bone in most women[8]. From the present study, the authors found that administration of 1 mg micronized estradiol significantly increased the serum estradiol level up to 117 pg/ml after 4 weeks in surgical meno-

Table 1. Indications for surgery

Indications for Total abdominal hysterectomy and bilateral salpingo-oophorectomy	n	%
Myoma uteri	17	47.22
Endometriosis	6	16.67
Adenomyosis	5	13.89
Ovarian cyst	3	8.33
Tubo-ovarian abscess	2	5.55
Pelvic pain	1	2.78
Molar pregnancy	1	2.78
CIS (Cervix)	1	2.78

Table 2. Serum estradiol level before and after taking micronized 17 β-estradiol 1 mg

Time			Estradiol level (pg/ml) Mean ($\pm$SD)	Range
Before			3.82 $\pm$ 6.30	0-22.17
After	4	weeks	117.11 $\pm$ 92.86	9.62-351.51
	8	weeks	135.28 $\pm$ 91.38	11.35-359.15
	12	weeks	164.48 $\pm$ 78.94	63.45-322.91

pausal women. These values were nearly equal to the previous study of Bomba et al, who reported the estradiol level of up to 100 pg/ml after receiving 6 weeks of standard dose (0.625 mg daily) conjugated estrogens (Premarin) in surgical menopausal women[9]. This dosage is also adequate to protect against bone mineral loss[10].

It was controversial whether the dosage of 1 mg or 2 mg daily of oral 17 β-estradiol was recommended to preserve an appropriate serum estradiol level. A dose-response relationship existed for serum estradiol level apparently achieved after oral estradiol administration. With regard to the present study, the authors suggested the 1 mg oral 17 β-estradiol daily was enough to increase the serum estradiol to the follicular phase level of the normal menstrual cycle. This amount of micronized 17 β-estradiol can give the efficiency level of estradiol enough to prevent bone loss. It was unnecessary to prescribe the higher dose which can create more side-effects.

Conclusion

A daily dose of 1 mg oral micronized 17 β-estradiol for 12 weeks increased the serum E_2 level to the follicular phase level of the normal menstrual cycle.

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ระดับเอสตราไดออลในสตรีไทยหมดระดูจากการผ่าตัดที่รับประทานยาไมโครไนซ์ 17 เบตา-เอสตราไดออล ขนาด 1 มิลลิกรัม

สมนึก วีระนรพานิช, สุวิทย์ บุณยะเวชชีวิน, สุรชัย ล้ำเลิศกิตติกุล

วัตถุประสงค์ *: เพื่อเปรียบเทียบเอสตราไดออลในน้ำเหลืองของสตรีไทยหมดระดูจากการผ่าตัดทั้งก่อนและหลังการได้รับยา 17 เบตา-เอสตราไดออลชนิดรับประทานขนาด 1 มิลลิกรัม*

ชนิดของการวิจัย *: การวิจัยเชิงทดลอง ชนิดก่อนและหลังการใช้*

สถานที่ทำวิจัย *: หอผู้ป่วยนรีเวชกรรม โรงพยาบาลศูนย์หาดใหญ่*

กลุ่มตัวอย่าง *: สตรีไทยก่อนวัยหมดระดูจำนวน 40 รายหลังได้รับการผ่าตัดมดลูกและรังไข่ทั้ง 2 ข้าง (วัยหมดระดูจากการผ่าตัด) ในช่วงระยะ 1 สัปดาห์ โดยมีข้อบ่งชี้ในการผ่าตัดจากก้อนเนื้องอกทางนรีเวชวิทยา นอกจากนี้ต้องไม่มีข้อห้ามในการรับประทานยาฮอร์โมนทดแทนและไม่ได้ใช้ฮอร์โมนใด ๆ มาก่อนการวิจัยนี้*

การกระทำ *: สตรีทุกรายได้รับยา 17 เบตา-เอสตราไดออล (Estrofem® , Novo Nordisk A/S, Denmark) ชนิดรับประทาน ขนาด 1 มิลลิกรัม วันละ 1 ครั้งก่อนนอนเวลา 20.00 น.*

ตัววัดที่สำคัญ *: ตรวจระดับเอสตราไดออลในน้ำเหลืองด้วยวิธี ELFA (Enzyme Linked Fluorescent Assay) ก่อนและหลังการรับประทานยาสัปดาห์ที่ 4, 8 และ 12*

ผลการวิจัย *: สตรีที่ถูกคัดออกจากการวิจัย 4 รายเนื่องจากขาดการติดตาม เหลือสตรีที่ศึกษาทั้งหมด 36 ราย มีอายุเฉลี่ย (± SD) 46.27 ± 5.74 ปี ดัชนีมวลกาย 23.72 ± 2.92 กิโลกรัมต่อตารางเมตร ระดับเอสตราไดออลในน้ำเหลืองหลังรับประทานยานาน 4, 8 และ 12 สัปดาห์เพิ่มขึ้นจากก่อนรับประทานยาอย่างมีนัยสำคัญทางสถิติ นั่นคือค่าเฉลี่ย ± ค่าเบี่ยงเบนมาตรฐาน จาก 3.82 ± 6.30 เป็น 117.11 ± 92.86,135.28 ± 91.38 และ 164.48 ± 78.94 พิโคกรัมต่อมิลลิลิตรตามลำดับ*

สรุป *: การรับประทานยา 17 เบตา-เอสตราไดออล ขนาด 1 มิลลิกรัมทุกวัน นาน 12 สัปดาห์ สามารถเพิ่มระดับเอสตราไดออลในน้ำเหลืองได้อย่างมีนัยสำคัญทางสถิติ และมีขนาดเท่าระยะฟอลลิคูลาร์ในสตรีที่มีรอบระดูปกติ*