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Hormone Replacement Therapy and Tear Volume in Postmenopausal Women with Dry Eye

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ABSTRACT

Objective To study the effects of hormone replacement therapy on the tear volume in postmenopausal women with dry eye.

Design A prospective randomized, double-blind controlled trial.

Settings Menopause clinic, King Chulalongkorn Memorial Hospital.

Subjects Thirty-two postmenopausal women were eligible for this study and randomly assigned into two groups.

Intervention Hormone replacement therapy (HRT) with conjugated equine estrogen (CEE) 0.625 mg plus medroxyprogesterone acetate (MPA) 2.5 mg daily in group I and placebo in group II.

Main outcome measures Measurement of the tear volume by the Zone Quick® test and assessment of ocular symptoms using visual analogue scale.

Results Twenty-nine cases completed the twelve-week study period, one case of the HRT group developed angina pectoris and two cases of the placebo group were lost to follow up. The initial tear volume in the HRT group (n=15) was 10.2±1.1 mm and placebo group (n=14) was 11.9±1.4 mm. After 12 weeks of treatment, the tear volume of the HRT group was 15.3±2.1 mm and the placebo group was 13.4±1.5 mm. There was no statistically significant difference between the two groups after 12-week of treatment. Nevertheless, the tear volume increased significantly in the HRT group after 12 weeks ($P<0.05$). The visual analogue scale of ocular symptoms were not significantly different between the two groups both before and after treatment.

Conclusion The hormone replacement therapy with CEE 0.625 mg plus medroxyprogesterone acetate 2.5 mg daily increased tear volume in postmenopausal women within twelve weeks. However, with the small sample size and short duration of this study, it did not have enough power to show the statistically significant difference when compared to the placebo group.

Key words: Tear volume, Dry eye, Hormone replacement therapy

Dry eye is an ocular surface disease that results from any condition that decreases tear secretion or increases tear evaporation[1] and is one of the common problems encountered in postmenopausal period. Forty-five percent of the population 65 years of age and over reported one or more symptoms of dry eye.[2] It is well known that dry eye is particularly common in women and frequently manifests following the onset of menopause.[3,4] There is also a gradual decline in tear function with age in women.[5] It has already been shown that the eye is a locus of action of female sexual hormones.[6] The cause of dry eye in menopause may be the reduction in naturally occurring estrogen. Topical estrogen has been reported to be successful in treating keratoconjunctivitis sicca, manifests mainly through a sensation of dryness in the congiunctival region, in postmenopausal women.[7] However, systemic estrogen has been used for the treatment of postmenopausal symptoms and prevention of osteoporosis. The aim of this study was to investigate the hypothesis that systemic hormone replacement therapy will produce an improvement of the tear volume and ocular symptoms in postmenopausal women with dry eye.

Material and Methods

This study was conducted between July 1, 1999, and February 15, 2000, at King Chulalongkorn Memorial Hospital. The research proposal was approved by the Ethics Committee of the Faculty of Medicine, Chulalongkorn University; all the participants gave their written informed consent. Thirty-two women visited the menopause clinic with dry eye were enrolled in the study. All of them were healthy and had been amenorrheic for at least one year with a follicle stimulating hormone (FSH) > 30 IU/L and an estradiol level of < 100 pmol/L. All the women did not receive any systemic or local hormone replacement therapy for the previous six months. The tear volume of all the participants measured by the Zone Quick® test was less than 20 mm. Patients with surgical menopause, severe climacteric symptoms, additional ocular diseases, abnormal uterine bleeding, history of breast or endometrial cancer, liver diseases, venous thrombosis or family history of breast cancer were excluded.

Thirty-two women were randomly assigned to one of the following two treatment groups: group I-hormone replacement therapy (HRT) with conjugated equine estrogen (CEE) 0.625 mg plus medroxyprogesterone acetate (MPA) 2.5 mg daily; group II-placebo. Both groups were treated for twelve weeks. Block of four randomization was performed and medication was distributed by a research nurse. The Zone Quick® test and visual analogue scale were measured by the ophthalmologist. The hormone and the control drugs were similar in color, consistency and smell. The Zone Quick® test was used to evaluate the tear volume before and after treatment : a sterile special cotton thread with a pH indicator phenol red ; the folded 3-mm end of the thread was placed into the palpebral conjunctiva at a point approximately 1/3 of the distance from the lateral canthus of the lower eyelid with the eye in the primary position (Figure 1). After 15 seconds, the length of the thread turning red was measured on a millimeter ruler. A color change of > 20 mm indicated a normal tear volume.

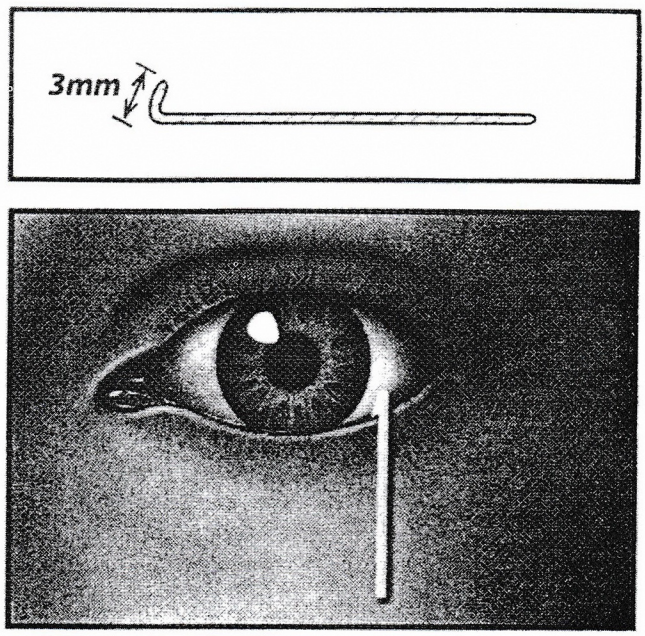


Fig. 1.

The ocular symptoms were recorded on a visual analogue scale 0-100 mm before treatment and after twelve weeks; these symptoms were sensation of dryness, sensation of foreign body, itching and excessive blinking.

The results are expressed as mean and standard error of mean (SE). Student's t test were used for statistical comparisons. P value < 0.05 were regarded as statistically significant.

Results

The two groups were not statistically different regarding their demographic data except for age (Table 1). One case of the HRT group developed angina pectoris during the study and two cases of the placebo group were lost to follow up.

The mean value of the tear volume by the Zone Quick® test obtained before and after twelve weeks of treatment for both groups are shown in Table 2. A comparison of the tear volume at the start of therapy and after twelve weeks revealed a significant difference in the HRT group (P=0.013), whereas in the placebo group no difference was found (P=0.192). There was no significant difference of the tear volume before and after treatment between the two groups. The difference of tear volume before and after treatment was not significant difference between the two groups (P=0.102).

The visual analogue score at the start of therapy compared with the score after twelve weeks in both groups showed no significant improvement in all four observed symptoms. No significant differences between the two groups before and after treatment in visual analogue scores of all symptoms.

Table 1. Baseline population characteristics

	HRT (n=15)	Placebo (n=14)	P value
Age (years)	53.7±1.0	50.8±0.8	<0.05
Year since menopause (years)	4.1±1.0	3.4±0.5	NS
Parity	2.6±0.3	2.1±0.4	NS
BMI (kg/m^2)	24.04±0.56	22.63±0.74	NS
Estradiol (pmol/L)	24.2±2.2	22.9±1.9	NS

Data are presented as mean ± standard error of mean (SE)
HRT = hormone replacement therapy
NS = no significance
kg/m^2 = kilogram / meter square
pmol / L = picomol / litre

Table 2. Mean tear volume by the Zone Quick(test in millimeters before and after 12 weeks of treatment

	HRT (n=15)	Placebo (n=14)	P value	95% CI
Pre-treatment (mm)	10.2±1.1	11.9±1.4	0.354	(-5.27, 1.96)
Post-treatment (mm)	15.3±2.1*	13.4±1.5	0.480	(-3.44, 7.12)
Difference of pre- and post- treatment (mm)	5.1±1.8	1.5±1.1	0.102	(-0.77, 7.90)

Data are presented as mean ± standard error of mean (SE)
HRT = hormone replacement therapy
CI = confidence interval
mm = millimeter
* P < 0.05 compared with baseline

Table 3. Visual analogue scale 0-100 mm (0 mm = no pain, 100 mm = maximum pain) of ocular symptoms

	Pre-treatment			Post treatment		
	HRT (n=15)	Placebo (n=14)	P value	HRT (n=15)	Placebo (n=14)	P value
Sensation of dryness	28.9±7.5	17.8±5.6	NS	25.9±6.6	15.8±6.0	NS
Sensation of foreign body	25.9±8.0	25.9±7.0	NS	22.0±8.1	23.6±8.6	NS
Itching	20.9±7.4	22.9±7.9	NS	18.3±6.7	26.2±9.6	NS
Excessive blinking	24.2±8.8	14.3±5.3	NS	9.9±4.7	15.3±6.0	NS

Data are presented as mean ± standard error of mean (SE)
HRT = hormone replacement therapy
NS = no significance
mm = millimeter

Discussion

Dry eye is particularly common in women which frequently manifests following the onset of the menopause.[4] Keratoconjunctivitis sicca is a common disease in postmenopausal women, affecting them significantly more often than men of the same age group.[8] This disorder is a specific deficiency of the aqueous component of the tear film[9,10] and manifests mainly through a sensation of dryness and foreign body in the conjunctival region. For younger women, there was a positive correlation between serum estradiol and tear function,[11] thus the reduction in estrogen during menopause may be the cause of dry eye in this transitional period. This study used the Zone Quick® test to measure tear volume because the phenol red thread was little which cause no sensation of eye irritation, easy procedure and was more statistically reliable with less intraindividual variation. The color changes of > 20 mm indicates normal tear volume. In our population, the tear volume was below normal level at the start of treatment. The results show statistically comparable demographic data, the tear volume and visual analogue score of all ocular symptoms except for age, the HRT group is older than the placebo group.

The tear volume at twelve weeks of treatment revealed no significant difference between the HRT and the placebo group. However, there was a

significant increase in the tear volume after 12 weeks of treatment when compared to baseline in the HRT group. This probably imply that the HRT could increase the tear volume to some certain level. However, with the small sample size and short duration of the study, this could not have enough statistical power to show statistically significant difference. Another reasons may be the older women have the less increased in the tear volume or the presence of a blood-eye barrier which prevents systemic estrogen from acting on the conjunctivae and lacrimal ducts or the effect of medroxyprogesterone acetate that obscure the effect of estrogen. Nevertheless, the previous study has shown that topical estrogen is successful in treating keratoconjunctivitis sicca.[7]

The visual analogue scale showed no significant improvement in all four observed symptoms. It may be because the visual analogue scale is very subjective which needs a great deal of patients understanding of the way to make this subjective expression. This might cause a vast interpersonal variation in giving the score which makes the difference of the visual analogue score by chance could not be excluded statistically.

In conclusion, this study has shown that the hormone replacement therapy with conjugated equine estrogen plus medroxyprogesterone acetate daily improved tear volume but not visual analogue scale of ocular symptoms within twelve weeks. However, there was no statistical difference between the two groups, so it is not possible to exclude the increase in the tear volume in the HRT group by chance. Further study with longer duration, larger size and other regimen of hormone replacement therapy are needed.

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