Effectiveness of Hormone Therapy for Treating Dry Eye Syndrome in Postmenopausal Women: A Randomized Trial

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Background: *The efficacy of hormone therapy (HT) on dry eye syndrome remains debatable.*
Objective: *To study the efficacy of HT on dry eye syndrome.*
Material and Method: *A randomized controlled, double blind, parallel group, community-based study in 42 post-menopausal patients was conducted. The patients had dry eye syndrome and were not taking any medications. They were assigned to one of two groups. Group A comprised 21 patients given transdermal 17β-estradiol (50mg/day) and medroxy progesterone acetate (2.5 mg/day) continuously for three months and group B comprised 21 patients given both transdermal and oral placebo. Participants in the study were included for final analysis. The improvement of dry eye symptoms were measured by visual analog scale, tear secretion, intraocular pressure, corneal thickness, and tear breakup time determined before treatment and at 6 and 12 weeks of treatment.*
Results: *At 12 weeks, the number of patients who reported improvement of dry eye symptoms was greater in the HT group than that in the placebo group. However, the difference was not statistically significant (RR 0.25, 95% CI 0.04-2.80 and 0.60, 95% CI 0.33-2.03 in right and left eye, respectively). For other parameters, there was no significant difference between the two groups.*
Conclusion: *According to the present study, there is no strong evidence to support the use of HT for treating dry eye syndrome. The limited number of participants included in the present study may have contributed to the insignificant effects.*

Keywords: *Hormone therapy, Menopause, Dry eye syndrome*

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Dry eye is defined as a disorder of the tear film due to tear deficiency or excessive evaporation which causes damage to the interpalpebral ocular surface and is associated with symptoms of ocular discomfort[1]. Dry eye is a common condition with a prevalence of 11%-17% in the general population[2-9]. In Thailand, the prevalence of the disease diagnosed on the basis of symptoms and dry eye tests was 34%[10]. This was approximately 2 to 3 times higher than that reported in Caucasians[10]. The prevalence is highest among women and the elderly[10, 11]. The burden of dry eye syndrome to the patient can be substantial, impacting visual function, daily activities, social and physical functioning, workplace productivity, and quality of life (QOL)[11]. The management of dry eye comprises both pharmacologic and no pharmacologic approaches, including avoidance of exacerbating factors, eyelid hygiene, tear supplementation, tear retention, tear stimulation, and anti-inflammatory agents[12]. In 2007, the American Academy of Ophthalmology and the International Task Force (ITF) Delphi Panel on Dry Eye has recommended that treatment selection be based on dry eye disease severity[13].

The relationship between dry eye disease and either menopause or HT is not well understood. At least six clinical trials have reported the effects of

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HT and dry eye but the results were conflicting[14-19]. The beneficial effects of HT on ocular symptoms were reported from two randomized controlled trials[15,16] while the four observational studies reported inconsistent outcomes[14,17-19]. For the randomized controlled trials, Sator et al conducted a randomized trial in postmenopausal women with dry eye[15]. The results of study showed that ocular symptoms were significantly improved in dry eye women who received 17 beta-oestradiol eye drops when compared to those who received a tear substitute[15]. The tear function also revealed a significant difference of results before and after treatment in the oestradiol group ($p < 0.0001$) while in tear substitute group no significant difference was found[15]. Affinito et al consistently reported the benefit of hormone therapy on ocular symptoms and tear function[16]. The incidence and severity of symptoms of dry eye in the participants who received transdermal oestradiol plus medroxy-progesterone actate were lower than those in untreated participants[16]. According to the existing evidence whether the treatment effects of systemic hormone on postmenopausal women presenting with dry eye is still controversial such that the authors conducted the randomized, double-blinded trial to determine the treatment effects of transdermal oestradiol plus medroxyprogesterone actate in postmenopausal women with dry eye syndrome.

Material and Method

The present study was conducted between April 2007 and March 2008 at Amphur Muang-Khon Kaen, Khon Kaen Province. The present study was a double-blind, randomized controlled trial among 50 postmenopausal women with dry eye syndrome to assess the efficacy of systemic HT for the syndrome. The authors defined clinically diagnosed dry eye syndrome as a self-reported diagnosis of dry eye syndrome by an ophthalmologist. No participants had contraindications such as HT, smoker, or contact lenses, and were free of systemic and ocular diseases. None of the patients in the study group had received any HT before the present study for at least three months. Before enrollment in the present study, all participants received complete gynecologic examination, ophthalmologic evaluation, mammogram, complete blood count, and liver function test. The protocol of the present study was approved by Khon Kaen University Ethics Committee. All women participating in the present study signed their consent after a full explanation of the procedures.

The participants were randomized to receive either transdermal patch of oestradiol 50 μg/day (Climara®) plus oral medroxyprogesterone acetate 5 mg/day or matching placebo. Neither tear substitute nor other eye preparation was allowed during the present study. Randomization was computer-generated with allocation concealment by number containers. The included participants, caregivers and those assessing the outcomes were blinded to group assignment. Main outcome measure was the number of participants who had symptom relief of at least 50%. Other outcomes were severity of dry eye symptoms, tear secretion, intraocular pressure (IOP), and corneal thickness. These outcomes were measured at baseline and then after 6 and 12 weeks of treatment.

All participants were asked if they experienced at least 50% improvement of the dry eye symptoms. In addition the severity of dry eye symptoms were graded by each participant into four degrees; 1 = no, 2 = sometimes, 3 = often, 4 = always. Ocular function was measured by an ophthalmologist. Tear secretion was assessed with Schirmer test strip with and without anesthesia. The Schirmer strip was placed over the lateral third of the lower lid for 5 minutes each. The amount of wetting of the strip from the fold was recorded in millimeters. IOP was measured with a Goldmann explanation tonometer (Carl Zeiss South East Asia Germany) for each participant, this was done three times, for each eye. The IOP was reported as the arithmetic mean of the three measurements performed on each eye. Corneal thickness was measured 3 times for each eye using with Pentacam device (32 K supply Co. LTD). The corneal thickness was reported at the arithmetic mean of all measurements obtained for each eye. Tear breakup time was measured 3 times each eye using fluorescein-impregnated strip wet with non preserved saline solution placing in the lower conjunctival sac and measuring the interval between a complete blink and the appearance of the first randomly distributed dry spot or hole in the precorneal tear film.

For the number of participants who had symptom relief of at least 50% in each group the authors used χ^2 test to calculate the relative risk and 95% confidence intervals (95% CI) to estimate the treatment effects of hormone therapy. The differences of ocular function and severity of dry eye symptoms between the two groups and within each group at different times were statistically evaluated by analysis of the variance followed by Mann-Whitney-U test, Wilcox on matched pairs signed rank test. The last data were

carried forward for intention to treat analyses. The authors calculated that to observe at least 50% of participants who experienced the improvement of dry eye symptoms and with a power of 95%, a sample of 20 participants in each group would be needed.

Results

The authors screened fifty postmenopausal women. Eight were excluded because they did not meet the inclusion criteria. Therefore, 42 participants were eligible for the present study. A participant in the placebo group dropped out for missing a visit at 3 months. The participant flow is shown in Fig. 1. No significant differences in baseline characteristics and ocular function of the participants were observed between the two groups at the beginning of the study (Table 1). At 12 weeks, the number of patients who reported improvement of dry eye symptoms was greater in the HT group than that in the placebo group. However, the difference was not statistically significant (RR 0.25, 95% CI 0.04-2.80 and 0.60, 95% CI 0.33-2.03 in right and left eye, respectively). The severity of dry eye and lachrymal secretion in the right eye was significantly improved from baseline in the HT group but not in the placebo group (Fig. 2). For other parameters, there was no significant difference from baseline in both groups (Fig. 2, 3). When compared to placebo, hormone therapy did not significantly improve any parameters of ocular function (Fig. 2, 3). The hormone therapy group was associated with a higher rate of breast tenderness and vaginal bleeding than that in the placebo group (Table 3).

Discussion

This is the first randomized controlled study evaluating the treatment effects of systemic hormone on dry eye syndrome. A non-significant improvement

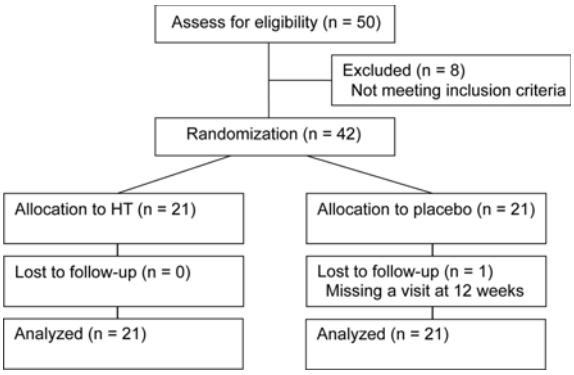

Fig. 1 Participant flow

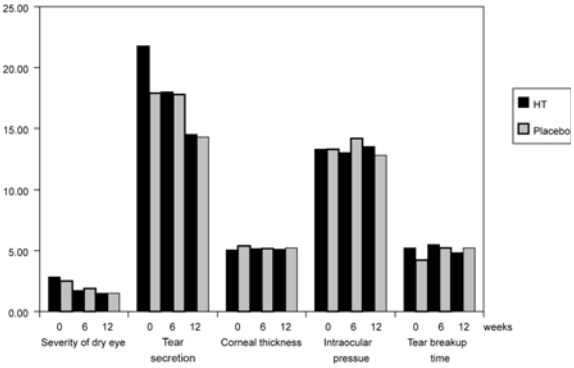

Fig. 2 Effects of HT on severity of dry eye and ocular function of the right eye

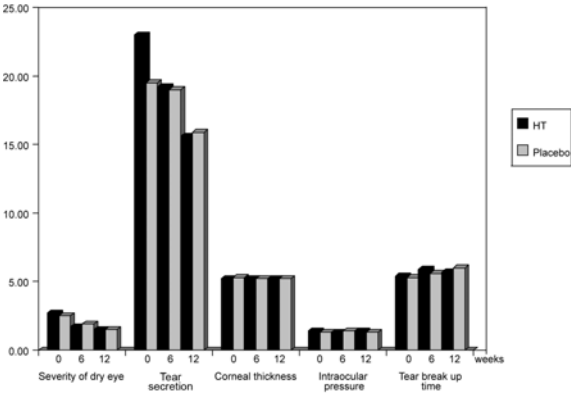

Fig. 3 Effects of HT on severity of dry eye and ocular function of the left eye

Table 1. Characteristics of participants

Characteristics	Hormone group (n = 21)	Placebo group B (n = 21)
Age(year)	56.26 ± 6.75	57.10 ± 4.74
Menarche(year)	15.52 ± 1.63	16.05 ± 1.76
Menopause(year)	47.52 ± 4.29	47.85 ± 3.88
Time since menopause (year)	9.75 ± 7.84	9.82 ± 5.06
BMI	36.79 ± 5.80	36.88 ± 4.22

Value express as mean ± SD

Table 2. The number of participants who had at least 50% improvement of dry eye symptoms

Duration of treatment	Hormone group (n = 21) < 50% improvement		Placebo group (n = 21) ≥ 50% improvement		Relative risk	95% CI
	No	Yes	No	Yes		
Right eye						
6 weeks	2	19	6	15	0.33	0.08-1.74
12 weeks	1	20	4	17	0.25	0.04-2.80
Left eye						
6 weeks	2	19	6	15	0.33	0.08-1.74
12 weeks	3	18	5	16	0.60	0.33-2.03

Table 3. The adverse event of the treatment

Adverse events	Hormone group (n = 21)		Placebo group B (n = 21)	
	6 weeks	12 weeks	6 weeks	12 weeks
Itching	2 (9.5%)	9 (42.9%)	11 (55.0%)	6 (30.0%)
Breast tender	5 (23.8%)	2 (9.5%)	1 (5.0%)	0 (0.0%)
Vaginal bleeding	6 (28.6%)	6 (28.6%)	0 (0.0%)	2 (10.0%)
No side effects	8 (38.1%)	4 (19.0%)	8 (40.0%)	12 (60.0%)

of dry eye is observed with systemic hormone therapy. As expected, breast tenderness and vaginal bleeding are more common adverse effects in the participants treated with systemic hormone.

The benefits of systemic hormone therapy on dry eye syndrome were previously reported by Affinito et al[16]. In postmenopausal women who received systemic hormone the incidence of dry eye syndrome was lower than that in nonusers[16]. However, in Sator's study when compared to the use of systemic hormone therapy alone the addition of topical estrogen eye drops to systemic hormone therapy was more effective in the treatment of dry eye syndrome[15]. The author explained that the blood-eye barrier might prevent systemic estrogens from acting on the conjunctivae[15]. In the present study, the limited number of the included participants as indicated by a wide 95% confidence interval may explain the non-significant benefits of systemic hormone therapy in women with dry eye. The differences in severity of dry eye syndrome between the studies may also contribute to the differing treatment effects of systemic hormone on dry eye syndrome[20, 21]. According to the International Dry Eye Workshop, four levels of the disease severity have been graded based on signs and symptoms. The selection of treatment has been based on this grading system.

If the authors focus on a role for the sex hormones in the etiology of dry eye there has been inconsistent evidence regarding the relationship between the high estrogen levels and dry eye. In a cohort study, postmenopausal estrogen therapy was an important risk factor for dry eye[14,22]. However, women with premature ovarian failure suffered from the symptoms and signs of dry eye, although their tear production is not affected[23]. In fact, endogenous estrogen levels in postmenopausal women are lower than the levels in premenopausal women. This cannot explain why the prevalence of dry eye is highest in the elderly.

As stated earlier the non-significant effects may attribute to the limited number of the including participants. The larger randomized controlled trial would demonstrate the statistically significant effect; however, tolerability is of concern as the participants in systemic hormone therapy experienced a high rate of adverse events.

For clinical implication, there is no strong evidence to support the use of systemic hormone as a treatment option for dry eye.

Author Contributions

Study concept and design: Somboonporn, Piwkumsribonruang, Luanratanakorn, Kaewrudee, Soontrapa

Acquisition of data: Somboonporn, Piwkumsribonruang, Luanratanakorn, Tharnprisan

Analysis and interpretation of data: Somboonporn, Piwkumsribonruang, Luanratanakorn, Tharnprisan

Drafting of the manuscript: Somboonporn, Piwkumsribonruang

Critical revision of the manuscript for important intellectual content: Somboonporn, Piwkumsribonruang, Luanratanakorn, Kaewrudee, Soontrapa

Statistical expertise: Somboonporn, Tharnprisan

Obtained funding: Somboonporn, Piwkumsribonruang

Administrative, technical, or material support: Tharnprisan

Study supervision: Somboonporn

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ประสิทธิภาพของการใช้ฮอร์โมนรักษากลุ่มอาการตาแห้งในสตรีวัยหมดประจำเดือน

ณรงชัย ผิวคำศรีบุญเรือง, วรลักษณ์ สมบูรณ์พร, พัฒนารี ล้วนรัตนากร, ศรีนารี แก้วฤดี, เพียงจิต เทียรไพศาล, สุกรี สุนทราภา

***ภูมิหลัง**: ผลของฮอร์โมนทดแทนที่มีต่อกลุ่มอาการตาแห้งยังเป็นที่ถกเถียงกัน*
***วัตถุประสงค์**: เพื่อศึกษาประสิทธิภาพของการใช้ฮอร์โมนในการรักษากลุ่มอาการตาแห้งในสตรีวัยหมดประจำเดือน*
***วัสดุและวิธีการ**: สตรีวัยหมดประจำเดือนในชุมชน 42 คน ที่มีกลุ่มอาการตาแห้ง และไม่ได้ใช้ยาอะไรจะได้รับการสุ่มเป็น 2 กลุ่ม กลุ่มละ 21 ราย กลุ่มแรกได้รับแผ่นแปะผิวหนัง 17β-estradiol (50 ไมโครกรัมต่อวัน) และรับประทานยาเม็ด medroxy progesterone acetate (2.5 มิลลิกรัมต่อวัน) กลุ่มที่สองได้รับยาหลอกในรูปแผ่นแปะผิวหนังและชนิดเม็ดรับประทาน เป็นระยะเวลาติดต่อกัน 3 เดือน ข้อมูลของผู้ป่วยทั้งหมดได้นำมาวิเคราะห์ผล การวัดผลที่สำคัญได้แก่ การดีขึ้นของอาการตาแห้ง ระดับน้ำตา ความดันลูกตา ความหนาของกระจกตา และระยะเวลา ของการระเหยของน้ำตาที่ 6 และ 12 อาทิตย์ หลังการได้รับยา*
***ผลการศึกษา**: ที่ 12 สัปดาห์จำนวนผู้ป่วยหญิงในกลุ่มที่ได้ฮอร์โมนที่มีอาการตาแห้งดีขึ้น มีจำนวนมากกว่ากลุ่มที่ได้รับยาหลอกแต่ความแตกต่างนี้ไม่มีนัยสำคัญทางสถิติ (RR 0.25, 95% CI 0.04-2.80 และ 0.60, 95% CI 0.33-2.03 ในตาข้างขวาและซ้ายตามลำดับ) สำหรับตัวชี้วัดอื่นไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติระหว่างสองกลุ่ม*
***สรุป**: ไม่มีหลักฐานที่ต่อต้านหรือสนับสนุนถึงการใช้ฮอร์โมนในการรักษากลุ่มอาการตาแห้ง ข้อจำกัดในด้านจำนวนกลุ่มตัวอย่างที่น้อยเกินไปอาจทำให้ความแตกต่างนี้ไม่มีนัยสำคัญทางสถิติ*