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The effects of hormone replacement therapy on dry eye syndromes evaluated by Schirmer test depend on patient age

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ABSTRACT

Purpose: This study was performed to explore the effects of hormone replacement therapy (HRT) on aqueous tear production and tear quality in dry eye syndrome (DES) patients of different ages.
Methods: Eighty-eight women with DES at least one year after spontaneous menopause were randomly divided into the HRT group that were treated with orally estrogen and medroxyprogesterone acetate or a control group that did not receive any treatment. The aqueous tear production and tear quality were measured by Schirmer test and tear film break up time (TBUT) before and after one month of treatment. The subjects were subdivided according to age; the HRT group was divided into groups A (age range: 44–49 years) and B (age range: 50–57 years), and the controls were divided into groups C (age range: 46–49 years) and D (age range: 50–55 years). The changes in results of Schirmer test and TBUT before and after treatment were compared within each group and were correlated with the age of the participants.
Results: After one-month follow-up, HRT use improved the Schirmer test but the effect was significant only for participants less than 50 years old. The improvement in Schirmer test result was negatively correlated with the age of the participants. The TBUT did not change significantly within each group after HRT use.
Conclusions: HRT use may improve aqueous tear production but not the quality of tears in DES, and the effect on tear production is dependent on age.

1. Introduction

Dry eye syndromes (DES) is a multifactorial disorder of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. DES is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface [1–4]. Dry eye is a common condition with a prevalence of 11–17% in the general population [5–9]. Common treatments for aqueous-deficient DES include increasing tear volume on the ocular surface by tear replacement with tear substitutes and lubricants or improving tear retention by occlusion of the drainage system [10]. However, such treatment is often unable to provide complete relief from the discomfort associated with the condition [10,11]. This is because these treatments attenuate the signs and symptoms of DES but do not cure the underlying pathophysiological mechanism of the disease, i.e., the imbalance between evaporation and generation of aqueous tear production. The prevalence of DES is much higher among women, and aging is a risk factor for this condition [12], suggesting that hormones may play key roles in the incidence and course of DES, especially in postmenopausal women [7]. Hormone replacement therapy (HRT) has been suggested as a strategy to reduce the symptoms and to improve ocular surface and tear functions in DES [8,9,13,14]. However, contrary results have also been reported. Schaumberg et al. [12] suggested that women receiving HRT with estrogen and estrogen plus medroxyprogesterone acetate were at increased risk of DES. A possible explanation for these conflicting conclusions is that the outcome of HRT depends on estrogen dosage and age of the individuals when therapy is first initiated. Estrogen may be only beneficial in younger women, whereas it may be detrimental and/or proinflammatory in older women [15]. The relationships between DES, HRT, and age are not well understood. The present study was performed to elucidate the effects of HRT on age-related tear function in DES patients.

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2. Methods

This was a double-blind randomized controlled trial. From March 2013 to May 2014, postmenopausal women with climacteric syndromes were recruited into the study. All subjects were informed about the project in detail, and provided signed consent to participation. The protocol of the study was approved by the ethical committee of The First Affiliated Hospital of Liaoning Medical University.

Before enrollment in the study, all women underwent complete medical history and ophthalmological evaluations, including general eye examination, slit lamp microscopy, tear film break up time (TBUT) and Schirmer test I. DES was diagnosed according to presence of symptoms, such as dryness, burning, itching, fatigue, discomfort, foreign body sensation, tearing, fluctuation of vision, etc., plus TBUT $\leq$ 5 s or Schirmer test I $\leq$ 5 mm/5 min.

Inclusion criteria were: (1) at least one year after spontaneous menopause and no medical history of DES or allergic ocular disease prior to menopause; (2) had not received any hormonal therapy before the study and no contraindications to HRT; (3) no use of contact lens during the last two years; (4) no hypertension or other systemic disease or medications deemed to have ocular implications; (5) no smoking.

A total of 150 women agreed to participate in the study. Of these, 112 met the inclusion criteria and were asked to agree to be randomized into the treatment or no-treatment group. Twenty-four women refused the randomization process, and therefore 88 women finally participated in the study. These women were randomly divided into the HRT group (44 patients) and control group (44 patients). The HRT group was treated with conjugated estrogen at a dose of 0.625 mg/day and medroxyprogesterone acetate at 5 mg/day in a continuous combined regimen (Premelle; Wyeth, Dallas, TX), and was further divided into group A ($\leq$50 years old, $n = 20$) and group B (>50 years old, $n = 24$). The control group did not receive any hormonal therapy and was divided into group C ($\leq$50 years old, $n = 21$) and group D (>50 years old, $n = 23$). No tear substitute or other eye preparation was allowed during the present study for all subjects. All participants underwent an eye examination at the beginning of the study and were followed up after one month. The data of the participants who were lost follow-up were not included in the final analysis. The flowchart of the participant selection process is shown in Fig. 1. In all cases, the ophthalmologist performing the examination was unaware of the treatment group. All of the subjects had DES in both eyes, and the data from the worse eye were included in the study.

Schirmer test I with proparacaine hydrochloride anesthesia for basal secretion was applied with a filter strip (Jingming Company, Tianjin, China). A 5-mm section of the strip was placed under the lowest eyelid near its center for 5 min without touching the cornea. The amount of wetting of the strip was recorded in millimeters and considered abnormal if less than 5 mm [16,17].

The quality of tear was evaluated by TBUT. Briefly, 5–10 μl of sodium fluorescein was dropped into the conjunctiva sac and the patients were asked to blink three to four times and look forward. The time interval between the last blink and the appearance of the first spot on the cornea, i.e., formation of a dry area, was recorded. The mean of three consecutive tear breakup tests was adopted as the final result, and a result of 5 s or less was considered abnormal [18].

All of the data are expressed as the mean ± SD. The data were analyzed with IBM SPSS Statistics 15.0. Paired t test was performed to compare the effects of HRT on aqueous tear production and tear quality. Pearson's correlations between change in Schirmer test result before and after treatment and age of HRT participants were analyzed. In all analyses, $P < 0.05$ was taken to indicate statistical significance.

3. Results

The characteristics of the participants are shown in Table 1. One-way ANOVA indicated that the age difference among the groups was statistically significant. Further post hoc comparison showed that the differences in age and duration of menopause were significant between group A and B and between C and D, but not between groups A and C or between groups B and D.

The Schirmer test results before and after the study for the four groups are shown in Table 2. Schirmer tests before treatment and

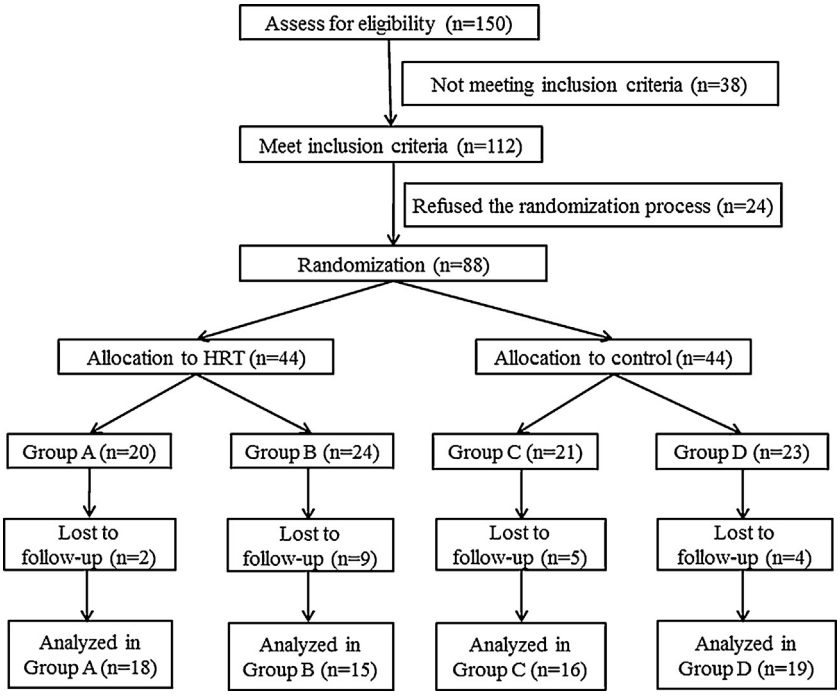

Fig. 1. Flowchart of participant selection process.