

Dry eye in post –menopausal Asian women on hormone replacement therapy

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Foundation item: Universiti Sains Malaysia under IRPA short term grant (304/PPSP/6131200)

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Received: 2008-04-24 Accepted: 2008-05-18

Abstract

• **AIM:** To compare the occurrence of dry eye in post-menopausal women between those with hormone replacement therapy and those without hormone replacement therapy (HRT).

• **METHODS:** A comparative cross-sectional study was carried out to determine the occurrence of dry eye in control subjects and those on HRT. Schirmer's test, tear film break-up time and Rose Bengal staining were performed on all participants.

• **RESULTS:** Fifty-four women were examined. Among them 30 (55.6%) were on hormone replacement therapy (Group 2), while the control group consisted of 24 (44.4%) women without any hormone replacement therapy (Group 1). In Group 2 (HRT), 11 patients were on estrogen (Group 2A) and 19 patients were on combined estrogen and progesterone (Group 2B). Dry eye was found in 29.2% of patients in Group 1 (Control) and in 70.0% of patients in Group 2 (HRT) ($P=0.003$). In Group 2 (HRT), dry eye was more common in Group 2B, 84.2% compared to Group 2A, 45.5% ($P=0.042$).

• **CONCLUSION:** Dry eye was found more commonly in post-menopausal women who took HRT in our study. Our finding has negated the previous assumption that HRT is a protective factor against dry eye.

• **KEYWORDS:** dry eye; hormone replacement therapy

Shaharuddin B, Ismail-Mokhtar SF, Hussein E. Dry eye in postmenopausal Asian women on hormone replacement therapy. *Int J Ophthalmol* 2008;1(2):158-160

INTRODUCTION

Keratoconjunctivitis sicca or 'dry eye' refers to a variety of disorders, which is characterized by ocular surface disease that results from any condition that decreases tear secretion or increases tear film evaporation sufficient to result in loss of water from the tear film^[1]. Although it may sound like a minor annoyance, dry eye is a potentially serious and chronic condition. It may severely limit a person's activity, and in extreme cases, cause blindness. After menopause, the level of estrogen in the blood decreases. Kramer *et al*^[2] in 1990 had shown that the eye is a locus of action of female sexual hormones. Sator *et al*^[3] proposed the reduction of naturally occurring estrogen as a possible reason for the occurrence of dry eye in menopausal women. 14.4% of the population in the Beaver Dam Eye Study had dry eye and the age-adjusted prevalence in women was 16.7% compared to 11.4% in men^[4].

It was initially assumed that HRT would be beneficial to reduce the occurrence of dry eye in post-menopausal women. However, the exact relationship between HRT and dry eye is still poorly understood. As many menopausal women are receiving HRT for their symptoms, it is interesting to examine the relationship between dry eye and HRT.

MATERIALS AND METHODS

Subjects Study participants were recruited from menopausal clinic of Hospital Universiti Sains Malaysia and selected based on the inclusion criteria as follows: Group 1 included selected menopausal women not receiving HRT who attended Eye Clinic, HUSM with non-inflammatory eye disorders; Group 2 included selected menopausal and peri-menopausal women receiving HRT for at least 6 months prior to the study who attended Menopause Clinic, HUSM. Furthermore, Group 2A included selected surgical menopausal women receiving estrogen only HRT for at least 6 months prior to the study who attended Menopause Clinic, HUSM; while Group 2B included selected menopausal and peri-menopausal women receiving combined estrogen and progesterone HRT for at least 6 months prior to the study who attended Menopause Clinic, HUSM.

We excluded patients with lid disorders, trauma, diabetes, contact lens wearers, previously diagnosed with dry eye and on medications which can cause dry eye. Informed consent was obtained from all study participants. This is a single blind clinical cross-sectional study with a non-purposeful sampling. This study received approval from the Research and Ethical Committee, School of Medical Sciences and the Bio-Medical Sciences and Health Committee, Universiti Sains Malaysia.

The diagnosis of dry eye or Keratoconjunctivitis sicca in this study is made according to the Copenhagen Criteria^[5]. Dry eye is present when two of the following tests are abnormal: (1) Schirmer's test (abnormal if ≤ 10 mm/5min); (2) Tear film break-up time (abnormal if ≤ 10 s); (3) Rose Bengal score (abnormal if ≥ 4 points)

Methods

Schirmer's test The Schirmer's test was performed in a confined room with the fan off. Topical anesthetic agent was not applied to the eye for this particular test as it would alter the results. Both eyes were subjected to the test simultaneously and the special standardized filter paper (Whatman's no.41) was inserted successively into each conjunctival sac of the lateral part of the lower eyelid of each eye at the shortest possible interval. The filter paper was removed after 5 minutes and was read immediately. The values were read as: <5 mm-pathological, 5-10mm-suspicious and >10 mm-normal.

Tear film break-up time (BUT) One drop of fluorescein 20g/L was instilled into both eyes from a standard minim after instillation of topical anesthesia. The patient was instructed to blink normally several times while placing her head on the slit-lamp support. Thereafter, the patient was instructed not to blink. The precorneal tear film was observed at $\times(10-20)$ magnification. The observer studied the fluorescein stained precorneal tear film, looking for a black gap (dry spot) formation. The observer stops the watch at the first appearance of a dry spot. The test was repeated three times on each eye and the mean was calculated for each eye separately. The result was interpreted through the Copenhagen Criteria^[5] as: >10 s-normal and ≤ 10 s-abnormal.

Rose bengal staining One drop of rose bengal 10g/L from a standard minim was instilled into both eyes after local anesthesia drops. The patient was asked to blink naturally while placing her head on the slit-lamp support. The staining was studied after 1-2 minutes when excessive stain in the precorneal film had disappeared. The grading of rose bengal staining was done by using the Bijterveld's method^[6] in

which the ocular surface is divided into three zones: nasal bulbar conjunctiva, cornea and temporal bulbar conjunctiva. This grading system graded the staining on the exposed parts of the cornea from 0 to 3: 0 - no staining, 1 - slight staining, 2 - moderate staining and 3 - intense staining. These scores were added up and a maximum score of 9 was obtained for maximum staining at all the three sites.

Statistical Analysis Data entry and analysis were performed by using SPSS version 10.0 software. Statistical analysis was done through using the Chi-square test for 2×2 table. Since samples were too small, Fisher's Exact test was used.

RESULTS

Fifty-four post-menopausal women who visited the Menopause Clinic and Eye Clinic, Hospital Universiti Sains Malaysia were included in the study. There were 41 Malay patients (75.9%), 12 Chinese patients (22.2%) and only 1 Siamese patient (1.9%). The mean age of patients in Group 1 (control) was 54.9 ± 5.5 years, with a median of 54.0 years. The mean age of patients in Group 2 (HRT) was 54.2 ± 5.0 years, with a median of 53.5 years.

Twenty-one out of 30 patients (70.0%) in Group 2 had dry eye as compared to only 7 out of 24 patients (29.2%) in Group 1, which was statistically significant (Chi-square test, $P < 0.05$).

In the group of patients taking HRT, 16 patients (84.2%) in Group 2B (combined, $n = 19$) were found to have dry eye, while only five (45.5%) in Group 2A (estrogen-only, $n = 11$) had the condition (Fisher's exact test, $P < 0.05$).

DISCUSSION

We have chosen to investigate this problem in a group of post-menopausal women in Hospital Universiti Sains Malaysia, which is located in a semi-rural district of Kelantan at the northeastern part of Malaysia. The diagnosis of dry eye encompasses an elaborate sequence of tests as well as symptoms. Many dry eye prevalence studies have been done previously^[7,8]. However, none has given a clear and repeatable guideline for the diagnosis of dry eye.

This study was designed to detect dry eye in a clinic setting, so the tests used were simple yet established in many studies to detect dry eye, namely the Schirmer's test, tear film break-up time and the rose bengal staining. The revised international classification criteria for Sjögren's syndrome proposed by the American-European Consensus Group^[9] and the Copenhagen criteria^[5] were used as guidelines.

Diagnosis of dry eye in our study was made with a combination of the results from the Schirmer's test, tear film

break-up time and rose bengal score. We did not use symptoms to diagnose dry eye as some authors have shown it to be unreliable [8]. Therefore the parameter of this study differs from the Women's Health Study [10]. Thus, direct comparison is not possible.

The ethnic distribution of the study sample reflects the local urban population of Kelantan with 41 Malay patients (75.9%), 12 Chinese patients (22.2%) and only 1 Siamese patient (1.9%). Age matching was done to ensure that both groups were comparable and to reduce bias. The mean age between both groups was almost similar, 54.9±5.5 years in the control group and 54.2±5.0 years in the HRT group. The median age in the control group was 54 years and in the HRT group was 53.5 years. This is slightly higher than the median age of Asian women with menopause, which is 51 years [11], but still comparable.

We found that dry eye was more common in the HRT group (70.0%) compared to the control group (29.2%). This is in parallel to the results by Schaumberg *et al* [10]. However, in contrast to this, when comparing two ways of taking HRT in Group 2, we found that women taking the combined estrogen and progesterone therapy had a higher occurrence of dry eye (84.2%) compared with those taking estrogen alone (45.5%) ($P=0.042$). This implies that the tear film is less stable in the group taking estrogen and progesterone replacement therapy when compared to those taking only estrogen therapy. This result again does not reflect the protective effect of progesterone as suggested by Schaumberg *et al* [10].

A possible reason for this is the fact that their conclusions were made from patients' symptoms and self-reported clinician's diagnosis. In our study, every patient had an ocular examination for dry eye by the same investigator and this reduced bias and standardized our diagnosis of dry eye.

Another postulated cause is the different genetic make-up between Asians and Caucasians. In the first report of population-based data of dry eye that includes symptoms and signs of elderly Asians, Lin *et al* [12] have shown that the prevalence of dry eye is relatively higher in an elderly Chinese population in Taipei as compared to Whites. The number of patients in Group 2A (Estrogen) was 11 compared to 19 in Group 2B (Combined). The effect of a small sample size is a dilution of the results, which reduces the probability of detecting dry eye in Group 2A.

We conclude that dry eye was found to be significantly higher in the group taking hormone replacement therapy

($P=0.003$) compared to controls. Our study also showed that patients on combined estrogen and progesterone therapy were more likely to develop dry eye compared to patients who took estrogen only replacement ($P=0.042$). This finding is very useful to the clinicians, as they need to be aware of the possibility of dry eye in these patients. Early referral to the ophthalmologist would prevent irreversible ocular surface damage. On the other hand, the ophthalmologist needs to keep in mind that HRT may aggravate a pre-existing dry eye. Acknowledgement: A special appreciation to Dr Shah Reza Johan Noor, Consultant Obstetrician and Gynaecologist, USM for his cooperation and guidance throughout the study. We are also grateful for the assistance of the doctors and staff nurses in the Ophthalmology Clinic, Obstetrics and Gynaecology Clinic and Endocrine Laboratory of Hospital USM for making this study an enjoyable and memorable pursue of knowledge.

REFERENCES

- 1 Gilbard JP. Dry-Eye Disorders. In (Albert & Jacobiec) Principles and Practice of Ophthalmology: Clinical Practice Volume 1. Philadelphia: W.B. Saunders Company, 1994:257-276
- 2 Kramer P, Lubkin V, Potter W, Jacos M, Labay G, Silverman P. Cyclic changes in conjunctival smears from menstruating females. *Ophthalmology* 1990;97:303-307
- 3 Sator MO, Joura EA, Golaszewski T, Gruber D, Frigo P, Metka M, Hommer A, Huber JC. Treatment of menopausal keratoconjunctivitis sicca with topical oestradiol. *Br J Obstet Gynaecol* 1998;105:100-102
- 4 Moss SE, Klein R, Klein BEK. Prevalence of and Risk Factors for Dry Eye Syndrome. *Arch Ophthalmol* 2000;118:1264-1268
- 5 Manthorpe R, Oxholm P, Prause JU, Schiødt M. The Copenhagen Criteria for Sjögren's Syndrome. *Scand J Rheumatol Suppl* 1986;61:19-21
- 6 Van Bijsterveld OP. Diagnostic tests in the sicca syndrome. *Arch Ophthalmol* 1969;82:10-14
- 7 McCarty CA, Bansal AK, Livingstone PM, Stanislavsky YL, Taylor HR. The epidemiology of dry eye in Melbourne, Australia. *Ophthalmology* 1998;105:1114-1119
- 8 Schein OD, Munoz B, Tielsch JM, Bandeen-Roche K, West S. Prevalence of dry eye among the elderly. *Am J Ophthalmol* 1997;124:723-728
- 9 Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carson SE, Daniels TE, Fox PC, Fox RI, Kassan SS, Pillemer SR, Talal N, Weisman MH; European Study Group on Classification Criteria for Sjögren's syndrome. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002;61:554-558
- 10 Schaumberg DA, Buring JE, Sullivan DA, Dana MR. Hormone Replacement Therapy and Dry Eye Syndrome. *JAMA* 2001;286:2114-2119
- 11 Purdie D, Crawford I. The menopause and its implications. *Pharm J* 1999;263:712-715
- 12 Lin PY, Tsai SY, Cheng CY, Liu JH, Chou P, Hsu WM. Prevalence of dry eye among an elderly Chinese population in Taiwan: the Shihpai Eye Study. *Ophthalmology* 2003;110:1096-1101