A COMPARATIVE STUDY ON THE OCCURRENCE AND SEVERITY OF DRY EYES BETWEEN MENOPAUSAL WOMEN NOT ON HORMONE REPLACEMENT THERAPY (HRT) AND THOSE ON HRT IN HUSM

BY

DR. SAIRA FAIRMA BINTI ISMAIL MOKHTAR
MBBS (MALAYA)

DISSERTATION SUBMITTED IN PARTIAL FULFILMENT
FOR THE DEGREE OF MASTER OF MEDICINE
(OPHTHALMOLOGY)

SCHOOL OF MEDICAL SCIENCES
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DISCLAIMER

I hereby certify that the work in this dissertation is my own except where assistance was specifically acknowledged. The sources of all references are clearly acknowledged.

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Dated 25-5-2002

Saira Fairma Ismail Mokhtar

PUM 0601

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(In the name of ALLAH, the Most Beneficient, the Most Merciful)

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BUT	Tear Film Breakup Time
DHEA-SO_4	Dehydroepiandrosterone sulfate
DSGS	The Dry Eye Severity Grading System
HRT	Hormone Replacement Therapy
HUSM	Hospital Universiti Sains Malaysia
RB	Rose Bengal
SD	Standard Deviation

ABSTRAK

Tajuk:

Perbandingan tahap penyakit mata yang kering (DES) dikalangan wanita putus haid yang menerima rawatan hormon dan yang tidak menerima rawatan hormon di Hospital Universiti Sains Malaysia (HUSM).

Pengenalan:

Adalah menjadi pegetahuan umum bahawa Sindrom Mata Kering (DES) berlaku lebih kerap di kalangan wanita yang berusia berbanding lelaki. Wanita yang telah putus haid mempunyai kekurangan hormon yang mungkin menyumbang kepada DES. Oleh yang demikian, rawatan gantian hormon (HRT) dijangka akan menghalang berlakunya DES. Walaubagaimanapun, ia belum pernah dibuktikan secara saintifik.

Objektif:

Untuk menyiasat kejadian dan tahap keterukan DES di kalangan wanita putus haid di HUSM dan untuk membandingkan keputusan di antara wanita yang mengambil HRT dan yang tidak mengambil HRT.

Tatacara:

Wanita putus haid di HUSM menjalani pemeriksaan mata yang terdiri dari ujian Schirmer, masa rekahan air mata (BUT) dan pewarna rose bengal. Sekurang-kurangnya 2 ujian perlu didapati positif untuk memberikan diagnosis DES. Selepas pemeriksaan mata, darah pesakit diambil untuk menguji paras estradiol, progesterone dan dehydroepiandrosterone sulfate.

Keputusan:

Lima puluh empat wanita telah diperiksa, di mana 30 orang (55.6%) menerima rawatan hormon (kumpulan HRT) manakala 24 orang (44.4%) tidak menerima rawatan hormon (kumpulan Kawalan). Di dalam kumpulan HRT, 11 pesakit menerima estrogen (kumpulan Estrogen) dan 19 pesakit menerima gabungan estrogen dan progesterone (kumpulan Gabungan). Di kalangan pesakit di dalam kumpulan Kawalan, 29.2% didapati mempunyai DES manakala 70.0% pesakit di dalam kumpulan HRT didapati mempunyai DES [$p<0.05$]. Perbandingan di antara pesakit yang mengambil rawatan hormon menunjukkan DES didapati lebih kerap di dalam kumpulan Gabungan (84.2%) berbanding kumpulan Estrogen (45.5%) [$p<0.05$]. Apabila dikaji secara berasingan, ujian pengesanan DES yang ketara secara statistik hanyalah ujian BUT di antara kumpulan Gabungan (94.7%) dan kumpulan Estrogen (45.5%) [$p<0.05$]. Perbezaan tahap keterukan DES di antara kumpulan-kumpulan tersebut didapati tidak ketara secara saintifik.

Kesimpulan:

DES didapati lebih kerap berlaku di kalangan wanita putus haid yang mengambil HRT di HUSM. Rawatan gabungan estrogen dan progesterone didapati menyebabkan kejadian DES yang lebih tinggi berbanding rawatan menggunakan estrogen sahaja. Oleh itu, ini adalah bertentangan dengan anggapan bahawa HRT dapat menghalang DES.

ABSTRACT

Title:

A Comparative Study on the severity of Dry Eyes between menopausal women not on hormone replacement therapy (HRT) and those on HRT in HUSM.

Introduction:

It is a known fact that Dry Eye Syndrome (DES) occurs more commonly in females of older age group compared to men. Menopausal women have lack of hormones that may contribute to dry eye. Hormone replacement therapy, therefore, is expected to prevent the occurrence of dry eye. However, this has never been scientifically proven.

Objective:

To investigate the occurrence and severity of Dry Eye in menopausal women in HUSM and to compare the results between women taking hormone replacement therapy and those not taking any hormone replacement therapy.

Methodology:

Menopausal women in HUSM underwent eye examination consisting of the Schirmer's test, the tear film breakup time and the rose bengal staining. At least 2 of the tests need to be abnormal to diagnose dry eye. After the ocular examination, blood was taken from every patient for estradiol, progesterone and dehydroepiandrosterone sulfate levels.

Results:

Fifty-four women were examined, 30 (55.6%) of which were on hormone replacement therapy (HRT group), while 24 (44.4%) women were not on any hormone replacement therapy (control group). In the HRT group, 11 patients were on estrogen (Estrogen group) and 19 patients were on combined estrogen and progesterone (Combined group). Dry eye was found in 29.2% of patients in the control group and in 70.0% of patients in the HRT group [$p<0.05$]. Comparing the patients in the HRT group, dry eye occurred more frequently in the combined estrogen and progesterone group (84.2%) as compared to the estrogen only group (45.5%) [$p<0.05$]. When analysed separately, the only dry eye test found to be statistically significant was a positive BUT test between the Combined group (94.7%) and the Estrogen group (45.5%) [$p<0.05$]. The severity of dry eye was not statistically significant between groups.

Conclusion:

Dry eye was found more commonly in menopausal women who took hormone replacement therapy in Hospital Universiti Sains Malaysia. Combined estrogen and progesterone therapy was associated with a higher occurrence of dry eye compared to estrogen only therapy. These results, therefore, are in contrast to the previous assumption that HRT would prevent dry eye.

INTRODUCTION

1.1 BACKGROUND

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 (Gilbard, 1994).

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. Dry eye syndromes can be divided into aqueous deficient dry eye syndrome due primarily to a lack of tear secretion from the lacrimal gland, and evaporative dry eye syndrome typically caused by lipid insufficiency related to meibomian gland dysfunction.

Dry eye commonly affects people in the older age group and is more common in women than men. Amongst the women with dry eye, it has been found to be commoner in menopausal women as compared to pre-menopausal women. Menopause is defined as the termination of the reproductive period of life in a woman, which is marked by the cessation of menstrual periods (Brudenell *et. al*, 1992). Menstruation generally ceases between the ages of 45 and 55 with a median age of 51 in the United States, Europe and Asia (Purdie & Crawford, 1999).

After menopause, the level of estrogen in the blood decreases. Kramer *et. al* in 1990 had shown that the eye is a locus of action of female sexual hormones. Sator *et. al* (1998) proposed the reduction of naturally occurring estrogen as a possible reason for

the occurrence of dry eye in menopausal women. According to a study done by Moss *et. al* in 2000, 14.4 % of the population involved in the Beaver Dam Eye Study was found to have dry eye. The age-adjusted prevalence in women was 16.7 % compared to 11.4 % in men (Moss *et. al*, 2000).

The role of androgens in the pathophysiology of dry eye is increasingly being understood. Androgen appears to maintain an anti-inflammatory environment surrounding the lacrimal gland and keeps the functioning unit working properly. The lacrimal gland becomes more vulnerable to inflammation when the level of supportive androgen drops, as in menopausal women, aging men and women, autoimmune disease, complete androgen insensitivity syndrome (CAIS) and use of anti-androgen medications. The use of topical androgen for the treatment of dry eye is currently being studied.

The methods used to diagnose dry eye includes subjective complaints and specific ocular examinations. The specific ocular examinations consist of measurement of tear quantity, tear quality, tear flow, tear film stability, and staining of devitalised and dead corneal epithelium. The measurement of tear quantity can be done by Schirmer's Test while Tear Mucus Ferning can measure tear quality. Several methods can be used for estimation of tear flow, two of which are Tear Meniscus Dilution Test and Fluorophotometry. Another criterion for diagnosis of dry eye is the tear film stability and this is done by measuring the Tear Film Breakup Time or BUT. In addition to diagnosis, staining of the corneal epithelium with special dyes such as rose bengal, fluorescein or lissamine green allows grading of the severity of dry eye.

Dry eye treatment is geared towards reducing symptoms and inflammation, and maintaining a normal ocular surface. Tear substitutes are the most frequent medication prescribed for dry eye patients. The use of topical androgen as a treatment for lacrimal and meibomian gland dysfunction in androgen deficient individuals is currently being studied. Sator *et. al* in 1998 demonstrated that dry eye in menopausal women was successfully treated with the topical estrogen, 17β-oestradiol.

As many menopausal women are receiving hormone replacement therapy for their symptoms, it is interesting to examine the relationship between dry eye and hormone replacement therapy (HRT). However, until now this is still poorly understood. This study aims to compare the severity of dry eye in menopausal women with regards to their HRT status and will hopefully give a better understanding of this relationship.

1.2 THE NORMAL TEAR FILM

The lacrimal reflex comprises of the lacrimal gland, conjunctiva, cornea and interconnecting innervation. This unit is known as the lacrimal functional unit (Zierhut *et. al*, 2002). Tears support the normal structure and function of the corneal and conjunctival surfaces. It is the sum of the secretions of the many orbital glands and the epithelium that line the ocular surface. The result is a normal tear film that consists of a three-layered structure, namely the mucin, aqueous and lipid layer. This structure is remarkably stable and able to respond to the challenges of the environment to protect the ocular surface. Recently however, there is evidence for a two-layered structure consisting of a superficial lipid layer and an underlying aqueous-mucin gel, in which

the mucins have a decreasing gradient of concentration from the epithelium to the surface (Rolando & Zierhut, 2001).

1.2.1 The Aqueous Layer

Over ninety percent of the tear film thickness consists of the aqueous layer, which lies between the mucin and lipid layer. This layer is produced by the main and accessory lacrimal glands and measures 7μm thick. The orbital and palpebral portion of the main lacrimal gland is thought to produce about 95% of tears while the rest comes from the accessory glands of Krause and Wolfring. The aqueous portion of the tears is secreted as an isotonic or slightly hypotonic solution.

The aqueous tears flow from the ductule openings of the main and accessory lacrimal glands (in the superior fornix) into the forniceal spaces, the lacrimal rivers and over the exposed portion of the cornea and conjunctiva. The fluid is drawn into the two punctal openings in a relaxation phase immediately subsequent to a blink. The majority of tears are lost from the eye by flowing through the lacrimal drainage system via the superior and inferior canaliculi, the common canaliculus, the lacrimal sac, and the nasolacrimal duct, through the inferior meatus and into nasal cavity. However, a considerable amount of this fluid is reabsorbed across the mucosa of the superior and inferior canaliculi, the common canaliculus and the nasolacrimal duct during this passage. Some aqueous fluid is also lost through evaporation and reabsorption through the conjunctival surface.

Aqueous tear secretion diminishes under conditions of considerable decrease in external stimuli, such as general anaesthesia and during sleep. This fact supports the probability that aqueous tear secretion is stimulus driven at all times, and it is not possible to separate it into basal and reflex tear secretion (Lemp, 1992).

1.2.2 The Lipid Layer

The most superficial layer is the lipid layer, which is produced by the meibomian glands of the eyelids. This layer measures 0.1μm thick. The lipid secreted by the meibomian gland is made up of a variety of lipid entities, including nonpolar sterol and waxy esters (around 58%), as well as other esters, free sterols, triglycerides and free fatty acids. About 15% of the meibomian gland secretion consists of polar lipids.

The meibomian lipid is secreted as a fluid which flows onto the aqueous preocular tear film with the polar component spreading fastest. The charged polar groups of this component are oriented towards the aqueous phase. The nonpolar component spreads slowly and covers the polar layer to form a thicker duplex film. The lipid layer undergoes considerable compression and decompression during blinking but its high degree of stability allows it to resist deformation when subjected to high mechanical demands.

There are at least three ways in which the stability of the tear film is enhanced by the lipid layer. Firstly, it tends to retard evaporation from the tear film. Secondly, meibomian gland secretion prevents contamination of the tear film by the more polar lipids secreted by the sebaceous glands of the eyelids, which tends to induce immediate

tear film breakup when applied to the eye. Finally, the lipid layer lowers the surface tension of the tears, which in turn draws water into the tear film, thickens the aqueous phase and allows it to spread evenly across the ocular surface (Lemp, 1992).

1.2.3 The Mucin Layer

The mucin layer is the layer adjacent to the corneal and conjunctival epithelium. It is the thinnest layer of the tear film and measures only 0.02μm to 0.05μm thick. This layer consists mostly of mucous (hydrated) glycoprotein associated with a mixture of protein electrolytes and cellular material. The source of the mucin layer is from the conjunctival goblet cells, and the corneal and conjunctival epithelial cells (Rolando & Zierhut, 2001). The largest part of the mucinous content is produced by the goblet cells of the conjunctiva. These are unicellular, mucus-secreting glands scattered throughout the bulbar and palpebral conjunctiva. The highest density is at the inferior nasal palpebral conjunctiva. This distribution has been found to be similar in different age groups, with a slight decline in the seventh decade of life or older.

Corneal epithelium is inherently hydrophobic due to the lipid content of the cell wall. Corneal and conjunctival epithelial cells secrete a glycoprotein forming an outer glycocalyx that is tightly bound to the epithelial cell surface. The mucin layer forms a loose adsorptive coating above this layer, which temporarily forms a new surface that is wettable by the overlying aqueous tear layer. The action of the lids adsorbs the mucin layer onto the corneal surface and this is thought to be a critical factor in establishing a new adsorbed layer over the corneal surface, which is wet by aqueous tears. In addition to increasing the affinity of tears for water, mucin also lowers the surface tension of

tears. Combination of these functions is thought to be sufficient to achieve complete wetting of the corneal surface (Lemp, 1992).

1.3 TEAR FILM FUNCTION

The term 'dry eye' is synonymous with 'Keratoconjunctivitis sicca' (KCS) and is often used interchangeably. However, more accurately, the term keratoconjunctivitis sicca is used for deficiency of the aqueous layer of the tear film. The National Eye Institute Workshop on clinical trials in dry eye had defined dry eye as a disorder of the tear film due to tear deficiency or excessive tear evaporation, which causes damage to the interpalpebral ocular surface and is associated with symptoms of ocular discomfort (Lemp, 1995). Several pre-ocular tear film functions are necessary for clear and comfortable vision. The pre-ocular tear film:

- Serves as the initial refracting surface of the eye
- Serves as the primary route of oxygen supply to the anterior cornea
- Provides the eye's antibacterial properties
- Provides lubrication for the eyelids
- Flushes away corneal metabolic waste products and other debris
- Provides a means for white blood cells to reach the avascular cornea to assist in healing (Scott *et. al*, 1995)

1.4 EPIDEMIOLOGY OF DRY EYE

The prevalence of dry eye increases with age and the condition occurs more commonly in women compared to men. Schein *et. al* in 1997 found that symptoms and signs of dry eye are common among a population-based sample of 2,520 elderly Americans. However, they found no association with age, sex or race. A study done by Moss *et. al* (2000) to estimate the prevalence of dry eye in a population of the Beaver Dam Eye Study showed that the overall prevalence of dry eye was 14.4 %. The age-adjusted prevalence in women was 16.7 % compared to 11.4 % in men. They also found a significant difference in the prevalence of dry eye between subjects younger than 60 years (8.4%) and those older than 80 years (19.0%). Another study done in Melbourne by McCarty *et. al* in 1998 showed a lower prevalence of dry eye based on symptoms. This study found a prevalence of 5.5 % for severe dry eye symptoms and 7.4 % for 2 or more symptoms of dry eye.

1.5 DRY EYE SYNDROME

Dry eye syndromes are of two major types: aqueous deficient dry eye syndrome, due primarily to a lack of tear secretion from the lacrimal gland, and evaporative dry eye syndrome, typically caused by lipid insufficiency related to meibomian gland dysfunction (Lemp, 1995). However, an aqueous deficiency often coexists with meibomian gland dysfunction, which may be a major factor in dry eye states, perhaps even more important than lacrimal gland dysfunction. In addition, the tear film responds to very delicate regulatory mechanisms involving neuroregulatory phenomena and hormonal stimulation (Baudouin, 2001).

The normal eye can become inflamed for a short time, perhaps from foreign body irritation or an infection, but it does not become chronic. However, if the level of supportive androgens drops, the lacrimal gland becomes more vulnerable to a "second hit," such as wind, low humidity or infection. This would produce rapid, chronic firing of the tear reflex that sets off inflammation within the lacrimal gland. T-cells normally migrating through the gland become activated and synthesize and secrete pro-inflammatory cytokines. These inhibit neurally induced tear secretion and cause inflammation to the ocular surface. In response to this inflammation, other circulating T-cells also migrate to the lacrimal gland. This promotes a chronic and self-perpetuating inflammation, which can ultimately shut down production of aqueous by the lacrimal gland.

Sullivan and Edwards (1997) tested the effect of androgen stimulation on lacrimal gland function in mouse models of Sjögren's syndrome. They found that androgen therapy enhances the functional activity of the lacrimal gland and causes a dramatic suppression of lacrimal gland inflammation in the mouse models. Androgens may also be involved in meibomian gland dysfunction. Human lacrimal glands, meibomian glands and other ocular tissues possess androgen receptors and the corresponding proteins. In a more recent study, Rocha *et. al*, (2000) found androgen receptor proteins in human lacrimal gland, meibomian gland, cornea, bulbar and forniceal conjunctiva, lens epithelial cells and retinal pigment epithelial cell. Sullivan *et. al* (2000) found androgen receptor proteins within acinar epithelial cell nuclei of rat meibomian glands. Both studies suggest that the meibomian gland is an androgen target organ. In addition, Sullivan and co-workers tested the effects of androgen deficiency on rabbit meibomian gland. The results showed that androgen deficiency was associated with alterations in

the lipid content of the rabbit meibomian gland but did not appear to influence the gross morphology of the meibomian tissue or to exert a demonstrable effect on the rabbit tear film lipid layer. Therefore, androgens appear to stimulate meibomian gland cells to produce lipids, which maintain tear film stability and prevent tear film evaporation (Sullivan *et. al*, 2000).

Decreased androgen levels that occur during menopause, aging in men and women, autoimmune diseases such as Sjögren's syndrome, complete androgen insensitivity syndrome (CAIS), and use of antiandrogen medications for prostatic hypertrophy or cancer appear to correlate with the presence of meibomian gland dysfunction and evaporative dry eye. Androgen deficiency appears to promote the progression of autoimmune diseases, such as Sjögren's syndrome, and severe dry eye that develops.

Moss *et. al* (2000) and Goebbles (2000) have found diabetic patients to be at higher risk of developing dry eye compared to general population. Moss *et. al* (2000) also studied other risk factors of dry eye in their study. They recruited 3703 patients from the Beaver Dam Eye Study. The patients were subjected to a medical history questionnaire as well as a complete ocular examination. They found that arthritis and thyroid disease are among the medical conditions associated with dry eye. They also found medications such as aspirin, antidepressants and multivitamin to be significantly associated with the prevalence of dry eye in the same study. The use of angiotensin-converting enzyme inhibitors, α- or β-antiadrenergic agents, calcium channel blockers, diuretics, methyldopa, reserpine, parasympathetic agents, antihistamines, antianxiety agents and antiemetics, however, were not related to dry eye.

Although decreased production of basal tears is typically part of the aging process, concomitant stenosis of the punctae usually results in maintaining a normal relationship between tear secretion and elimination in older individuals. Even though they are free from dry eye symptoms, these patients often have epiphora from secondary reflex tearing (Patel *et. al*, 1990). However, others have consistent symptoms related to tear layer inadequacies. Mathers *et. al* (1996) have shown that there is a decline in tear flow function throughout life and when compared to previous studies, the tear flow is considerably less than previously estimated.

1.6 MENOPAUSE AND DRY EYE

The term menopause refers to the cessation of the menstrual period (Purdie & Crawford, 1999). It ranges between the ages of 48 to 52 years, with 51 years as the median age. Common transient symptoms of dry eye are vasomotor symptoms (such as hot flushes, night sweats and palpitations) and psychological symptoms (such as insomnia, poor memory, lost of confidence, mood changes, anxiety, loss of libido, diminished energy, difficulties in concentration and making decisions, irritability and crying spells). Perimenopausal and early postmenopausal women in Western industrialized countries commonly complain of these acute, transient symptoms. The long-term effects of estrogen withdrawal following menopause are more serious and include cardiovascular disease and osteoporosis.

Menopause has also been associated with dry eye as lack of estrogen and progesterone causes reduced lacrimal secretion. This tear film deficiency results from progressive degeneration of the lacrimal glands due to postmenopausal hormone

deficiency and meibomian gland dysfunction during aging (Baudouin, 2001). Kramer *et. al* in 1990 clearly showed that the conjunctiva is an estrogen sensitive epithelium. Their study showed that serum estrogen levels correlate with the maturation index of conjunctival epithelium and there is absence of cyclical changes in the conjunctival smears of postmenopausal women. Therefore, they suggested that estrogen deficiency might be of etiological importance in the pathogenesis of keratoconjunctivitis sicca.

In addition, meibomian gland dysfunction may be linked to abnormal estrogen receptor activity. In a study done by Esmaeli *et. al* (2000), estrogen receptors were found to be present in the meibomian glands of the upper eyelid in humans. Modulation of the lipid layer of the tear film may involve the estrogen receptors and their activity may be linked to meibomian gland dysfunction and dry eye syndrome as well. Nevertheless, the relationship of sex hormones and dry eye, while long suspected, has not been defined in well-controlled studies.

Data from the United States in 1995 showed that approximately 38% of post-menopausal women in the United States used hormone replacement therapy (Keating *et. al*, 1999). The most frequent indications for hormone replacement therapy are vasomotor symptoms and associated short-term signs. 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.

Recent studies have shown that hormone replacement therapy should not be used for prevention of heart disease. The Women's Health Initiative (WHI) conducted a

study to investigate the risk and benefits of hormone use in healthy postmenopausal women (Writing Group, 2002). After 5.2 years of follow up, they found that the overall health risks exceeded the benefits from use of combined estrogen plus progestin and recommended that the regime should not be initiated or continued for primary prevention of coronary artery disease. Nelson *et. al* (2002) conducted a meta-analysis of eighteen observational studies and found that the benefits of using hormones include prevention of osteoporotic fractures and colorectal cancer, while the harmful effects includes coronary artery disease, stroke, thromboembolic events, breast cancer with 5 or more years of use and cholecystitis. However, both the studies did not find an increased mortality in patients using hormone replacement therapy as compared to controls.

1.7 DIAGNOSIS OF DRY EYE SYNDROME

1.7.1 Subjective Complaints

Patients with dry eyes frequently complain of pain, itching, sandy sensation, stickiness, or other irritative symptoms, but not necessarily of dry eye. Questionnaires have been formulated to assess dry eye symptoms. Among the available Dry Eye Questionnaires are the McMonnies Questionnaire and the Ocular Surface Disease Index Questionnaire (Schiffman *et. al*, 2000). Majority of the irritative symptoms suggest environmentally induced dry eye. Some examples include prolonged exposure to dry and smoky environments, after swimming in fresh chlorinated water, working in 'sick' buildings with abundance of fleecy materials, sites with inadequate dust exhausts, turpentine vapours and prolonged work with data processing machines.

Affective tearing where epiphora occurs in response to psychogenic weeping may be absent in patients with dry eye. Provoking tear secretion, for example by peeling onions, may also fail. An interesting phenomenon in patients with dry eye is called the paradoxical epiphora. This is most commonly seen in elderly patients with impaired tear secretion combined with reduced outflow of tears. These patients have age related atrophy of the lacrimal gland as well as impaired strength of the muscular fibres of the tear pump around the lacrimal sac or an abnormal nasolacrimal duct. Reflex stimulated tear secretion exceeds the reduced outflow of tears when these patients are out-doors, thus producing epiphora. When indoors, the nonstimulated tear secretion is minimal and the patient complains of dry eye.

Therefore, subjective complaints seem to be of limited value in the diagnosis of dry eye. Although some authors regard symptoms as the most important method for detection of dry eye, there are still many dry eye patients who do not exhibit any symptoms. This necessitates the use for objective methods to diagnose dry eye. With regards to this, we have opted for the use of 3 dry eye tests in this study: the Schirmer's test, tear film stability breakup time (BUT) and rose bengal staining.

1.7.2 Tear Quantity

Tear production is measured per unit of time and is usually performed by absorption on filter paper. Schiffman *et. al* (2000) has shown that Schirmer's Tear Test correlates well with the patient's symptoms of dry eye. Whatman's no. 41 filter paper is used to do the test. Its short folded end is inserted into the conjunctival sac of the lateral part of the lower eyelid and the reading is taken after 5 minutes (Norn, 1992). When

Schirmer initially described the test, measurement was preferred on an open eye. However, a closed eye method is more convenient for the patient and would be independent of blinking. Most authors prefer to do the Schirmers test using the closed eye method. The use of anesthesia may alter the results, thus this test should be performed without any topical anesthesia prior to any other test for dry eye.

1.7.3 Tear Flow

A normal tear flow suggests that there is a proper relationship between tear production and tear outflow. Introduction of a dye or radioactive substance into the conjunctival sac followed by measurement of its concentration after a certain period allows tear flow to be assessed. Several methods can be used to measure tear flow such as the Tear Meniscus Dilution Test (using a mixture of rose bengal and fluorescein dye), scintigraphy (using saline solution containing technetium) and fluorophotometry (using fluorescein dye).

1.7.4 Tear Quality

When tears dry up on a glass slide, it forms fern-like crystals. If tear quality is poor from dry eye of different causes, crystallization is less pronounced. Tear Mucus Ferning is a method to determine tear quality by observation of the crystallization of tears when it dries.

1.7.5 Tear Film Stability Breakup Time

The Tear Film Breakup Time (BUT) measures the time taken for the first randomly distributed dry spot to appear after the patient's last blink, in an eye stained with fluorescein (Kanski, 1999). Vanley *et. al* in 1977 found that the BUT is not a closely reproducible phenomenon in an individual eye. Nevertheless, the BUT is a unique parameter for dry eye and cannot be replaced by other parameters. The BUT is independent of age, sex, size of palpebral fissure, ethnic origin, environmental temperature and moisture, although uncertain tendencies have been demonstrated (Norn, 1992).

1.7.6 Mucus Tests

A few dyes can be used to stain mucus thus allowing it to be assessed. Alcian blue alone or with tetrazolium can be used for this purpose. Alcian blue stains mucus specifically (chondroitin and mucoitin sulfate complexes stains blue) while neutrophilic leucocytes and mildly degenerated epithelial cells stains red with tetrazolium. Measurement of the mucous thread in the inferior fornix can also be done with alcian blue or rose bengal. The dimensions of the mucous thread are increased in patients with keratoconjunctivitis sicca, and when stained with rose bengal it appears to be thicker than normal. This is due to increased epithelial desquamation and abated mucous flow leading to accumulation of mucus in the inferior fornix.

As mucus is produced by the goblet cells, determining the density of the goblet cells is clearly useful in diagnosing dry eye syndrome. The imprint technique is a non-

invasive method of determining goblet cell density and characteristically shows snakelike nuclear chromatin in keratoconjunctivitis sicca patients. Biopsy can also be easily performed for the same reason.

1.7.7 Lipid Tests: Tear Film Interference

A thin lipid layer superficially covers the preocular tear film, which prevents evaporation even on blinking. The thickness of this layer can be measured by using a slit lamp with an adjustable lamp (goose neck lamp) or merely by using the slit lamp alone. This test is interpreted by observation of the interference pattern of the lipid layer. In keratoconjunctivitis sicca, slower elimination of the tear film due to a diminished aqueous phase may increase the thickness of the lipid layer. On the other hand, some environmentally induced dry eye may lead to evaporation of the lipid layer into the atmosphere, therefore producing a thinner lipid layer on tear film interference.

1.7.8 Staining

Dry eye can be diagnosed with staining methods by demonstrating areas of dessication in the exposed region of the epithelium. The first reported ocular use of rose bengal was by Romer, Cobb and Lohle in 1914. In 1933, Henrik Sjogren introduced rose bengal for detection of keratoconjunctivitis sicca. Lissamine green and fluorescein stain have also been used to diagnose dry eye. Rose Bengal (4,5,6,7-tetrachloro-2′,4′,5′,7′-tetraiodofluorescein sodium) belongs to the hydoxyxanthene group of dye. It is a fluorescein derivative and is the preferred stain for diagnosis of dry eye because it stains dead, degenerate and dessicated epithelial cells as well as mucus (Norn, 1992). In

addition, rose bengal also possess antibacterial, anti protozoal and antiviral properties (Roat *et. al*, 1987). The only drawback is that rose bengal causes a smarting pain when instilled, while fluorescein and lissamine green do not.

Feenstra & Tseng (1992a) showed that rose bengal staining could be blocked by tear components such as mucin and albumin. This suggests that normally negative rose bengal staining is due to the protective function of the preocular tear film and is not dictated by lack of cell vitality. In contrast to rose bengal, fluorescein lacks the ability to be blocked by mucin and albumin in tears (Feenstra & Tseng, 1992b).

Van Bijsterveld in 1969 developed a scoring system for rose bengal dye. This grading is practical and universally accepted. It has proved invaluable in clinical studies and as a tool in quantitatively following up KCS patients. He reported that the scoring system has a sensitivity of 95% and a specificity of 96%.

1.8 TREATMENT

Dry eye treatment is geared towards reducing symptoms and inflammation, and maintaining a normal ocular surface. As dry eye conditions can exist without evidence of ocular surface damage (Lemp, 1995), the primary goal in treatment should be to improve symptoms. There are many causes of dry eye and therapy should be tailored towards the specific causes. Tear substitutes are the most frequent medication prescribed for dry eye patients. These so-called artificial tears usually contain methylcellulose in the form of hydroxyethylcellulose, hydroxypropylcellulose or hydroxypropylmethylcellulose.

The use of topical androgen as a treatment for lacrimal and meibomian gland dysfunction in androgen deficient individuals is currently being studied. However, the results of most clinical trials involving estrogen containing eye drops have been rather disappointing; with inconsistent improvement in tear film breakup time or Schirmer's test result. Vécsei *et. al* (2000) attempted to localize immunohistochemical estrogen and progesterone receptor staining in the human cornea. They found no nuclear immunohistochemical reaction in the epithelial and endothelial layers of the cornea. This shows no morphological basis in the human cornea for the use of topical steroid hormone therapy in postmenopausal women with keratoconjunctivitis sicca. On the other hand, a study by Sator *et. al* in 1998 demonstrated that dry eye in menopausal women was successfully treated with the topical estrogen, 17β-estradiol. They observed a statistically significant difference in ocular symptoms between patients receiving 17β-estradiol and those receiving tear substitutes. In addition, the Schirmer's test revealed a significant difference before and after treatment in the estradiol group. The presence of estrogen receptors in the meibomian glands of the upper eyelid (Esmaeli *et. al*, 2000) may be linked to the success of topical estrogen therapy.

Pharmaceutical treatment of dry eye includes mucolytic agents (eg. acetylcysteine), eye ointments as lubricants, vitamin A, tear production stimulants (eg. bromhexine, eledoisin) and corticosteroids. In more severe dry eye, surgical treatment such as tarsorraphy, temporary or permanent occlusion of the lacrimal point, ectropionization of the lower lacrimal point or transposition of the parotid duct may be needed. When the eye is open, additional methods such as wearing tight-fitting goggles, moist

chambers, hot eye patches or spectacles with infusion pumps help to reduce the evaporation of the residual tear volume.

OBJECTIVES

2. OBJECTIVES

2.1 GENERAL OBJECTIVE

The aim of this study is to compare the occurrence and severity of dry eyes in menopausal women on HRT and those not on HRT.

2.2 SPECIFIC OBJECTIVES

1. To compare the occurrence of dry eye among menopausal women on HRT and not on HRT in HUSM.
2. To compare the severity of dry eye among menopausal women on HRT and not on HRT in HUSM.
3. To compare the occurrence of dry eye between menopausal women on estrogen therapy and those on combined estrogen and progesterone therapy.
4. To compare the severity of dry eye between menopausal women on estrogen therapy and those on combined estrogen and progesterone therapy.
5. To investigate the association of estradiol, progesterone and dehydroepiandrosterone levels with the severity of dry eye.

2.3 NULL HYPOTHESIS

There is no difference in the severity of dry eye between menopausal women on hormone replacement therapy (HRT) and those not on HRT.

MATERIALS

AND

METHODS

3. MATERIALS AND METHOD

3.1 RESEARCH STRATEGY

Comparative evaluation of dry eye severity between menopausal women on HRT and not on HRT.

3.2 POPULATION, SETTING AND TIME

Study population:

1. Selected perimenopausal and menopausal women receiving HRT who attended the Menopause Clinic, HUSM during the period of study.
2. Selected menopausal women not receiving HRT who attended the Eye Clinic, HUSM during the period of study.

Period of study: 1st October 2001 to 1st October 2002

Place of study: Ophthalmology Department, Hospital Kota Bharu.

3.3 STUDY DESIGN

This is a Clinical Cross-sectional study.

3.4 SAMPLING AND SAMPLE SIZE

3.4.1 Sampling method

Non-probability Purposive Sampling

3.4.2 Sample size calculation

Sample size calculation (done by the Epi Info 6 Program) = 31 samples

- Unmatched cross sectional study
- Analysis by uncorrected chi-square test
- Power of study: 80%
- Confidence interval: 95%
- Probability of exposure in controls: 16.7% (Moss *et. al*, 2000)
- Probability of exposure in cases: 50%
- Ratio of controls to case - 1:1

Perimenopausal and menopausal women receiving HRT (Case) = 31

Estrogen only HRT = 15 samples

Estrogen and Progesterone HRT = 16 samples

Menopausal women not receiving HRT (Control) = 31

Total sample size = 62