MANAGEMENT OF DRY EYE

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Introduction

Dry eye is a common condition which causes discomfort and irritation. While discomfort can be relieved with adequate treatment, the disease is usually not curable. Its chronicity may lead to frustration on the part of both the doctor and the patient. Optimal communication between the patient and doctor to define the goals and limitations of treatment is essential in the management of dry eyes.

Definition

A definition and classification scheme for dry eye disease was proposed at the (US) National Eye Institute's Industry Workshop[1] (December 13-14, 1993 and December 5-6, 1994). Dry eye was defined as "a disorder of the tear film due to tear deficiency or excessive evaporation that causes damage to the interpalpebral ocular surface and is associated with symptoms of discomfort."[1] Consistent with this definition is a proposed classification scheme which stratifies patients with dry eyes into those with decreased tear production and those with increased evaporative loss (Fig 1).

Epidemiology

A recent population-based prevalence study[2] in the United States found that 14.6% of the 2482 subjects aged 65 years and older reported symptoms of dry eyes to be present often or all the time. Another study from Melbourne Australia[3] with 926 subjects aged 40 years and older found a higher prevalence of dry eye diagnosed by rose Bengal testing in women 50 to 69 years old than in men of the same age group. Murube [4] has observed that the increasing longevity of the population and the increasing consumption of medication (both systemically and topically) have adverse effects on tear production and hence seem to be resulting in the increasing prevalence of dry eyes. Pflugfelder postulated that increased computer usage, more patients having LASIK and more people taking medication with side effects which cause dry eye has led to an increase in the prevalence of dry eye syndrome.

Associated Conditions

Lacrimal gland secretory dysfunction results in the ocular surface condition known as keratoconjunctivitis sicca (KCS). The severity of aqueous tear deficiency is positively correlated with the secerity of KCS. Decreased aqueous tear production can be congenital, as in Riley-Day syndrome (familial dysautonomia), congenital absence of lacrimal gland, aanhidrotic ectodermal dysplasia, Adie syndrome and idiopathic autonomic dysfunction (Shy-Drager syndrome). However, acquired lacrimal gland dysfunction is more common. This includes inflammatory diseases (primary and secondary Sjogren syndrome), infiltrative processes (sarcoidosis, lymphoma), infections (HIV, mumps) and trauma to the lacrimal glands. Systemic medications such as atropine, diuretics and beta-adrenergic blockers (atenolol, propanolol, metoprolol) also decrease tear production (Table I). There is loss of reflex tearing in cases of VIIth nerve palsy.

Lacrimal gland obstruction is seen in diseases such as cicatricial pemphigoid and Stevens-Johnson syndrome.

Sjogren Syndrome is defined as "dry eyes and dry mouth associated with systemic immune dysfunction". It is characterized by infiltration of the lacrimal gland and salivary glands with lymphocytes, with secondary compromise of gland function. Patients with primary Sjogren Syndrome have nonclassifiable systemic disease and symptoms which may include arthralgia, myalgia or fatigue. Those with secondary Sjogren Syndrome have a defined connective tissue disease, such as SLE, rheumatoid arthritis, scleroderma, polymyositis, dermatomyositis and primary biliary cirrhosis.

Local conditions which increase evaporative loss include meibomitis, blepharitis, eyelid malposition and lagophthalmos. Environmental conditions such as reduced humidity, evaporative loss from wind, air conditioning and heating may exacerbate the ocular discomfort of patients with dry eye. Exogenous irritants and allergens, although not believed to be causative, may increase the ocular discomfort and irritation.

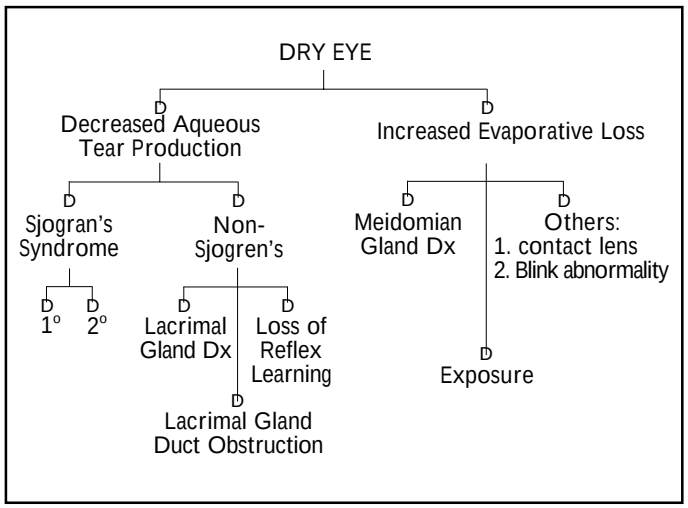

Fig 1. Diagnostic Classification Scheme for dry eye proposed by National Eye Institute/ Industry Workshop

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Table 1

Systemic medication with anti-cholinergic side effects

Antihypertensives	:	clonidine (alpha blocker), prazosin (alpha blocker), propanolol (beta blocker), reserpine, methyldopa, guanethidine
Antidepressants and psychotropics	:	amitryptyline, nortriptyline, imipramine, desipramine, clomipramine, doxepin, phenelzine, tranylcypromine, amoxapine, trimipramine, phenothiazines, nitrazepam, diazepam
Anaesthetics	:	enflurane, halothane, nitrous oxide
Cardiac anti-arrhythmia drugs	:	disopyramide, mexiletine
Muscle spasm medication	:	cyclobenzaprine, methocarbamol
Decongestants	:	ephedrine, pseudoephedrine
Parkinson disease medication	:	trihexphenidyl, benztropine, biperiden, procyclidine
Anti-ulcer agents	:	atropine-like agents, metoclopramide, other drugs which decrease gastric motility
Antihistamines		

In addition, dry eye is also an undesirable sequela of refractive surgery[5]. The cause mainly involves decreased corneal sensation, resulting in decreased feedback to the lacrimal gland and decreased tear production. Other causes may include increased evaporation, inflammation or toxicity of medication.

Clinical Presentation

The clinical spectrum ranges from mild ocular irritation with minimal ocular surface disease to severe discomfort, occasionally associated with sight-threatening corneal complications. Symptoms tend to worsen towards the end of the day, with prolonged use of the eyes or with exposure to environmental extremes.

Signs of dry eye include conjunctival injection, decreased tear meniscus, irregular corneal surface and increased debris in the tear film.

Diagnostic Tests

- *Tear Break-up Time*

Saline moistened fluorescein strips are instilled in the inferior cul-sac to stain the tear film. After several blinks, the tear film is examined using a broad beam of the slit lamp with a blue filter. The time lapse between the last blink and the appearance of the first randomly distributed dry spot is the tear break-up time. Dry spots that appear in less than 10 seconds are considered abnormal[6].

- *Ocular Surface Dye Staining*

Fluorescein, rose bengal or lissamine green dye may be used to assess the ocular surface. Fluorescein stains corneal and conjunctival epithelial cells when there is disruption of intercellular junctions, thereby allowing access to the dye. Mild fluorescein staining can be observed in normal eyes and this staining may be more prominent in the morning. An exposure-zone fluorescein staining pattern is observed in dry eye and it is more obvious on the cornea than on the conjunctiva.

Rose Bengal staining of the tear film may be performed using a saline-moistened strip or 1% solution. Strips require prolonged contact with saline to achieve adequate solubilization of the rose bengal, which causes irritation to the eye. Areas of the ocular surface are stained where tear mucous/agar is discontinuous. Debris in the tear film is also stained. This staining is observed with a red-free filter. Exposure zone staining of the cornea and bulbar conjunctiva is seen in cases of dry eyes[7].

Lissamine green dye has a staining profile similar to that of the Rose Bengal but causes less ocular irritation.

- *Schirmer Test (fig 2)*

This test quantifies aqueous tear production by measuring the amount of wetting. A narrow strip of filter paper is placed in the inferior cul-de-sac. Less than 5 to 10 mm of wetting in 5 minutes is suggestive of an abnormality in patients tested without anaesthetic[6].

Fig 2.

- *Other tests*

Other tests which have been described but have limited availability include tear osmolarity, fluorescein clearance, impression cytology, tear function index and tear protein analysis (e.g lactoferrin). Patients with primary Sjogren Syndrome are very likely to have anti-La autoantibodies. Minor (labial) salivary gland biopsy is occasionally performed by oral surgeons to confirm the diagnosis of Sjogren syndrome.

Treatment

The principles of treatment are as follows:

1) Treat underlying cause, e.g immunosuppression and anti-inflammatory therapy for systemic diseases like rheumatoid arthritis, SLE; correct lid abnormality
2) Eliminate exacerbating exogenous factors
3) Replace aqueous
4) Decrease loss

Therapeutic options can be divided into psychological treatment, control of environment, medical therapy and surgical treatment.

Psychological treatment

Frustration can be minimized if the goals of treatment are clearly understood at the outset. In the case of dry eyes, the goals are the preservation of vision and the relief of discomfort. It should be emphasized to patients that there is generally no cure but with adequate treatment, good vision can be preserved and discomfort can be avoided.

Control of environment

To treat dry eyes, patients need still air, humid air and pure air. To get still air, one should avoid being under the direct flow of air conditioners, ventilators and fan. One can also keep the car's windows closed to maximize still air. The patient's location within a room should be in a corner, protected from the flow of air coming through doors and windows. Humid air is obtained by humidifiers and wearing spectacles. Just by wearing regular spectacles, the humidity between the eyes and the spectacles rises by 2% as there is decreased evaporation. Spectacles with side-panels/ moisture shields and goggles should be reserved only for very severe cases. Pure air is obtained by avoiding tobacco smoke and polluted cities. Murube[4] proposed that the exposed ocular surface should be as small as convenient posture allows. People with dry eyes should avoid reading or working at the computer with their eyes looking down. In this position of gaze, the exposed ocular surface is greater than that at up gaze or while looking straight.

Medical therapy

Artificial tears

Tear substitutes (eye drops and less frequently night time eye ointments) are the mainstay of therapy. Demulcents are polymers added to artificial tear solutions to improve their lubricant properties[8]. These are mucomimetic agents which can briefly substitute for glycoproteins lost late in the disease.

Until recently, all demulcent solutions contained preservatives. Preservative-free demulcent solutions were introduced after it was recognized that preservatives – although preventing bacteria growth – have increased corneal desquamation. Thus, the use of single-dose preservative-free eyedrops has led to improved corneal barrier function. Several different multidose artificial tear preparations with disappearing preservatives are also available[9]. (fig 3)

It is known that many patients with dry eyes develop problems during the night and upon awakening, presumably owing to further decrease of aqueous during sleep. The application of an ointment (fig 4) before sleeping provides a useful adjunct to the use of artificial tears throughout the day. Approximately 1/8 inch of the ointment is sufficient.

About 15 years ago, sustained-release artificial tear inserts (Lacriserts) became available in the US. These 5 mg hydroxypropylcellulose rods dissolve on contact with the ocular surface and release a viscous watery coating which lasts 6 to 12 hours. However, their high cost and difficulty in using them has limited their usefulness.

Fig 3.

Fig 4.

Cyclosporine

Pharmacologic stimulation of tear secretion has been attempted with many compounds, like topical cyclosporine and oral bromhexine. Cyclosporine is a potent immunomogulatory agent that inhibits T cell activation and down-regulates the production of many inflammatory cytokines. A prospective double-masked randomized placebo-controlled trial[10] has shown significant improvement in the cyclosporine-treated group.

Mucolytic agents

Filamentary keratopathy can be treated with debridement of the filaments and application of a topical hypertonic saline solution or topical mucolytic agents like acetylcysteine 10% eyedrops.

Topical steroids

Topically applied corticosteroids have been reported[11, 12] to remarkably improve the irritation symptoms and ocular surface signs of keratoconjunctivitis sicca. Steroids decrease levels of chemotactic cytokine IL-8 in the conjunctival epithelium. Currently, topical corticosteroids are used for

patients who experience intolerable irritation despite maximal aqueous enhancement therapy (artificial tears and punctal occlusion).

Treatment of Meibomian Gland Dysfunction
Performing lid hygiene with warm soaks and lid margin massage will clean the lid margins and prevent meibomian gland retention of secretions. When combined with preservative free artificial tears, basic tear secretion is significantly increased. Hence, tear break-up time is prolonged and symptoms are relieved.

The effects of Hormone Replacement Therapy
Recent clinical research has shown that hormonal replacement therapy did not appear to alter the incidence of dry eye symptoms in women prior to or during menopause.

Surgical treatment

Surgical procedures can be divided into 2 groups:
1. Those which attempt to retain the tears produced
2. Those which try to bring tear substitutes onto the ocular surface.

Punctal occlusion
Patients with moderately dry eyes may be helped by punctal occlusion (occlusion of lacrimal pathways), although this occasionally results in chronic epiphora. Temporary punctal occlusion by collagen implants or silicone punctal plugs is easy. However, these plugs frequently irritate the eye/eyelid and can be inadvertently forced into the nasolacroimal system. When patients have successfully tolerated temporary punctal plugs, permanent punctal occlusion can be performed by daithermy or cautery. Punctal occlusion by laser is barely used now because of unreliable results.

Punctal patch technique
The most efficacious technique for permanent occlusion of lacrimal system is the punctal patch technique, using autologous conjunctiva as devised by Murube[4]. A square of epithelium and subcutaneous tissue surrounding the punctum is removed, exposing a rough surface. A bigger piece of bulbar conjunctiva of the inferior cul-de-sac is excised and transplanted to the punctal wound.

Mucous membrane grafting
Mucous membrane grafting from buccal mucosa is particularly useful in patients with severely scarred conjunctiva (chemical burns, ocular pemphigoid and the Stevens-Johnson syndrome). The failure rate is very high. More successful is auto-transplantation of areas of normal conjunctiva from one eye to another, particularly in cases of chemical burns.

Corneal prostheses
In severe cicatricial diseases such as ocular pemphigoid and the Stevens-Johnson syndrome, severe trachoma and chemical burns, corneal prostheses have been implanted. Although some of these have resulted in impressive improvement of vision, most of these corneal transplants have ultimately been extruded[13].

Parotid duct transplantation
Parotid duct transplantation in which ducts leading from the parotid gland are transplanted so that they empty out to the conjunctival surface[14]. The parotid secretion is different from normal tear secretion and is much more copious. Complications associated with the copious secretion of such a foreign fluid into the ocular surface include a strange type of epiphora, which has led to the virtual abandonment of this procedure.

Dacrio Reservoir systems
The Dacrio Reservoir systems are reserved for very dry eyes which have corneal opacity and require penetrating keratoplasty. The cornea graft will survive only if permanently bathed by tears from this reservoir. Murube has developed a new dacrio reservoir system which is totally buried under the skin of the abdomen. It liberates the artificial tears through a tube which travels subcutaneously upwards through the thorax, neck and lateral side of the face until this penetrates the superior fornix of the conjunctival sac. This reservoir must be refilled every 45 days by injection through the abdominal wall.

Lid Surgery
Correction of local lid malposition such as ectropion and entropion may be useful. In patients with severe ocular surface disease, in particular persistent epithelial defects, a tarsorrhaphy is essential.[13]

New approaches to dry eye therapy

New artificial tears

1. Hyaluronic Acid

A double-blind multicentre study using 0.1% hyaluronic acid for the treatment of 104 dry eye patients found significant improvement in corneal fluorescein but not rose Bengal staining[15].

2. RGD Peptide

RGD consists of three amio acids – arginine, glycine and aspartate – which form the binding site for fibronectin, other RGD-containing ligand for integrin and the surface glycoprotein for mediating cellular adhesion. Tsubota[16] et al has had some success with a new artificial tear compound containing 18 peptides with the RGD sequence, combined with chondroitin sulfate. Both the RGD and chondroitin sulfate can mediate adhesion to the corneal to the corneal epithelium, acting as mucin and prolonging the tear film breakup time. They may also prevent bacterial adhesion to the epithelium.

3. High-viscosity Methylcellulose

Feenstra and Tseng[17] have shown that rose bengal stains epithelim uncovered by mucin or other viscous proteins, and methylcellulose has been shown to prevent rose bengal staining

in vitro. Low concentration methylcellulose has been used as a visco-elastic material in artificial tears for years; drops containing very high concentration of methylcellulose have only been introduced recently.

4. Epidermal Growth Factor

EGF – which is present in tears – is essential in the normal maintenance and wound healing of corneal epithelium. In dry eye patients, the epithelium may not receive sufficient EGF. The use of EGF in dry eye is under investigation but preliminary results are not promising.

5. Aldose reductase Inhibitor

In diabetics, aldose reductase is activated to produce excess sorbitol which accumulates inside and interferes with cell function. Although diabetic patients typically have epithelial staining by fluorescein, they do not complain as much as ordinary dry eye patients. This is presumably due to the decreased sensitivity of their ocular surface. Corneal epithelial morphological changes in diabetic patients can be reversed by topical aldose reductase inhibitor.[18]

6. Vitamin A

Promising results have been obtained with artificial tears containing retinol, 500 IU/ml; brush cytology showed a decrease in keratinized cells.

K Immunotherapy with interferon-alpha

Epstein-Barr virus (EBV) is believed to be associated with the development of Sjogren's syndrome. Preliminary studies reveal that concentrations as low as 20 units/ml of interferon-alpha can suppress EBV in vitro[19]. An optimal dosing regimen remains to be determined.

Conclusion

With attention on the part of the doctor and compliance on the part of the patient, the vast majority of patients with dry eyes can be successfully managed and they are able to maintain good vision and remain symptom free. From the description of the various methods of treatment presented in this paper, it is evident that we still have no permanent solution to what is arguably the most common disorder in ophthalmology. Fortunately, extensive research to identify the pathogenesis is ongoing. Hopefully, this will allow us to direct our therapy more specifically and more accurately in the near future.

REFERENCES

1. Lemp MA. Report of the National Eye Institute/ Industry Workshop on Clinical Trials in Dry Eyes. *CLAO J* 1995; 21:222-32.
2. Schein OD, Munoz B, Tielsch JM et al. Prevalence of dry eye among the elderly. *Am J Ophthalmol* 1997; 124:723-8.
3. McCarty CA, Bansal AK, Livingston PM, et al. The epidemiology of dry eye in Melbourne, Australia. *Ophthalmology* 1998; 105:1114-19.
4. Murube J, Tsubota K. Dry Eye: What is new in understanding its nature and effective management? *Highlights of Ophthalmology* Bi-monthly Journal , vol 24, No 5, 1996 series.
5. Robert T Ang, D.A Dartt, K Tsubota. Dry eye after refractive surgery. *Current Opinion in Ophthalmology* 2001; 12:318-22.
6. Pflugfelder SC, Tseng SC, Sanabria O, et al. Evaluation of subjective assessment and objective diagnostic tests for diagnosing tear-film disorders known to cause ocular irritation. *Cornea* 1998; 17:38-56.
7. Pflugfelder SC, Tseng SC, Yoshino K, et al. Correlation of goblet cell density and mucosal epithelial membrane mucin expression with rose Bengal staining in patients with ocular irritation. *Ophthalmology* 1997; 104:223-35.
8. American Academy of Ophthamology Basic and Clinical Science Course Section 8: *External disease and Cornea*; 79-88.
9. Pflugfelder SC, A Solomon. ME Stern. The Diagnosis and management of dry eye. *Cornea* vol 19(5):644-9; 2000.
10. Sall K, et al. Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. *Ophthalmology* 2000; 107:631-9.
11. Prabhasawat P, Tsecng SCG. The frequent association of tear clearance in ocular irritation. *Br J Ophthalmolol* 1998; 82:666-75.
12. Marsh P, Pflugfelder SC. Topical non-preserved methylprednisolone therapy of KCS in Sjogren's syndrome. *Ophthalmology* 1999; 106:811-6.
13. Lemp Ma. General measures in management of the dry eye. *Int Ophathlmol Clin* 1987; 27(1);36-43.
14. Bennett JE. The management of total xerophthalmia. *Arch Ophthalmol* 1969; 81:667-82.
15. Shimmura S, et al. The effect of sodium hyaluronate ophthalmic solution on dry eye. *J Eye* 1993; 10:611-6.
16. Tabbara KF, Wagoner MD. Diagnosis and management of dry eye syndrome. Int Ophtrhalmol Clin 1996 Spring; 36(2):61-75.
17. Feenstra R, Tseng S. What is actually stained by rose bengal? *Arch Ophthalmol* 1992; 110:984-93.
18. Tsubota K, Chiba K, Shimazaki J. Cornea epithelium in diabetic patients. *Cornea* 1991; 10:156-60.
19. Kure S, Tada K , Wada J, et al. Inhibition of EBV infection in vitro by recombinant human interferon alpha and gamma. *Virus Res* 1986; 5:377-90.