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The Treatment of Dry Eye

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Abstract. The most widely used therapy for dry eye disease is tear replacement by topical artificial tears. Punctal occlusion to prevent the drainage of natural or artificial tears is the most common non-pharmacological treatment. These and other traditional therapies for dry eye disease are only palliative, however, as they replace or conserve the tears without necessarily correcting the underlying disease process. As our understanding of the pathology of dry eye disease improves, new treatment strategies are being developed. Topical anti-inflammatory and immunomodulatory agents, such as cyclosporin A, are under investigation in the treatment of dry eye, as it is anticipated that they will correct the vicious cycle of inflammation and cell damage on the ocular surface and lacrimal glands. (**Surv Ophthalmol 45(Suppl 2)**:S227–39, 2001. © 2001 by Elsevier Science Inc. All rights reserved.)

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Traditional therapies for dry eye are palliative, in that their purpose is to replace or conserve the patient's tears without correcting the underlying disease process. As our understanding of the pathology of dry eye disease improves, we will be able to develop new strategies to treat the condition. An important factor in the success of dry eye therapy is that the patient is fully informed as to the nature of his or her dry eye disease and the goals of the clinician's choice of therapy, so as to encourage compliance with the treatment regimen.[30,58,83]

Currently, the choice of therapy for dry eye disease may be determined by the severity of the condition. Mild cases of dry eye, in which there are no signs of damage to the conjunctiva or cornea, may be successfully managed with artificial tears applied up to four times per day. In moderate cases of dry eye, examination will reveal mild damage to the cornea, such as superficial punctate keratopathy (SPK) limited to certain zones. In these cases, more frequent treatment will be required, e.g., use of unpreserved artificial tears up to 12 times per day and an unpreserved lubricating ointment at bedtime. Severe dry eye can be characterized by keratinization of the conjunctiva and moderate to severe corneal damage, including SPK, filaments, epithelial defects, and a subsequently higher risk of secondary infections. In addition to frequent instillation of unpreserved artificial tears and lubricating ointment at night, severe cases of dry eye will require other treatment strategies, such as tear-conserving therapies. This review describes the current treatment options for dry eye and discusses future developments.

Tear Substitution: Artificial Tear Substitutes and Lubricants

Tear replacement by topical artificial tears and lubricants is currently the most widely used therapy for dry eye, and a variety of components are used to formulate a considerable number of commercially available preparations (Table 1).[30,58,59,73,76,83] The goal of using tear substitutes is to increase humidity at the

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ocular surface and to improve lubrication, with subsequent secondary benefits. For example, a recent study demonstrated that artificial tears smooth the corneal surface of dry eye patients, an effect that may contribute to improved vision.[63] Moreover, the intraoperative and postoperative use of carmellose artificial tears has been shown to help restore the ocular surface after refractive surgery.[60]

The use of artificial tears has obvious limitations, however. Natural tears have a complex composition of water, salts, hydrocarbons, proteins, and lipids, which artificial tears cannot completely substitute. In addition, the integrity of the three-layered lipid, aqueous, and mucin structure, vital to the effective functioning of the tear film, cannot be reproduced by these artificial components.[58,76,83]

Furthermore, artificial tears are delivered intermittently, rather than continuously as are natural tears. To try to overcome this problem, formulations contain additional ingredients to increase their contact time with the ocular surface. These ingredients are designed to have mucoadhesive properties; that is, they adhere to and simulate the mucous layer of the tear film.[79] Fig. 1 shows the mucoadhesive forces between the mucous layer and various polymers commonly used in ocular lubricants.[18,48,82,100] Many of these mucoadhesive components are formulated as viscous gels,[14,15,79,97] which can tend to cause irritation, blur vision, make the eyelid sticky, and create a sensation of heavy eyelids.

More than 20 years ago, sustained-release artificial tear inserts (hydroxypropylcellulose rods) were developed. These release their viscous coating on contact with the ocular surface, and need to be used in addition to other artificial tears to initiate the dissolving process. However, their high cost, the difficulty in handling them, and the intense foreign body sensation they create have discouraged their use.[59] Related to this system is a new preservative-free lyophilisate drug delivery system, in which hydroxypropylmethylcellulose detaches from a polymeric carrier upon contact with the tear film. Although the tolerability of this system appears to be satisfactory, its clinical efficacy remains to be demonstrated.[22]

It seems, however, that problems associated with highly viscous materials can be overcome by different formulation strategies, such as bipolymeric systems that allow less viscosity while retaining mucoadhesive properties.[79] Alternatively, formulations can simply use less viscous materials.[14,15,97] A slightly different approach aims to increase the preocular residence time by the use of topical chitosan, a mucoadhesive polymer. This chitinous material has been found in ocular mucus[2] and is presently being tested in ophthalmology.[27] Artificial tear formulations teresting,[2] as, in addition to its bioadhesive characteristics, chitosan has been shown to have lubricating properties.[61]

Almost no attempt has been made to find a substitute for the mucus layer of the tear film, in spite of the fact that this layer is frequently altered in dry eye disorders. Some unfortunate patients with keratoconjunctivitis sicca (KCS) have a highly viscous and stringy mucus that form plaques and filaments on the ocular surface, and these are a major source of irritation and pain.[59] The application of mucolytic solutions can be of help, and although a 10% acetylcysteine ophthalmic solution in an artificial tear-base has been proposed,[20] major drawbacks are that it has to be kept refrigerated and remains stable for only 60 days, which precludes its commercialization.

Lipids are usually formulated as ointments, and there are some preservative-free formulations on the market that can provide relief for patients experiencing symptoms during the night and upon awakening.[59] Lipids have also been proposed as eyedrops,[90] but there is no conclusive evidence of their utility.[116] A new petrolatum ointment containing calcium carbonate placed on the lower lid skin has recently been shown to be helpful in dry eye patients.[124]

One of the most important drawbacks of many of the commercially available artificial tear substitutes and lubricants is the fact that they must contain preservatives, stabilizers, and other additives. These components supply stability and retard germ contamination and growth, thus ensuring the long shelf-life required for commercialization. The most common preservatives currently used in artificial tear preparations are quartenary ammonium compounds (benzalkonium chloride, benzododecinium bromide, cetrimide, polyquad), alcohols (chlorobutanol), and other compounds (chlorhexidine, sorbic acid, potassium sorbate, boric acid, biguanides, etc).[73,118] Mercurial agent thimerosal, much used in the past, has been abandoned because of its high potential to provoke not only toxic but also allergic reactions.[117,118]

Even though the concentration of preservatives in artificial tear preparations is generally low, their prolonged presence on an already compromised ocular surface, such as that of a dry eye, can cause serious iatrogenic effects, worsening the ocular surface disease.[6,7,16,21,64,118,130] Especially toxic to the ocular surface cells is the cationic detergent benzalkonium chloride, which emulsifies cell wall lipids, subsequently breaking intercellular unions.[6,9,16,21,64,118,130] This risk may be increased in patients with therapeutically blocked tear ducts, since the agent persists longer in the tear sac, relatively undiluted by lacrimal fluid.[65,136] Patients who require the application of tear substitutes more than four times daily on a long-term

TABLE 1: *Properties of Some Components Used in Artificial Tear Substitutes*[73,76]

Component	Properties	Advantages	Disadvantages
lose ethers (e.g., hypromellose, droxyethylcellulose, methylcellulose, boxymethylcellulose [carmellose])	•Viscoelastic polysaccharides •Increase the viscosity of tears •Large increase in viscosity when concentration is moderately increased •Sometimes co-formulated with electrolytes, as hypotonic •Available as sustained-release artificial tear inserts (hydroxypropylcellulose rods)	•Good retention time on ocular surface •Mix well with other ophthalmic products •Viscosity not influenced by blinking	•Only of benefit in aqueous tear deficiency •Hypromellose can cause crusting of eyelids, mimicking blepharitis
omers (polyacrylic acid)	•Synthetic polymers •High viscosity when eye is static, shears thin during blinking or eye movement, maximizing thickness of the tear film while minimizing drag	•Good retention time on ocular surface	•Tend to blur vision •Often uncomfortable to patients
inyl alcohol	•Synthetic polymer •Low viscosity but optimal wetting characteristics at a concentration of 1.4%	•Beneficial in lipid, aqueous, and mucin layer deficiencies •Water soluble, does not cause blurring of vision	•Short retention time on ocular surface •Does not mix well with other ophthalmic products
um hyaluronate	•Mucopolysaccharides •Viscous formulation	•Good retention time on ocular surface •Beneficial in corneal wound healing	•Little clinical experience
one (polyvinyl pyrrolidone)	•Synthetic polymer •Co-formulated with electrolytes •Superior wetting ability when co-formulated with polyvinyl alcohol	•Beneficial in mucin layer deficiency	•Little clinical experience
lcysteine	•Breaks down mucin molecules •Can be co-formulated with another lubricant such as hypromellose	•Useful for complications resulting from very dense mucus in severe dry eye	•Not commercially available as a topical agent
s (e.g. petrolatum [paraffin, vaseline, neral oil] lanolin, lecithin)	•Organic substances •Formulated as drops and ointments	•High viscosity and, therefore, high retention •Contribute to re-build the lipid layer •Useful adjunct to other artificial tears when used at night	•Cause blurred vision •Little clinical experience with lipid eyedrops

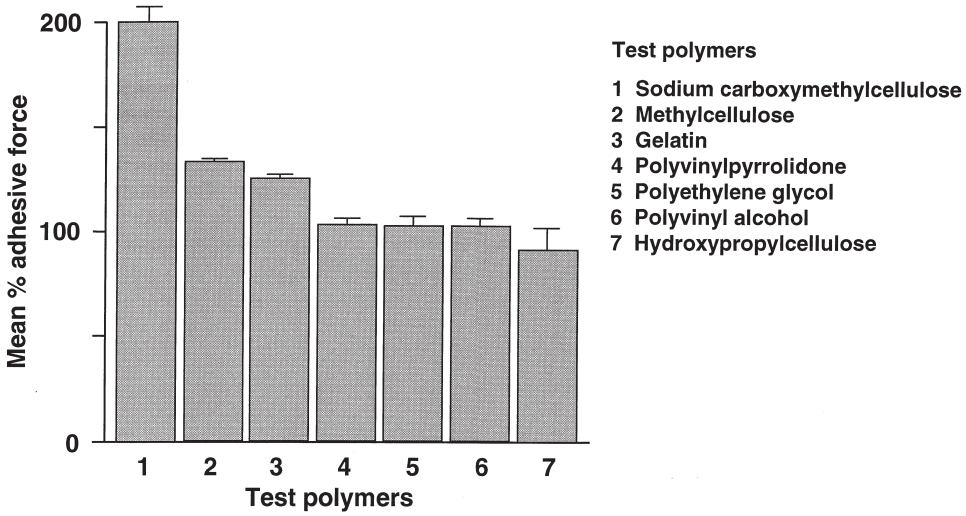

Fig. 1. Rank order of mucoadhesive force between the mucous layer and various polymers found in ocular lubricants (data from references[18,48,82,100]). The clinical significance of these in vitro data is unknown.

tions and use only unpreserved (usually unit-dose) formulations.[9]

The introduction of preservative-free solutions can be considered the single most important contribution in the formulation of tear substitutes. Two drawbacks exist, however, with these single unit-dose tears. First, they are more expensive than preserved preparations. Second, they can induce lack of compliance, because patients must carry numerous vials to maintain adequate dosage over 24 hours or more. One of the possible solutions could be the so-called "ABAK bottle," which has an eyedrop dispenser system that contains an adsorbent to retain benzalkonium chloride before instillation. Although an artificial tear based on this technology has been commercialized in some countries, the clinical efficacy of this system has not yet been well documented.[85]

Other common additives used in artificial tear preparations are buffers, which have the purpose of maintaining the pH of human natural tears (7.4) as closely as possible when they are applied to the ocular surface.[73] This is important, as it has been widely demonstrated that the pH of the tear film should be kept constant to maintain the normal function of the epithelial cells in the ocular surface.[17] It has also been shown that pH decreases after instillation of eyedrops, and then rapidly becomes more alkaline before normalizing after about 2 minutes.[135] Since the chemical buffering capacity of natural tears depends mostly on bicarbonates,[73] this and also other components (phosphates, acetates, citrates, borates, sodium hydroxide) are frequently added to artificial and the more alkaline solutions seem to be more comfortable than neutral or acidic preparations.[50] It is important to keep in mind that the neutralization process of tears depends not just on their chemical buffering capacity, but also largely on the tear turnover rate.[135] Therefore it can be altered when tear clearance is delayed, such as in dry eye states and after therapeutic blocking of the tear drainage system.[136]

In addition, hypotonic electrolyte-based formulations have been developed based on the recognition of the importance of tear osmolarity and electrolytes in maintaining the ocular surface.[37,39,40,59,128] In fact, tear film osmolarity and tear electrolyte (sodium, potassium, calcium, magnesium, bicarbonate) levels have been shown to be increased in dry eye states caused by meibomian gland disease and/or lacrimal gland disease.[37] One of these electrolytes, bicarbonate, seems to be an essential component in the recovery of the damaged corneal epithelial barrier and in the maintenance of normal ultrastructure.[128] One artificial tear formulation, not just hypotonic but also with a unique electrolyte-based composition, seems to increase corneal glycogen and conjunctival goblet cell density in a rabbit model of KCS[39,40] and to decrease rose bengal staining and tear film osmolarity in dry eye patients.[40]

Finally, surgical approaches aimed at substituting the absent natural tears with natural saliva by autologous transplantation of salivary glands has been proposed as an alternative for desperate dry eye conditions.[36,71,72,74] The quality and effects of this condensed saliva secretion on the ocular surface has

Tear Preservation

OCCLUSION OF THE TEAR DRAINAGE SYSTEM

Occlusion of the lacrimal puncta or canaliculi prevents the drainage of natural and artificial tears and is currently the most common nonpharmacological therapy for dry eye disease.[59,74]

Canalicular or punctal occlusion has been claimed to improve the quantity and the quality of the aqueous component of the tear film, relieving symptoms and signs of dry eye, making patients more comfortable and reducing the need for artificial tears.[74,133] Controversy remains, however, about many of those claims, as some authors have reported disadvantages to these techniques. For instance, a study suggested that punctal occlusion can decrease tear production, clearance, and ocular surface sensation.[136] It is believed that many of the problems that can be caused by occlusion of tear film drainage are derived from delayed tear clearance and turnover, and it has to be kept in mind that this delay is already present in dry eye states.[65] Delayed tear clearance can result in increased concentration of proinflammatory cytokines in the tear film, causing desensitization of the corneal surface and promoting inflammation.[65,84,136] It is also possible, as already mentioned, that delayed tear clearance can result in increased toxicity of preservatives present in other ocular medications that the dry eye patient might need.

As a consequence of all the above mentioned factors, some patients may experience little, only temporary, or no relief at all from therapeutic occlusion of the tear drainage system. In addition, epiphora can occur after occlusion, causing a great deal of discomfort to the patient. To minimize this risk, most authorities advise assessing the result of temporary occlusion with absorbable or removable plugs or inserts before proceeding with permanent occlusion.[59,74] More rarely reported complications include rupture of the punctal ring, pruritus and discomfort, suppurative canaliculitis, intrusion/extrusion of some plugs, and canalicular stenosis.[74] Finally, silicone punctal plugs have sometimes been associated with the formation of pyogenic granulomas.[88,132]

In conclusion, the decision to block the tear drainage system should be taken with care, as it may not be the treatment of choice for every dry eye state. Most authors reserve this method for moderate to severe dry eyes, and only after frequent use of unpreserved artificial tears and lubricants remains insufficient. The reported specific criteria for punctal or canalicular occlusion are quite variable,[74] but most authors agree that the nasolacrimal duct has to be permeable before therapeutic blocking; otherwise sion of only one punctum in each eye, usually the inferior punctum, provides sufficient relief from the symptoms of dry eye for many patients, occlusion of both inferior and superior puncta may be necessary for severe cases.

METHODS OF OCCLUSION

Many surgical, thermal, and tamponade methods of occlusion have been reported (reviewed by Murube and Murube[74]). The following are the most used today.

Surgical methods are not usually performed, as they are extremely difficult to reverse with the exceptions of "transfer of the punctum to dry dock" and the punctum patch.[74] The punctum patch, which covers the punctum with autologous conjunctiva, seems to be easy to perform, producing complete and permanent occlusion, and it can be removed if occlusion needs to be reversed.[75]

Thermal methods (cautery, diathermy, or laser) produce canalicular occlusion by destroying and shrinking the canaliculi walls.[74] Cautery uses an electrically heated probe to seal the punctum permanently. The probe can be placed in the vertical portion of the canaliculus only or through the whole length of the canaliculus, thereby reducing the risk of healing without occlusion. Diathermy (Hyfrecator) uses an electrode to deliver a high frequency current to the tissues, which produces heat and coagulation. Laser canaliculoplasty uses argon laser to cauterize the punctal opening.[8] This method offers more flexibility than thermal occlusion, as the puncta can be either fully or partially occluded. The slit-lamp delivery method also allows more precise placement of burns than does cautery. Recanalization is, however, more common with this method of punctal occlusion.

Tamponade methods occlude the drainage system with a foreign body (Fig. 2). They are by far the most popular and commonly performed techniques, as they require no surgery and can be easily performed as an outpatient procedure. An additional advantage is that a large body of clinical experience exists with these procedures.[43,55,59,62,74,89,133]

Absorbable inserts are used before a more permanent occlusion is made to assess the patient's tolerance of punctal occlusion and to avoid subsequent epiphora.[55,59,74] The manufactured inserts are made of hydroxypropyl cellulose or collagen and are inserted into the vertical or the horizontal canaliculus after topical anesthesia and punctal dilatation (Fig. 2, left). There, the inserts dissolve slowly at body temperature, the hydroxypropyl cellulose inserts lasting up to 18 hours and the collagen inserts up to

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