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Review Article

DRUG DELIVERY AND PHARMACOTHERAPY FOR DRY EYE DISEASE

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ABSTRACT

Dry eye disease is one of the most frequently encountered ocular morbidities a growing public health problem in the urban and rural population of India. Due to a wide variety of symptoms, it's often difficult to ophthalmologist as well as patients. The conventional and main approach in the treatment of dry eye disease was lubricating eye drops and tear substitutes. During last decade there were tremendous changes in the drug delivery systems and approaches for pharmacotherapy of dry eye disease. This review article focuses on the available drug delivery approaches and the treatment options like house hold remedies, acupuncture, hydrophilic bandage contact lens, approach in ayurveda and many more, for better pharmacotherapy of dry eye disease.

Keywords: Dry eye disease, Cyclosporine A, Artificial tears

INTRODUCTION

Dry Eye Syndrome, which has been recently termed as Dry Eye Disease (DED) is the most frequent disorder in Ophthalmology.[1] Dry eye can also be known as keratoconjunctivitis sicca, either due to insufficient tear production or excessive tear evaporation, both resulting in tears hyperosmolarity that leads to symptoms of discomfort and ocular damage.[2,3] Dry eye syndrome is a prevalent disease that affects visual acuity, activities of daily living, and quality of life. A number of contributory factors affect the severity of dry eye syndrome, including autoimmune disease, environmental surroundings, contact lens use, hormonal changes, anatomical features, chronic inflammation, infections, and iatrogenic factors, such as medications or surgery.[4] The modern definition of dry eye disease is based on the concept of the three layers of the tear film.[5] Secondary factors such as pathological changes to the eyelids, cornea, or conjunctiva, can themselves disturb the normal function of the tear film. Neurotransmitters, hormones, and immunological processes play an important role in the regulation of the tear production by the lacrimal gland.[6,7] Various environmental factors like contact lenses, pollution, working at video display terminals can affect the tear film.[8] Symptoms of Keratoconjunctivitis sicca [2,9] are like dry sensation, foreign body or "gritty" sensation, redness-blurred vision, irritation/redness, contact lens intolerance, mucous discharge-burning/stinging and increased frequency of blinking-tearing. No authentic prevalence survey has been conducted in India but it is noted that out of the patients above the age of 30 years attending the outdoor, one out of every four has a complaint pertaining to dry eye. In a community study in Sweden the prevalence rate of 15% was found in the general population aged 55-72 years.[2]

A recent survey conducted in year 2007 based upon a well characterized population of adult men and women in the USA identified a prevalence of 5 to 30 percent at various age groups. These rates extrapolate to potentially 9.1 million dry eye patients in USA alone. About 5 million Americans above 50 years of age have mild to moderate dry eye disease.[9] In women at the age of 45 to 52 when menopause usually sets in, an imbalance occurs between the estrogen and androgen hormone due to decrease of androgens after the menopause. Decrease in androgen levels, excites inflammation in lachrymal gland and ocular surface, disrupting the normal homeostatic maintenance of the lacrimal gland and ocular surface.[10,11]

Drug used in treatment of dry eye disease

The therapies describe above only improve the signs and symptoms of dry eye. New findings have demonstrated that a chronic immune-mediated inflammatory process plays an essential role in the pathogenesis of dry eye disease. The following are the main Immunomodulatory, anti-inflammatory or hormonal therapeutic agents tested or under investigation for the treatment of dry eye disease.

Immunomodulatory agents

Cyclosporine A

Cyclosporine A (CsA) is a well-known immunomodulatory, most commonly used to prevent rejection after organ/tissue transplantation.[13] It also confers anti-inflammatory activity and, in dry eye disease, thereby prevents T-cells from releasing cytokines (primarily interleukin-6) that incite the inflammatory component of dry eye. Early studies suggesting its utility in dry eye disease came from dog studies in which topical application of cyclosporine ophthalmic emulsion twice daily reduced lymphocyte infiltration in the lacrimal glands and conjunctiva.[14] Cyclosporine A also was associated with reduced apoptosis of lacrimal glands and conjunctival epithelial cells in dogs, effects that contribute to reduced inflammation and clinical improvement of dry eye. The earliest human studies in keratoconjunctivitis sicca revealed that topical eye treatment with cyclosporine A relieved the signs and symptoms of the disease.[15-17] the drug also has the ability to block c-Jun NH2-terminal kinase and p38 MAPK cascades, which contribute to T-cell activation.[58] Lastly, conjunctival epithelial apoptosis may decrease in response to CsA administration, although these findings have varied among dry eye studies.[18-20]

Anti-inflammatory agent

In light of the consistent research findings of inflammatory mediators in DES, the use of anti-inflammatory therapy has been gaining popularity.[2] The major anti-inflammatory agents currently in use include topical corticosteroids and immunomodulatory agents. Androgen therapy, tetracycline antibiotics, and nutritional supplements also show promise in treating the inflammatory component of DED.[21] Several older studies observing corticosteroid treatment, on the other hand, provided substantial evidence for further investigation into the role of inflammation in DED. To evaluate the clinical use of these anti-inflammatory agents, the mechanisms, efficacy, indications, advantages, and disadvantages of each type of therapy are assessed.[14]

Sex hormones

The relationship between hormone levels and tear production in obviously complex but it is still unclear how the different hormones regulate the functional activity of this tissue. Androgens receptors found in lacrimal glands, meibomian glands, cornea and conjunctiva. A Strong role for androgen in maintaining an anti-inflammatory state of the ocular surface has been hypothesized.

Investigations have shown that the systematic androgen therapy suppresses the inflammation and stimulate the functioning of the lacrimal glands in female mouse models Sjogren's syndrome.[22,23]

Oestrogen receptors are found in the meibomian glands. Symptomatic improvement of dry eyes with systemic oestrogen deficiency has been reported. A clinical trial reported on the use of oestrogen as a potential therapy for dry eyes. Another study has shown increase in dry eye symptoms in post-menopausal woman on systemic oestrogen therapy.[2,3]

Topical corticosteroids

Several studies have found that topical corticosteroids effectively treat dry eye.[56] This therapy is useful for short-term treatment to reduce the initial inflammation. Long-term use would be hampered with the significant risk of side effects like raised intraocular pressure, cataract formation, and secondary infections. Topical steroids (preferably non-preserved) are therefore, more suitable for acute management of dry eye exacerbations.[2,24] Fluorometholone 0.1%, like loteprednol etabonate, has a good safety profile and was used to treat patients with moderate to severe dry eye who did not experience relief from artificial tears alone.[25] After 1 week of using fluorometholone 0.1% 4 times daily, symptoms improved in all patients, and by the end of 1 month, significant improvement in objective signs of dry eye occurred as well. Objective measures included tear breakup time, Schirmer I scores, conjunctival hyperemia, and corneal fluorescein staining.[14]

Systemic tetracycline

Tetracyclines decrease the production and activity of inflammatory cytokines, decrease nitric oxide production, and inhibit matrix metallo proteinases production and activation.[26,27] When blepharitis is the underlying cause or a contributory element of dry eye, it must be properly managed. Lid hygiene, correctly performed on a long-term basis, is the single most important intervention. Occasionally, topical antibiotics or steroids, alone or in combination, may be required. In severe blepharitis, especially in rosacea associated meibomitis (especially if associated with keratoconjunctivitis), oral tetracycline and its derivatives (e.g. doxycycline) have become the treatment of choice.[28,29]

Topical autologous serum

Some authors have proposed the use of autologous serum as a way to deliver components such as Vitamin A, EGF, and TGF-beta to the ocular surface of patients with Sjogren's syndrome.[2,29] Patients using autologous serum diluted 20% in saline for four weeks showed improvements in Rose Bengal and fluorescein staining. 122 Practical problems in the use of such a product are obvious, as the patient's blood needs to be extracted and processed and the serum can only be kept refrigerated for a short period of time. However, it may be an option to consider for selected cases of severe dry eye, especially for those patients with secondary persistent epithelial defects, as the topical application of autologous serum has also been shown to be of help in this condition. [31] The disadvantage is that the patient's serum needs to be drawn and the serum can be kept refrigerated only for a short period of time.[32]

Antiviral agents

As viruses have been implicated in the pathogenesis of dry eye and dry mouth in patients with Sjogren's syndrome, some antiviral agents have been investigated for the treatment of dry eye conditions.[33] In a recent study, dogs with KCS were treated with oral interferon-alpha 2 (IFN-a2).[34] A favorable response with good tolerability was observed in 55% of subjects. IFN-a2 has also been tested in patients with Sjogren's syndrome, improving tear and salivary function and being well tolerated.[35,36] The antiretroviral drug zidovudine has been recently tested in an open, uncontrolled trial in primary Sjogren's syndrome; it was well tolerated and produced improvement in symptoms and signs of ocular dryness.[37]

Botulinium toxin

Injection of Botulinium toxin into the orbicular is oculi of Sjogren's syndrome patient with severe xerophathalmia and blpherospasm has been shown to increase tearing, and its injection into the medical aspect of the eyelids of both normal controls and dry eye patient produced a decreased lacrimal drainage. Its actual clinical utility is yet to be evolved.[23] In a recent prospective study, injection of botulinum toxin in the medial part of the eyelids of both normal controls and dry eye patients produced a decreased lacrimal drainage measured using the drop test.[38,39]

Types of polymer used for dry eye disease

The polymers are used to improve the ocular bioavailability of drugs and to increase the viscosity of the preparation. Polymer hydration results in the relaxation of stretched; twisted macromolecules witch exposes the adhesive sites. The high molecular weight polymers capable of forming hydrogen bonds and cannot crosses the biological membrane can ultimately increase the residence time also, which are mentioned in Table 1.

Drug delivery systems and approaches for dry eye disease

A. Tear substitution

Tear replacement by topical artificial tears and lubricants is currently the most widely used therapy for dry eyes. The aims of using tear substitutes are used to increase humidity at the ocular surface and to improve lubrication with the secondary benefit of visual improvement.[2,48,49] Topographic studies have shown that after instillation of artificial tears, the surface regularity index, the surface asymmetric index and potential visual acuity is better in a patient with dry eye. As the drop is washed off within a few minutes, tear substitutes have been improved by the addition of absorptive polymers in their formulations. Among the various available tear molecules, carboxymethyl cellulose seems to have the highest retention rate on the ocular surface.[2,40,51]

Most commercially available preparation contains preservative that provides stability and prevents contamination. Use of tears with preservatives on long term in an already compromised ocular surface can aggravate the surface damage. The common preservatives used are benzalkonium chloride, chlorbutanol and thiomersal. Tears with preservative are preferred in condition, which require artificial tears on a short term basis.[52-54] the introduction of preservative free tears is the single most important contribution in the formulation of tears substitutes. However, these are expensive and require patient compliance.

B. Tear preservation

Punctal occlusion is one of the most useful and practical therapies for conserving tears. This technique increases tear volume, and the retention of aqueous tears also may increases the concentration of biologically active constituents in tears. [29,55-56] Many surgical, thermal, and tamponade methods of occlusion have been reported. 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.[57] 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 re-moved if occlusion needs to be reversed.[58]

Thermal methods (cautery, diathermy, or laser) produce canalicular occlusion by destroying and shrinking the canaliculi walls.[59] 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.[60] 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 cautery. Recanalization is, however, more common with this method of punctal occlusion.

Tamponade methods occlude the drainage system with a foreign body. 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 this procedure.[58,60-65] The punctal plugs block the flow of the tears through the canaliculi which connects eyes to the nose. Insertion of punctal plugs has been reported to improve tear film stability and tear osmolarity.[66-67]

C. Decreasing tear viscosity

Patients with clinically observable stagnant mucus tend to develop filamentous and/or coarse mucus plaques. Acetylcysteine in 10-20% concentration can decrease the viscosity of the mucin and lead to an alleviation of symptoms. The solution; however are irritating, costly and malodorous.[68]

D. Stimulation of tears

A number of medications have been used to stimulate the lacrimal glands to produce tears. These include mucolytic agents (bromhexine and ambroxol), cholinergic agents (carbachol, bethanecol, pilocarpine and eledosin. Oral bromhexine and its derivative ambroxol have demonstrated variable results in clinical trials but have sometimes been associated with side effects such as generalized nausea, sweating and rashes and therefore have not achieved widespread use. These agents may not be useful when the disease process has already caused extensive damage to the lacrimal gland parenchyma or blocked the lacrimal ducts through conjunctival scarring. Stimulation of previously inflamed lacrimal glands and conjunctiva could deliver pro-inflammatory tears to the ocular surface, worsening the disease. Improvement in reports of DED symptoms and an increase in tear production have been reported after six months of omega-6 EFA treatment.[69,70]

Other alternative treatments for dry eye disease

A. House-hold remedies

Several aspects are to be considered while treating dry eye patients.

- Like controlling the humidity by using a humidifier in the living and working areas, particularly the bedroom. Ideally, the humidity should remain at 40 to 50 percent.
- Four drops of preservative free artificial tears in each eye every day.
- Reduction or discontinuation of systemic drugs for allergies, insomnia and nervous disorders.
- As in mild dry eye good lid hygiene should be advised.
- As suggested washing the faces with a Turkish face cloth twice a day, followed by a 30-73 second warm tap-water compress using a face cloth over both closed eyelids, also benefits such patients. After the warm (as opposed to hot) tap-water compress, the lower lid margin of each eye should be wiped once with a tightly wound dry cotton-tipped applicator. The heat and mild friction created with a single wipe from side to side removes excess oils, mucous and debris from the lower lid margin. Also, this will draw reflex tearing from the lacrimal gland, if it is available. Even a small amount of reflex tearing will decrease the need for artificial tear solutions. Moist chamber spectacles can also be considered when patient compliance is not a problem.[2,71]

B. Acupuncture

Although the mechanism of action is still speculative, acupuncture has shown beneficial effects for the treatment of Sjogren's syndrome related xerostomia[72] and non-Sjogren's syndrome related dry eye.[31] More studies are needed to address the real utility of this ancient technique for dry eye disease.

C. Hydrophilic bandage contact lenses

It is used in cases of corneal ulceration or corneal surgery. Patients with dry eye disease, however, may have difficulty with contact lenses becoming dry and falling off the eye. In addition, contact lenses will exacerbate the already increased risk of corneal infection in dry eyes. Although a specific type of contact lens has shown to produce a barrier to evaporation in dry eye disease.[15] the therapeutic value of contact lenses in dry eye patients is minimal. Furthermore, prolonged contact lens use can ultimately cause dry eye.[57,73-75]

D. Room humidifiers

The room humidifiers are a simple, noninvasive way of reducing the evaporation of tears. Wearing tight-fitting goggles, moisture chamber spectacles, or tear-feeding spectacles are also effective, but are some-times inconvenient for the patient.[76,77] hydrophilic bandage contact lenses are often used in cases of corneal ulceration corneal surgery.[78-80]

E. Special glasses with moist inserts

The moist inserts on the side panels increase the ambient humidity, resulting in a decrease in the tear evaporation from the ocular surface. Another type of moist chamber is obtained more easily and less expensively by using swimming goggles. The most favorable range of relative humidity for minimizing tear evaporation is reported to be 40% to 50 %. Wet gauze mask is an alternative treatment modality.[9]

F. Eyelid scrubs and cleaners

Eye scrubs are one of the best forms of preventative eye stye treatment, as they are great for cleaning the areas around the eye, specifically the eyelid margins. These scrubs are specially formulated to both treat and prevent eye styes.

G. Ayurveda

According to Ayurveda, dry eye is not merely an ocular surface disorder; rather this is one of the manifestations of the deranged metabolism/depreciation of body tissue. *Ashru* (tear film) is the byproduct of *Rosa, Meda, and Majja dhatus* and without narmalzing/altering them we cannot treat dry eye syndrome optimally. Dhiman studied systematic holistic approach of ayurveda on a patient of dry eye disease as a case study.[81] In the case drug induced auto immune reaction was responsible for oral lichen planus and dryness of the eyes which probably was over looked hence patient could not get the relief. Thus taking a holistic view point in the understanding of the disease *shushkakshipaka* (dry eye disease) and planning the treatment protocol accordingly; has proved much effective than the prevailing management modalities. Subjective and objective parameter clearly indicates that the condition of dry eye, in which the three component of tear film were involved, was not only due to chronic meibomitis but due to autoimmune reaction. Hence, systemic and holistic approach to treat the disease *shushkakshipaka,* (*sarvagata Vata-Pitta/raktaja Netra Rosa*) and managing this humeral imbalance, along with local/topical therapeutic procedure, the condition could be managed well.

Dhiman[80] further concluded that *Vata-pittahara* oral, local, *nasya* (*Snehana*) therapy with the prescribed medicine found better. But *vata* was managed first with *Anutaila nasya and dashmool kwatha* + castor oil orally. A close watch on *Jatharagni* (digestion) was kept and corrected as well. With treatment ocular discomfort was relieved and then *Avipattikarchoorna* was added for regular *pitta, virechana* action as well as the *Anu taila, brihmana nasya*. Milk + Shunti Seka (irrigation) was added as another local snehana and relieved the mucous debris too. Thus, snehana with Anutaila, Ghrita, Eranda, sneha, Kshreebala taila systemically and *Keshanjana,* Milk + *Shunthi* locally on eye and *Pitta-virechana* along with *vata-pita hara* oral *Rasayana* (anabolic) medicine worked well in relieving the ocular discomfort of *shushkakshipaka* (dry eye disease).

Table 1: Different polymers used for dry eye disease drug delivery

Polymer	Properties
Cellulose ethers (hypromellose, hydroxylethylcellulose, methylcellulose, Carboxymethylcellulose)[29,30,40,41,42,49,50]	Viscoelastic polysaccharides increase the viscosity of tears; large increase in viscosity when concentration increased,
Polyvinyl alcohol[29,30]	Low viscosity, optimal wetting of 1.4%,
Carbomer (polyacrylic acid)[29,41,42]	high molecular weight polymer of acrylic acid; high viscosity when eye is stain, the tear thickness of dynamically changes during blinking to maximize the thickness and longer retention time than polyvinyl alcohol,
Povidone (polyvinyl pyrrolidone)[29]	Wetting is improved when combined with polyvinyl alcohol,
Hyallironic acid, autologous tears[50]	Glycosaminoglycan biopolymers that exhibit long retention times. However, expense prohibits these as usual alternatives,
PLGA or poly(lactic-*co*-glycolic acid or poly(lactic-*co*-glycolic acid [43,45,47]	Biodegradable and biodegradable polymer,
Eudragit RL 100 [44,45]	a suitable inert nanocarrier for ophthalmic drug delivery system, absence of any toxic or irritant effects on ocular tissues,
Polyethylene glycol (PEG 400) [46]	Used as solvent and lubricant

CONCLUSION

Dry Eye Disease is recognized as a growing health problem and one of the most frequent reasons for seeking eye care. In India, the rural as well as urban population suffers from dry eye disease. The incidence is quite higher amongst outdoor workers and people from rural areas with poor socioeconomic status. Due to the modern life style, global warming, contact lens wear and environmental conditions (like allergens, cigarette smoke, wind, dry climate, air travel, chemicals, some perfumes and pollution), the polulation suffering from dry eye disease are increasing day by day. Very few researchers worked on dry eye patient's studies for its prevalence. Thus it is the need of hour to explore the research possibilities in this disease for the better pharmacotherapy to the suffering DED patients.

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