Review article Available online www.ijrpsonline.com ISSN: 2249–3522

International Journal of Research in Pharmacy and Science

Simplifying Dry Eye Management:A Structured Approach

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ABSTRACT

Dry eye is a chronic condition that, unfortunately, is affecting a growing number of people every year. Partly the product of an aging society, partly the result of a modern lifestyle, the condition is becoming increasingly widespread, causing discomfort and anxiety. The multifaceted nature of the condition makes it difficult for us to recommend an effective therapy for dry eye patient. Most of us try to manage this condition with artificial tear supplements only, without taking into account the exact pathogenesis behind the condition .As a number of tear substitutes are available in market ,we keep on switching from one brand to another with the hope that one will help the patient and the results are frustrating for both us and patient . With so many causes of dry eye and nearly as many therapeutic approaches, we shouldaim for combination therapy, with different treatment line for aqueous deficient and evaporative type of dry eye. It is important that we listen to patients symptoms as well as any visible signs and attack dry eye in a systematic way. With the aim to improve the approach for management of dry eye by general ophthalmologist this review provides a structured approach which will enhance our capability of diagnosing and treating this condition.

Key words: Dry eye, structured approach, diagnosis, management, newer developments.

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1. INTRODUCTION

In 2007 ,DEWS (Dry Eye Workshop) group defined dry eye as, "A multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface[1].This definition encompasses many factors that are critical to consider when identifying and treating patients with dry eye. In an effort to help clinicians detect and combat this prevalent ocular condition, this review provides essential information on structured i.e step by step approach for diagnosis and management of dry eye.

2. DIAGNOSIS

For practicing ophthalmologist diagnosis of dry eye disease is based on patient history that is supported by clinical examination and clinical tests. Based on history and examination clinician should be able to grade dry eye as mild (symptomatic on stress ,no signs) moderate (symptomatic without stress with reversible signs) and severe (disabling symptoms with permanent signs).He should also be able to classify dry eye as aqueous deficient or evaporative type.

Table 1: Grades of Dry Eye Disease

Tests	Mild	Moderate	Severe
TBUT	5-10 seconds	<5 seconds	Immediate
Rose Bengal staining (van Bijsterveld grading)	No staining	+1 to +2 staining	+3 staining
Schirmer 1 (after 5 minutes)	10-15 mm	5-10 mm	<5 mm
Tear fern test	Branching less with abundant spaces	Ferns thicker and smaller with little branching and very large spaces between them	No ferning but amorphous pattern

3. TREATMENT

Treatment of dry eye is very complicated as it needs a multipronged approach .Mild cases usually respond with education , environmental modifications , removal of risk factors and treatment of associated ocular and systemic condition in addition to artificial tear substitutes. For moderate cases in addition to this, reduction of ocular inflammation and irritation with anti-inflammatory drugs (NSAIDS, corticosteroids , cyclosporine, tetracycline and autologous serum) and antiallergics is needed. For severe cases , in addition to this conservation of tears (punctual occlusion or tarsorrhaphy) ,amniotic membrane grafting or secretogogues can be tried .For evoprative type of dry eye which is usually because of meibomian gland dysfunction ,maintenance of lid hygiene 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 oral tetracycline and its derivatives (e.g., doxycycline) should be prescribed.

3.1 Conservative Management: Most important aspect of management is education of the patient to help him understand the need for and the rationale behind any recommended therapy. It should be emphasized that dry eye is chronic disease and long term treatment is required. Alerting patients to environmental conditions that aggravate dry eye and activities that provoke tear film instability will help them adjust their environment or adapt their treatments to times of greatest stress on the tear film. A local increase in humidity can be achieved with moist chamber goggles or side shields[2,3] to glasses if this is cosmetically acceptable.

Figure 1 –Glasses with side shield

Figure 2- Radiator humidifier

Benzalkonium chloride used as preservative of various topical ocular drops (used for other ocular pathology like glaucoma ,ocular allergy) is toxic to epithelium and thus can aggravate ocular surface damage . So use of such drops should be reduced .Use of preservative free eye drops should be recommended for patients with dry eye .

Importance of lid hygiene should be emphasized on patients with meibomian gland disease (posterior blepharitis).Hot compresses of lidswith clean washcloth soaked in hot water is done for 5 to 10 minutes which loosens the collarets deposited in cilia base. After this lid scrubs (either commercially prepared surfactant containing eyelid cleansing kit or baby shampoo) should rubbed gently over the lid margin to remove the deposits at base of lashes and decrease the number of attendant bacteria. This must be repeated initially twice daily, tapering to once a day as the condition becomes controlled. This should be accompanied with expression of meibomian glands twice daily to relieve obstruction of ducts and orifices. In cases with grossly overt keratinised plugs ophthalmologist should express the glands in his OPD . Such therapy is known to show improvements in comfort and an increase in tear film break-up time in as little as two weeks.

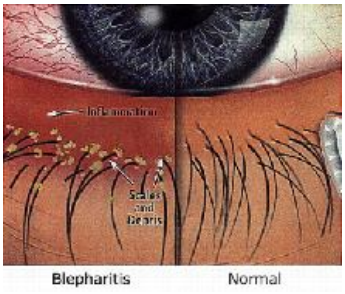

Figure 3 – Deposits in cilia base in case of blepharitis

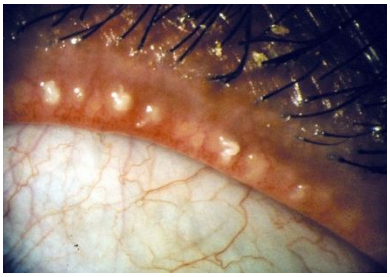

Figure 4 – Blocked meibomian glands

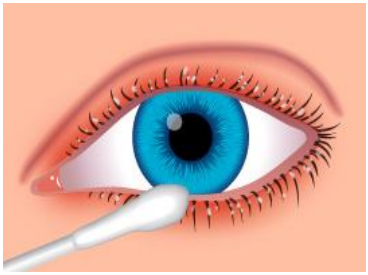

Figure 5- Cleaning lids with cotton applicator soaked in lid scrub

3.2 Tear substitution : Artificial tears remain the quintessential agent used in the treatment of dry eye irrespective of cause or type .To be effective artificial tear substitutes must stay in contact with ocular surface for long time for which a viscosity enhancing component (hydrogels) is added .The hydrogels commonly used in artificial tears are Hydroxypropyl Methylcellulose (HPMC),Carboxy methylcellulose (cmc), Polyvinyl alcohol (pva), Carbopol, Polyvinylpyrrolidone, Polyethylene glycol ,Dextran, Hyaluronic acid and Carbomer 940 (polyacrylic acid).

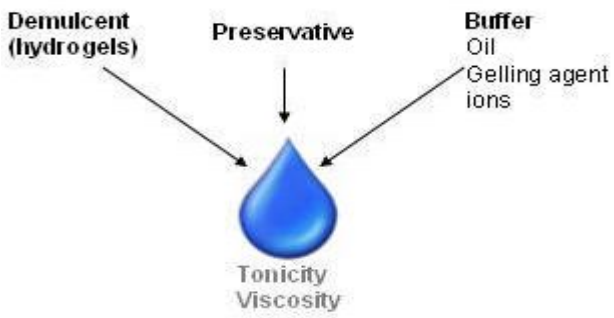

Figure 6- Important components of artificial tear substitutes

The choice artificial tear depends on two features - one the type of preservative used (Benzalkonium (BAK), Purite, Polyquad or GenAqua) and other presence of inactive ingredients that confer unique surface protective properties to artificial tears (e.g. compatible solutes in OPTIVE help surface healing by Osmoprotection ,HP-guar in SYSTANE ULTRA forms a cross linked viscoelastic gel

providing protection for damaged epithelial cells, Hyaluronic acid in BLINK TEARS helps in surface heal).BAK is toxic to corneal epithelium. Purite degrades to chloride ions and water after instillation. GenAqua is converted to water and oxygen on contact with tear and thus preservative free or Purite or GenAqua containing eye drops are preferred.

Certain patients of dry eye have a highly viscous and stringy mucus that form plaques and filaments on the ocular surface which are a major source of irritation and pain. In such patients application of mucolytic solutions(10% acetylcysteine) can be of help .The only problem with 10% acetylcysteine ophthalmic solution is that it has to be kept refrigerated and it remains stable for only 60 days, which precludes its commercialization.

The most important goal in treating dry eye is to lower elevated tear film osmolarity while addressing any concomitant inflammatory lid disease. In a formulation osmolarity study [4], 40 patients with Sjogren Syndrome (SS) were enrolled. Group 1 patients received hypotonic (150 mOsm/L) 0.4% hyaluronate drops (Ialurex, FidiaOftal, Catania, Italy), and group 2 patients received isotonic 0.4% hyaluronate drops (Dropstar TG, Farmigea, Pisa, Italy) instilled 6 times daily for 90 days. Both groups had significant improvement in tear film breakup time (TBUT) scores, corneal and conjunctival staining, as well as impression cytology after 2 weeks of treatment as compared with baseline. Patients who received the hypotonic solution did better and had a normal cytology by day 30. There was no change in Schirmer test results in either group.

3.3 Reducing ocular inflammation and irritation : There is increasing evidence that inflammation may be an important factor in the pathogenesis of dry eye. Inflammatory cell infiltration, predominantly T lymphocytes, has been seen in the conjunctival tissues and lacrimal glands of patients with SS [5,6,7]. Several studies have reported the effects of topical anti-inflammatory therapy for the treatment of SS-associated dry eye[8,9,10,11].The various anti inflammatory drugs are – NSAIDs, corticosteroids, cyclosporine A , autologous serum ,tetracyclines and androgens .

Topical NSAIDS have inhibitory effect on fibroblastic activity at the base of the filaments and thus useful in filamentary keratitis. Furthermore the increased comfort afforded by these drugs may result in a reduced blink rate, which in turn would lead to a reduction in number of filaments produced.

Topical steroids have been observed to significantly improve TBUT and Schirmer test results with increase in number of conjunctival goblet cells on impression cytology Nonpreserved topical

methylprednisolone ,fluoromethalone (FML) and rimexolone can be given to reduce inflammation associated with dry eye.

Cyclosporine (CsA , 0.05%, 0.1 %) is a neutral, hydrophobic, cyclic undecapeptide metabolite of the fungus Tolypocladiuminflatum. Its major clinical effect is disruption of expression of interleukin-2 by helper T cells, preventing T-cell proliferation.[6,7,8,9]. However, effect of cyclosporine is not immediate. Patients tend to notice reduction in photophobia, itching and dryness after one month of therapy. After three months, objective improvements are noted with peak effect at 6 months. Owing to the therapeutic time scale involved, it is useful to start concurrent steroid in order to expedite abrogation of signs and symptoms .

Tears contain essential components for maintaining the ocular surface, such as epidermal growth factor, vitamin A, fibronectin, and other cytokines. Because these components are also found in serum, the application of autologous serum is thought to offer advantages over artificial tears, which lack such essential components [9,10,11,12 ,13].Autologous Serum (20%) is prepared from patients own venous blood (centrifugation), refrigerated and stored for 2 weeks.Autologous serum drops have been reported to improve ocular irritation symptoms and conjunctival and corneal dye staining in Sjögren syndrome-associated KCS in several small clinical trials [12,13].

Healthy individuals produce anti-inflammatory androgens and that as long as this hormone is maintained at normal circulating levels, the lacrimal glands and ocular surface remain in a non-inflammatory state [14,15,16] and when androgen levels fall, for example, with age or at menopause, a precipitating stimulus, such as infection or a dry environment, inflammatory immune response tend to occur on the ocular surface or in the lacrimal glands. T-cells are activated, resulting in the release of inflammatory mediators, causing further inflammation and damage to the ocular surface. Investigations have shown that systemic androgen therapy suppresses the inflammation and stimulates the function of the lacrimal glands in female mouse models of Sjögren's syndrome. As androgen receptors are widely distributed on the ocular surface and lacrimal gland tissues, they are potential target sites for topical application of androgens as an effective therapy for aqueous-deficient and evaporative dry eye. However, no experimental studies using this topical route have been conducted and no human studies of any kind have been reported with androgens as potential therapy for dry eye.

Many patients with dry eye also have meibomitis. Systemically administered tetracyclines are recognized widely for their ability to suppress the inflammation and improve the symptoms of meibomitis [17]. The dosage is generally 50 mg of doxycycline once a day. For extremely obese patients

the dose may need to be increased to 100 mg a day. Tetracycline is administered for about three months. Nevertheless, if no improvement is observed after eight weeks, it is unlikely that any further improvements will be experienced.

Some researchers have postulated that allergy predisposes eye to dryness by causing loss of conjunctival goblet cells . By contrast, the supposition that aqueous deficient dry eyes may predispose patient to ocular allergy is based on the fact that reduction in tear film volume would allow a higher concentration of allergen to come in contact with ocular surface. Irrespective of the mechanism involved, it is obvious that use of topical antiallergic medications like nedocromil , olopatadine or levocabastine may quell the symptoms associated with this cohort.

3.4 Tear Preservation : Punctal occlusion is the most often used method to retain and preserve tears [18,19]. The puncta can be occluded temporarily by collagen stents . Various temporary punctal plugs are available to close the lacrimal puncta, and they typically have a mushroom shape to increase retention . These plugs are usually well tolerated but occasionally they can provoke a mild inflammatory response around the puncta that can progress to granulation tissue[20]. One caution is that the use of a punctal plug in a patient with inflammatory dry eye, particularly active Sjögren syndrome, may result in increased irritation because the retention of proinflammatory mediators and cytokines [21]. Temporary punctal occlusion is preferred before permanent closure of the puncta. Permanent closure is by use of thermal or electrocautery procedures. Laser treatment of the puncta also can be used to occlude the opening.

3.5 Oral Antioxidant : Vitamin A,C,E Zinc, Selenium and molybdenum together with other key nutrients are involved in tear metabolism.It has been shown ,within a normal, healthy, symptom free population group , that the blood plasma levels of essential antioxidants such as vitamin C can be so low that they reach near pathological levels.Within a normal , allegedly healthy symptom free population group , either vitamic C (1000mg/day),vitamin A (2250 mcg/day), or anti oxidant mixture (1 tablet /day of redoxan™ ,La Roche) can substantially improve tear stability after 7-10 days of treatment.[22,23]

4 .FUTURE PROSPECTS

Agents that trigger a secretion or release of another substance from eye surface cells are termed as "secretagogues". A secretagogue is applied to the cornea and causes the secretion of mucin from the epithelial layer.Pilocarpine (5mg) and Cevemeline(30 mg) are oral muscarinic cholinergic parasympathomimetic agonists that bind to M3 receptors causing stimulation of exocrine glands causing secreton of tears and saliva.Side effects of sweating and diarrhea often limit tolerance to the medication, but the improvement in symptoms has been documented in at least two studies [24,25].A promising medication to increase aqueous tear volume and stimulate mucin secretion is a novel P2Y2 receptor agonist (Diquafosoltetrasodium ,INS365; Inspire Pharmaceuticals). This topical agent has been shown to increase the flow of sodium and water across conjunctival membranes and to stimulate mucin production from goblet cells [26]. Preliminary clinical trials demonstrate an amelioration of clinical symptoms and signs of surface staining in patients with dry eye [27].

Injection of botulinum toxin into the orbicularis oculi muscle of Sjögren's syndrome patients with severe xerophthalmia and blepharospasm has been shown to increase tearing [28].

Liposomal Lipid Spray are under research whose active component is Phosphatidyl choline phospholipid liposomes (94%),which is most common phospholipid in natural tear. It is sprayed on to closed eyelids from distance of approximately 10cms.After a few minutes liposomes start migrating from lid margin into tear film, where it is thought to improve quality or quantity of polar surfactant layer of tears. This product needs more clinical trials. Liposome preparations have shelf life of 3 years.

Omega-6 fatty acid (linoleic acid) present in evening prime rose, black current seeds and fish oils ,increases amount of anti inflammatory prostaglandin PGE1 thereby increasing cAMP levels and thus increasing aqueous tear secretion. Improvement in the inflammatory features of Sjögren syndrome by oral administration of gamma-linolenic acid from oil of primrose have been observed [29].Omega -3 fatty acid present in flax seeds and fish oils(alpha linolenic acid) increases amount of anti inflammatory PGE3 and LTB5.It also decreases cholesterol levels and thereby improves quality of meibomian secretion .Unfortunately long term use of omega -3 depletes serum vitamin E.

5. SUMMARY

To reach our collective goal of ocular surface protection, we must heal the damage and reduce inflammation and irritation. It is important that we listen to patients symptoms as well as look for any

visible signs and attack dry eye in a systematic way .Armed with this knowledge , you can definitely combat patient's symptoms effectively and this will raise patient's confidence in you.

6. REFERENCES

1. Lemp MA, Baudouin C, Baum J, et al. The definition and classification of dry eye disease: Report of the Definition and Classification Subcommittee of the International Dry Eye Workshop (2007). Ocular Surf. 2007;75-92.
2. Tsubota K. New approaches to dry eye therapy. IntOphthalmolClin. 1994;34:115–128
3. Tsubota K, Yamada M, Uruyama K. Spectacle side shield panels and moisture sponge for treatment of dry eye patients.Cornea. 1994;13:192–201
4. Aragona P, di Stefano G, Ferreri F, et al. Sodium hyaluronate eye drops of different osmolarity for the treatment of dry eye in Sjögren's syndrome patients. Br J Ophthalmol. 2002;86:879–884
5. 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;104:223–235
6. Gündüz K, Ozdemir O. Topical cyclosporin treatment of keratoconjunctivitissicca in secondary Sjögren's syndrome. ActaOphthalmol (Copenh). 1994;72:438–442
7. Fan WS, Hung HL, Liao HP, Lai NS. Topical cyclosporine therapy for keratoconjunctivitissicca in Sjögren's syndrome. Tzu Chi Med J. 2003;15:85–89
8. Jain AK, Sukhija J, Dwedi S, Sood A. Effect of topical cyclosporine on tear functions in tear-deficient dry eyes. Ann Ophthalmol (Skokie). 2007;39:19–25
9. Hess AD, Colombani PM, Esa AH. Cyclosporine and the immune response: basic aspects. Crit Rev Immunol. 1986;6:123–149 Fox RI, Chan R, Michelson JB, Belmont JB, Michelson PE.
10. Beneficial effect of artificial tears made with autologous serum in patients with keratoconjunctivitissicca. Arthritis Rheum. 1984;27:459–461
11. Kono I, Kono K, Narushima K, et al. Beneficial effect of the local application of plasma fibronectin and autologous serum in patients with keratoconjunctivitissicca of Sjogren's syndrome. Ryumachi. 1986;26:339–343
12. Tsubota K, Goto E, Fujita H, et al. Treatment of dry eye by autologous seum application in Sjogren's syndrome. Br J Ophthalmol. 1999;83:390–395

13. 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;104:223–235
14. Stern ME, Beuerman RW, Fox RI. The pathology of dry eye (the interaction between the ocular surface and lacrimal glands). Cornea. 1988;17:584–589
15. Sullivan DA, Krenzer KL, Sullivan BD, et al. Does androgen insufficiency cause lacrimal gland inflammation and aqueous tear deficiency?. Invest Ophthalmol Vis Sci. 1999;40:1261–1265
16. Sullivan DA, Wickham LA, Rocha EM, et al. Androgens and dry eye in Sjogrens syndrome. Ann NY Acad Sci. 1999;876:312–324.
17. Esterly NB, Koransky JS, Furey NL, et al. Neutrophil chemotaxis in patients with acne receiving oral tetracycline therapy.ArchDermatol. 1984;120:1308–1313
18. Murube J, Murube E. Treatment of dry eye by blocking the lacrimal canaliculi. SurvOphthalmol. 1996;40:463–480
19. Yen MT, Monroy D, Pflugfelder SC. Punctal occlusion decreases tear production, clearance, and ocular surface sensation.InvestOphthalmol Vis Sci. 1999;40:S980
20. Balaram M, Schaumberg DA, Dana MR. Efficacy and tolerability outcomes after punctal occlusion with silicone plugs in dry eye syndrome. Am J Ophthalmol. 2001;131:30–36
21. Will DV, McNally LM, Roth RE. Pyogenic granuloma complicating Parasoltm (Odyssey™) silicone punctal plug occlusion: a series review. Invest Ophthalmol Vis Sci. 2000;41:S69
22. Patel S, Plaskow J, Ferrier C (1993).The influence of vitamins and trace elements on staility of precorneal tear film. ActaOphthalmologica ,71:;825-829
23. Patel S, AsfarAJ, Nabili S (1993) Effect of vitamin a on stability of precorneal tear film. Optometry and Visual Science 70 (12 supplement):64
24. Nelson JD, Friedlander M, Yeatts RP, Yee R, et al. Oral pilocarpine for symptomatic relief of keratoconjunctivitissicca in patients with Sjogren syndrome: the MGI PharmaSjogren syndrome study group**.** AdvExp Med Biol. 1998;438:979–98
25. Mathers WD, Dolney AM. Objective demonstration of tear stimulation with oral pilocarpine in dry eye patients**.** Invest Ophthamol Vis Sci. 2000;41:S60

26. Li Y, Kuang K, Yerxa B, Wen Q, Rosskothen H, Fischbarg J. Rabbit conjunctival epithelium transports fluid, and P2Y2 (2) receptor agonists stimulate Cl(−) and fluid secretion. Am J Physiol Cell Phys. 2001;281:C595–C602
27. Foulks G, Sall K, Greenberg M, et al. Phase 2 dose ranging efficacy trial of INS365 ophthalmic solution, a P2Y2 agonist, in patients with dry eye. ARVO Abstracts. Invest Ophthalmol Vis Sci. 2001;42:S713
28. Boroojerdi B, Ferbert A, Schwarz M, et al**.** Botulinum toxin treatment of synkinesia and hyperlacrimation after facial palsy**.** J NeurolNeurosurg Psychiatry. 1998;65:111–114
29. Horrobin DF. Essential fatty acid and prostaglandin metabolism in Sjogren syndrome, systemic sclerosis, and rheumatoid arthritis**.** Scand J Rheumatol. 1986;61(suppl):242–245.