Review Article

REVIEW OF THE LITERATURE ON EXISTING MANAGEMENT OF DRY EYE DISEASE

Abstract:

Dry eye disease (DED)is a multifactorial disease, in which there is loss of homeostasis of tear film, along with other ocular symptoms such as tear film instability and high osmolarity, neurosensory abnormalities and ocular surface inflammation and damage. DED is a condition of lacrimal apparatus which is responsible for tear production. Tear film is a mixture of mucin, aqueous (water and solutes like NacI, sugar, urea, proteins) and lipids secreted by goblet cells, lacrimal glands and meibomian glands respectively. It keeps the eye moist, provides oxygen to the cornea and has antibacterial properties. The evaporation of aqueous is prevented by the lipid layer. DED is categorized into (i)Aqueous-tear deficiency, characterised by deficiency of lacrimal glands to secrete tears , (ii)Evaporative DED, associated with increased tear loss by evaporation because there is deficiency of the meibomian glands. The mechanism of DED might be loss of tear through evaporation or insufficient aqueous production, or a combination of the two. DED is a very common eye problem, which is often left untreated. It causes irritation, itching, dryness, foreign body sensation and discomfort, Severe case causes conjunctival congestion, keratinization, erosion of the corneal epithelium and plaque formation. It can be vision threatening if left untreated, leading to complications like corneal ulceration and perforation. Various clinical tests are used for diagnosing of DED, which include tear breakup time, tear osmolality, Schirmer test, Rose Bengal staining, and expression of inflammatory markers. There is no cure of DED at present. The following modalities are used for its treatment:

1. use of punctual and canalicular plugs,
2. artificial tear products like polyethylene glycol/propylene glycol with guar HP,
3. consuming food rich in omega 3 fatty acids, antioxidants zeaxanthin and lutein,
4. use of anti-inflammatory drugs, mucolytics, secretagogues.
5. reducing or avoiding mild risk factors like prolonged reading, prolonged use of contact lenses, excessive screen time, etc.
6. treatment of causative disease.

To ensure patient satisfaction and adherence to the treatment appropriate management and establishing reasonable patient expectations are necessary.

Keywords – Punctal plugs, Canalicular plugs, Dry Eye Disease, Lubricating eye drops,

Introduction:

Many people worldwide are affected by Dry Eye Disease (DED). According to the International Dry Eye Workshop II (DEWS II) 2017 report, dry eye disease is "a multifactorial disease of the ocular surface, in which homeostasis of the tear film is lost, and is accompanied by ocular symptoms, where aqueous layer instability and high osmolarity, neurosensory abnormalities and ocular surface inflammation and damage play important role. [1] DED is a condition of lacrimal apparatus, which comprises of lacrimal glands and lacrimal passages including puncta, canaliculi, lacrimal sac and nasolacrimal duct. The main lacrimal gland is situated supratemporarily and is responsible for reflex secretions. LPS muscle divides it into 2 parts: Orbital part and Palpebral part. All the ducts are connected to the Palpebral part, which is small. The orbital part is larger and is almond shaped. It has two surfaces that are superior and inferior. Lacrimal artery supplies the main gland. Accessory glands include Glands of Krause and Wolfring.They are situated in fornix and are responsible for basal secretions. The sensory supply comes from the lacrimal nerve. The secretomotor fibres are derived from Superior salivary nucleus → facial and greater petrosal nerve → Pterygopalatine ganglion → Zygomatic and lacrimal branches of ophthalmic division of Trigeminal nerve. Puncta is a small opening in the medial point of lower and upper eyelids. From here the drainage starts and it goes into lower and upper canaliculi, then into the lacrimal sac and finally into the nasolacrimal duct, which opens into inferior meatus of the nose and is guarded by valve of Hasner. LacrimaI sac is separated from middle meatus by lacrimal bone.

With the increasing age the prevalence of DED increases, and is more common in people more than 50 years of age. This is due to the fact that these individuals have high chances of systemic drug effects, refractive surgeries and also autoimmune diseases. The estimated range of prevalence of DED depending on comorbidities is from 5 to 50%. In postmenopausal women under the age of 50 the incidence has increased from 5.7% to 9.8% and up to 75% in those aged 75. [2,3] Patients with helicobacter pylori diseases are also likely to be affected by DED. Sensitivity to light, sensation of foreign body, graininess, and visual disturbances, reported up to 34% impairment in daily activities, significantly affecting patients' quality of life [4,5]. Etiological classification of DED is as follows:

1. Aqueous-tear deficiency, in which there is deficiency of the lacrimal glands to secrete tears
2. Evaporative DED, associated with increased loss of tears by evaporation due to a deficiency of lipids secreted by the meibomian glands. [6]

However, most DED (>80%) is a mixed condition in which there is deficiency of both lacrimal and meibomian glands. [7] Insufficient tears lead to damage of the interpalpebral eye surface and is related with discomfort. DED is associated with reduced ability to perform various activities like reading, driving, screen related work, affecting people’s quality of life. This review talks about tear film, the causes of dry eye, recommended treatments, limitations faced in the current management of the DED, and how to establish reasonable patient confidence towards the management of DED. [8]

Tear Film

The structure of the tear film was described by WOLFF. He called it the precorneal film. Film has 3 layers - Mucus layers, Aqueous layers and lipid or oil layer, from posterior to anterior. The mucus layer is the innermost layer. It contains mucin which is secreted by Goblet cells and Glands of Maurz. It helps in adhesion. Aqueous layer is the middlemost

layer and it comprises mainly water and some solutes like NaCl, Sugar, etc. This is the reason why tears are alkaline and salty in taste. It also contains Antibacterial substances. Lipid is the outer layer and is thin. It contains secretions from Meibomian, Zeis and Moll glands and helps in preventing the aqueous evaporation. Following are the functions of the tear film-

1. Moistens cornea and conjunctiva.
2. Provides oxygen to corneal epithelium.
3. Removes debris and Irritants.
4. Prevents infection.
5. Allows movement of the lids.

The main lacrimal gland is responsible for reflex secretions and the accessory glands are responsible for basal secretion of tears. Reflex secretion occurs in response to conjunctival and corneal sensations produced by evaporation or breakup of tear film. Large amount of tear is lost by evaporation and the remaining is drained by the lacrimal passage into the nasal cavity. 70% of the tear is drained by inferior canaliculus and 30% by the superior canaliculus. Downward flow of tear is also influenced by gravity.

Etiology and nature of DED

The chief mechanism of development of DED might be loss of tear through evaporation or insufficient production of aqueous, or a mixture of the two, leading to high osmolarity, inflammation and damaging of tissues. The premature rupture of the tear film due to subsequent development of punctate epitheliopathy and instability of tear film exacerbates the hyperosmolarity and leads to a "dangerous cycle" of DED. [9] Both the categorizations of DED exist on an overlapping spectrum.

- Aqueous-deficient DED or KCS is characterised by decreased lacrimal secretions because of hyperosmolarity and is usually seen in association with conditions which affect the function of lacrimal gland, example, Sjögren syndrome, sarcoidosis, tumours, post radiation, fibrosis of lacrimal gland and surgical removal. It can occur due to lacrimal gland duct obstruction as seen in cases of trachoma, chemical burns, SJ Syndrome. It can also occur in hypersecretory states such as Familial dysautonomia, reflex sensory block, 7th cranial nerve damage, decreased corneal sensations.
- Evaporative dry eye is due to lipid deficiency and thus there is increased evaporation of the aqueous. It is seen in meibomian gland dysfunction (MGD), chronic posterior blepharitis, rosacea, congenital absence of meibomian glands. [9, 10] It also occurs in lid disorders such as lagophthalmos, defective blinking as seen in parkinsonism, progressive external ophthalmoloplegia. It can also occur following allergic eye disease and vitamin A deficiency.

Apart from clinical conditions like MGD, Sjögren's, and disorders of the connective tissue, demographic characteristics such as female age, gender, and race, environmental conditions, androgen deficiency, use of digital devices, use of drugs, and wearing contact lenses are the established population risk factors for DED. [11] Other possible risk factors of DED include social beauty trends, use of cosmetics, and various cosmetic procedures and medical surgeries (LASIK), use of CPAP masks, application of botulinum toxin. [12]

Symptoms suggestive of DED include irritation, dryness, FB sensation, itching, ocular discomfort. Sometimes it can also be associated with discharge and blurred vision. Symptoms get worse in dry weather because the temperature is high and humidity is less. Signs of dry eyes include presence of mucosa in the tear film, mildly congested conjunctiva, punctate epithelial erosion, signs of causative disease such as posterior blepharitis, conjunctival scarring disorders (trachoma, SJ syndrome) and lagophthalmos may be depicted. Rose Bengal or Lissamine green staining may depict conjunctival and corneal lesions.

Tear film tests used in diagnosis include questionnaires, tear breakup time, tear osmolality, Schirmer test, expression of inflammatory markers, Tear Function Index, Rose Bengal staining, Phenol Red Thread test.[13] Understanding this cacophony can help in guiding the eye care practitioners in making a diagnosis and developing a specific treatment plan for each individual. [14,15].

- Tear breakup time is the time between a complete blink and appearance of the first dry spot in the cornea. It is examined Under blue light of a slit lamp after putting a drop of fluorescein. It is an indicator of the effectiveness of the mucin component of tears. 15-30 Seconds is the normal value. If the value is less than 10 that means the tear film is unstable and there is mucin deficiency. If the dry spot always appears at the same spot, it indicates a corneal disease.
- Schirmer test is a quantitative test, it measures the total tear production. It is done using a 5×35mm strip of Whatman-41 filter paper, which is kept in the lower fornix at the junction of medial 2/3rd and lateral 1/3rd, the patient is instructed to look up and not to blink or close the eyes. Wetting of filter paper is measured after waiting for 5 minutes. Normal values are more than 15mm. If the value ranges from 5-10mm it is suggestive of moderate to mild KCS and less than 5mm means severe KCS.
- Rose Bengal staining is very useful in detecting wild cases of KCS. Depending on the severity there are three staining patterns - C pattern means mild/ early case with fine punctate stains; B pattern means moderate cases with extensive staining; A pattern means confluent staining of conjunctiva and cornea.
- Phenol Red Thread Test is done using a thread impregnated with PhenoI Red dye (yellow in colour). It turns red on coming in contact with tears. In 15 seconds the part of the thread that has turned red is measured. Normal values are more than 15mm. Value less than 6mm indicates a dry eye.

- Tear function index is a sensitive test for quantitative measure of tear production and drainage. Its value is obtained by dividing Schirmer test value in millimetres by tear clearance rate. The higher the value of TFI the better the eye surface. Value less than 96 indicates dry eye.

The severity of dry eye is graded into 4 levels based on the severity of signs and fear film tests:

1. Level I- Mild Dry eye
2. Level 2 - Moderate Dry eye
3. Level 3 -Severe Dry eye
4. Level 4- Very Severe Dry eye

Management of Dry Eye

Cure has not been found at present. The following treatment modalities have been tried.

[A] Punctal and Canalicular Plugs.

In Patients with moderate dry eye the tear drainage system can be blocked with a plug. This can be done using collagen implants, cyanoacrylate tissue adhesives, electrocauterization, and surgical occlusion. The American Academy of Ophthalmology published an article that reviewed the literature to evaluate safety and effectiveness of punctal and canalicular plugs. Lacrimal plugs improve the symptoms and it also reduces the use of lubricant in DED. Conditions causing dry eyes, like SJ syndrome, Sjogren's syndrome, superior limbic keratoconjunctivitis and contact lens use can effectively be treated by punctal occlusion. [16-17]

[B] Artificial Tear Products

ATP is a lubricating eye drop used to manage decreased aqueous content and severe itching in DED. These are titre solutions, which may or may not have preservatives, and contain surfactants, electrolytes and one or more lubricating agents which are derivatives of guar or cellulose including hydroxypropyl(HP) guar, propylene glycol [PG], glycerine, polyvinylpyrrolidone, dextran, sodium hyaluronate, polyvinyl alcohol and polyethylene glycol [PEG] 400, to improve or replace the tear film. [18-22]
PEG/PG Lubricating Eye Drops with Guar HP are kept at pH 7.9 whereas Guar HP, borate and sorbitol live in equal harmony where sorbitol enhances the droplet viscosity. [23] The pressure applied on the bottle during instillation decreases the ability of the drop to resist flow, upon instillation, due to solubility of sorbitol in water, the concentration of sorbitol decreases, allowing efficient and uniform spread. A cross-linked bioprotective gel is formed on interaction of borate ions present in Systane with galactomannan [23-25] In addition to this, the density of the crosslinks is increased by the ionic properties of the aqueous layer and it allows detention of active demulcents which stabilizes the tear film, thereby reducing vaporization of the aqueous and protecting it's superficial layer. The friction between blinks is also reduced by the Guar Borate/HP Gel Matrix.[24]
The above-mentioned properties make Polyethylene Glycol/ Propylene glycol with HP Guar the ideal lubricating drops for both KCS and evaporative DED as well as for the mixed DED conditions.

[C] Nutritional Impact

Selected nutritional intake can help in obtaining various eye health benefits such as good vision and decrease age-related macular degeneration (AMD). The Omega-3 fatty acid supplements like salmon, sardine, fish oil and flaxseed oil, which are good for overall health, are effective and useful in the reduction of topical medicines. Vitamin A supplement for deficiency is also useful.[26]
Chew et al. discovered that the antioxidants lutein and zeaxanthin containing green leafy vegetables reduce the chances of AMD. [27]

[D] Medical Therapy

Following medical therapies are used:

1. FDA approved anti-inflammatory drug, LIFITEGRAST used for DED treatment acts by inhibiting binding of integrin to ICAM-1, which is an intracellular adhesion molecule. [28,29]

2. Low potency anti-inflammatory steroids like fluorometholone are effective for acute exacerbations.
3. Topical cyclosporine is reported to be very effective; it reduces cell mediated inflammation of lacrimal tissue and ocular surface.
4. Chloroquine eye drops are also effective as anti-inflammatory drugs.
5. Cholinergic agonists like pilocarpine and cevimeline given orally to patients with Sjögren's syndrome may reduce symptoms and dry mouth.
6. Mucolytics such as 5% acetylcysteine (4 times a day) helps in dispersing the mucus threads and decreasing the tear viscosity.

7. Cyclosporin A is used for Sjogren syndrome.

[E] Treatment of causative diseases

Treating the causative disease is found to be useful, for example:

1. Systemic tetracycline and lid hygiene in patients with chronic posterior blepharitis.
2. Treatment of the cause of lagophthalmos.
3. Vitamin A supplement because due to deficient vitamin A there is loss of mucin.

[F]Educational counselling and reassurance

Primary health care physicians (PHCP) can recommend initial steps in giving dry eye guidance to decrease or prevent mild risk factors like excessive reading, increased screen timings, excessive use of contact lenses, and direct chemical exposure such as expired cigarette smoke, all of which is temporary [28-34].
Using digital devices and being on laptops or mobile phones for a prolonged time significantly reduce blinking rate and cause straining of eyes.[35-39]

Conclusion:

In spite of the wide understanding of DED, the emergence of multiple forms of multifaceted therapy, many challenges and limitations still remain. Appropriate management of DED and establishing reasonable patient confidence are necessary to ensure patient satisfaction. Many types of punctal occlusion plugs are accessible in the market. Their use is not only restricted to the non-pharmacological management of dry eye disease, but is procuring admiration in a number of other eye conditions. To reduce the risk of complications new designs are being developed. However, these plugs have certain drawbacks and close monitoring is required once they are placed. Further studies are required to compare the various types of caps and tracking their results over a period of time. With new technologies and continuing research, punctal occlusion plugs will continue to play a major role in the treatment of various eye problems.

The use of PolyethyleneGlycol /PropyleneGlycol with Guar HP improves the symptoms of DED associated with cataract surgery, contact lens use and environmental conditions. Clinically, PolyethyleneGlycol/PropyleneGlycol Lubricant Eye Drops with Guar HP has shown to improve the stability of aqueous layer, visual function, contact lens comfort, and visual acuity. It is used for DED treatment for over a decade now and is found to be effective, convenient and well tolerated.
Early diagnosis by primary health care physicians and newer treatments could allow rapid intervention and palliative care for the patient before more severe symptoms such as epithelial breakdown, corneal ulceration or perforation develops.

References:

1. Craig JP, Nichols KK, Akpek EK, Caffery B, Dua HS, Joo CK, Liu Z, Nelson JD, Nichols JJ, Tsubota K, Stapleton F. TFOS DEWS II Definition and Classification Report. Ocul Surf. 2017;15:276-283.
2. Schaumberg DA, Sullivan DA, Buring JE, Dana MR. Prevalence of dry eye syndrome among US women. Am J Ophthalmol. 2003;136(2):318–26.
3. Rouen PA, White ML. Dry eye disease: prevalence, assessment, and management. Home Healthc Now. 2018;36(2):74–83.
4. Patel VD, Watanabe JH, Strauss JA, Dubey AT. Work productivity loss in patients with dry eye disease: an online survey. Curr Med Res Opin. 2011;27(5):1041–1048.
5. O'Brien PD, Collum LM. Dry eye: diagnosis and current treatment strategies. Curr Allergy Asthma Rep. 2004;4(4):314–319.
6. International Dry Eye WorkShop Study Group. The epidemiology of dry eye disease: report of the Epidemiology Subcommittee of the International Dry Eye WorkShop (2007). Ocul Surf. 2007;5 (2):93–107.
7. Messmer EM. The pathophysiology, diagnosis, and treatment of dry eye disease. Dtsch Arztebl Int. 2015;112(5):71–81.
8. Shen Lee B, Kabat AG, Bacharach J, Karpecki P, Luchs J. Managing Dry Eye Disease and Facilitating Realistic Patient Expectations: A Review and Appraisal of Current Therapies. Clin Ophthalmol Auckl NZ. 2020;14:119–26.
9. Bron AJ, de Paiva CS, Chauhan SK, et al. TFOS DEWS II pathophysiology report. Ocul Surf. 2017;15:438–510.
10. ones L, Downie LE, Korb D, et al. TFOS DEWS II management and therapy report. Ocul Surf. 2017;15:575–628.
11. Stapleton F, Alves M, Bunya VY, et al. TFOS DEWS II epidemiology report. Ocul Surf. 2017;15:334–365.
12. Gomes JAP, Azar DT, Baudouin C, et al. TFOS DEWS II iatrogenic report. Ocul Surf. 2017;15:511–538.
13. Wolffsohn JS, Arita R, Chalmers R, et al. TFOS DEWS II diagnostic methodology report. Ocul Surf. 2017;15:539–574.
14. Ong ES, Felix ER, Levitt RC, Feuer WJ, Sarantopoulos CD, Galor A. Epidemiology of discordance between symptoms and signs of dry eye. Br J Ophthalmol. 2018;102:674–679.
15. Vehof J, Sillevis Smitt-Kamminga N, Nibourg SA, Hammond CJ. Predictors of discordance between symptoms and signs in dry eye disease. Ophthalmology. 2017;124:280–286.
16. M. M. Marcet, R. M. Shtein, E. A. Bradley et al., "Safety and efficacy of lacrimal drainage system plugs for dry eye syndrome: a report by the American Academy of Ophthalmology," Ophthalmology, vol. 122, no. 8, pp. 1681–1687, 2015
17. A. M. Alfawaz, S. Algehedan, S. S. Jastaneiah, S. Al-Mansouri, A. Mousa, and A. Al-Assiri, "Efficacy of punctal occlusion in management of dry eyes after laser in situ keratomileusis for myopia," Current Eye Research, vol. 39, no. 3, pp. 257–262, 2014.
18. Nassiri N, Rodriguez Torres Y, Meyer Z, Beyer MA, Vellaichamy G, Dhaliwal AS. Current and emerging therapy of dry eye disease. Part A: pharmacological modalities. Exp Rev Ophthalmol. 2017;12 (4):269–297.
19. Sutu C, Fukuoka H, Afshari NA. Mechanisms and management of dry eye in cataract surgery patients. Curr Opin Ophthalmol. 2016;27 (1):24–30.

20. Gayton JL. Etiology, prevalence, and treatment of dry eye disease. Clin Ophthalmol. 2009;3:405–412.
21. Che Arif FA, Hilmi MR, Kamal KM, Ithnin MH. Evaluation of 18 artificial tears based on viscosity and pH. Malaysian J Ophthalmol. 2020;2(2):96–111
22. Springs C. Novel ocular lubricant containing an intelligent delivery system: details of its mechanism of action. Dev Ophthalmol. 2010;45:139–147.
23. Springs C. Novel ocular lubricant containing an intelligent delivery system: details of its mechanism of action. Dev Ophthalmol. 2010;45:139–147.
24. Benelli U. Systane lubricant eye drops in the management of ocular dryness. Clin Ophthalmol. 2011;5:783–790.
25. Meadows DL, Ketelson HA, Davis J. Extensional rheological properties of an artificial tear delivery system. Invest Ophthalmol Vis Sci. 2008;49(13):1545.
26. McCusker MM, Durrani K, Payette MJ, Suchecki J. An eye on nutrition: the role of vitamins, essential fatty acids, and antioxidants in age-related macular degeneration, dry eye syndrome, and cataract. Clin Dermatol. 2016;34(2):276–85.
27. Age-Related Eye Disease Study 2 (AREDS2) Research Group, Chew EY, Clemons TE, et al. Secondary analyses of the effects of lutein/zeaxanthin on agerelated macular degeneration progression: AREDS2 report No. 3. JAMA Ophthalmol. 2014;132(2): 142–9.
28. Semba CP, Gadek TR. Development of lifitegrast: a novel T-cell inhibitor for the treatment of dry eye disease. Clin Ophthalmol. 2016;10:1083–94.
29. Tauber J, Karpecki P, Latkany R, et al. Lifitegrast ophthalmic solution 5.0% versus placebo for treatment of dry eye disease: results of the randomized phase III OPUS-2 study. Ophthalmology. 2015;122(12):2423–31.
30. Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II definition and classification report. Ocul Surf. 2017;15(3):276–83.
31. Lee JH, Lee W, Yoon JH, Seok H, Roh J, Won JU. Relationship between symptoms of dry eye syndrome and occupational characteristics: the Korean National Health and Nutrition Examination Survey 2010-2012. BMC Ophthalmol. 2015;15:147.
32. Comprehensive Review of the Literature on Existing Punctal Plugs for the Management of Dry Eye Disease - PubMed [Internet]. [cited 2021 Aug 15]. Available from: https://pubmed.ncbi.nlm.nih.gov/27088009/
33. Srinivasan S, Manoj V. A Decade of Effective Dry Eye Disease Management with Systane Ultra (Polyethylene Glycol/Propylene Glycol with Hydroxypropyl Guar) Lubricant Eye Drops. Clin Ophthalmol Auckl NZ. 2021;15:2421–35.
34. Verjee MA, Brissette AR, Starr CE. Dry Eye Disease: Early Recognition with Guidance on Management and Treatment for Primary Care Family Physicians. Ophthalmol Ther. 2020 Dec;9(4):877–88.
35. Khungar, Priyanka Naresh, Rohit Ashok Mistry, Sweta Kale Pisulkar, Trupti M. Dahane, Anjali Bhoyar Borle, and Surekha Dubey Godbole. “Prosthetic Rehabilitation of an Ocular Defect - A Case Report.” MEDICAL SCIENCE 24, no. 103 (June 2020): 1061–66.
36. Sathe, Seema, Sweta Pisulkar, Sharayu Vinod Nimonkar, Vikram Belkhode, and Anjali Borle. “Positioning of Iris in an Ocular Prosthesis: A Systematic Review.” JOURNAL OF INDIAN PROSTHODONTIC SOCIETY 20, no. 4 (December 2020): 345–52. https://doi.org/10.4103/jips.jips_374_19.
37. Lohiya S, Pardasani R. Ocular Manifestations of Cytomegalovirus (CMV) - A Case Report. JOURNAL OF EVOLUTION OF MEDICAL AND DENTAL SCIENCES-JEMDS. 2021 Feb 1;10(5):319–22.

38. Singh KA, Taksande A. Diagnostic Accuracy of Red Reflex Test (RRT) for Early Detection of Ocular Abnormalities in Newborn. JOURNAL OF PHARMACEUTICAL RESEARCH INTERNATIONAL. 2021;33(32B):185–91.
39. Kedia, Palak, and Bhushan Madke. "Unilateral Molluscum Contagiosum Following Eyebrow Grooming." JOURNAL OF CLINICAL AND DIAGNOSTIC RESEARCH 13, no. 11 (November 2019): WD01–2. https://doi.org/10.7860/JCDR/2019/42600.13283.