



Review of the Literature on Existing Management of Dry Eye Disease

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Dry eye disease (DED) is a multifactorial disease in which the tear film's homeostasis is lost, 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. The tear film is a mixture of mucin, aqueous (water and solutes like NaCl, sugar, urea, proteins.), 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 lipid layer prevents the evaporation of the aqueous. DED is categorized into (i) Aqueous-tear deficiency, characterized by a deficiency of lacrimal glands to secrete tears, (ii) Evaporative DED, associated with increased tear loss by evaporation because there is a 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 widespread 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. If left Univision- threatening vision-threatening, leading to complications like corneal ulceration and perforation. Various clinical tests are used to diagnose DED, including tear breakup time, tear osmolarity, Schirmer test, Rose Bengal

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staining, and expression of inflammatory markers. There is no cure for DED at present. The following modalities are used for its treatment:

1. use of punctal and canalicular plugs,
2. artificial tear products like polyethylene glycol/propylene glycol with guar HP,
3. consuming food rich in omega-three 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.

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

Keywords: Punctal plugs; canalicular plugs; dry eye disease; lubricating eye drops.

1. 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 an essential role [1]. DED is a lacrimal apparatus condition that comprises lacrimal glands and lacrimal passages, including puncta, canaliculi, lacrimal sac, and nasolacrimal duct. The main lacrimal gland is situated supratemporally and is responsible for reflex secretions. LPS muscle divides into two parts: The orbital part and the Palpebral part. All the ducts are connected to the Palpebral part, which is small. The orbital part is more significant and is almond-shaped. It has two surfaces that are superior and inferior. The lacrimal artery supplies the central gland. Accessory glands include the Glands of Krause and Wolfring. They are situated in the fornix and are responsible for basal secretions. The sensory supply comes from the lacrimal nerve. The secretomotor fibers are derived from the Superior salivary nucleus → facial and the greater petrosal nerve → Pterygopalatine ganglion → Zygomatic and lacrimal branches of the ophthalmic division of the Trigeminal nerve. The punctum is a small opening in the medial point of the lower and upper eyelids. From here, the drainage starts, and it goes into the lower and upper canaliculi, then into the lacrimal sac, and finally into the nasolacrimal duct, which opens into the inferior meatus of the nose and is guarded by the valve of Hasner. The Lacrimal sac is separated from the middle meatus by lacrimal bone.

With the increasing age, the prevalence of DED increases and is more common in people more than 50 years because these individuals have high chances of systemic drug effects, refractive surgeries, and autoimmune diseases. The estimated range of prevalence of DED depending on comorbidities is from 5 to 50%. In postmenopausal women under 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, the 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 a 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 lacrimal and meibomian glands are deficient [7]. Insufficient tears damage the interpalpebral eye surface and are related to 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].

2. TEAR FILM

WOLFF described the structure of the tear film. He called it the precorneal film. The film has 3

Mucus, Aqueous, and lipid or oil layers, from posterior to anterior. The mucus layer is the innermost layer. It contains mucin, which is secreted by Goblet cells and Glands of Mauritz. It helps in adhesion. The 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. It also contains antibacterial substances. Lipid is the outer layer and is thin. It contains secretions from Meibomian, Zeis, and Moll glands and helps prevent aqueous evaporation. Following are the functions of the tear film-

1. Moistens cornea and conjunctiva.
2. Provides oxygen to the 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 the basal secretion of tears. Reflex secretion occurs in response to conjunctival and corneal sensations produced by evaporation or breakup of the tear film. A large amount of tear is lost by evaporation and the lacrimal passage drains the remaining into the nasal cavity. 70% of the tear is drained by the inferior canaliculus and 30% by the superior canaliculus. The downward flow of tears is also influenced by gravity.

3. ETIOLOGY AND NATURE OF DED

The dominant 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 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 characterized by decreased lacrimal secretions because of hyperosmolarity and is usually associated with conditions that affect the function of the lacrimal gland, for example, Sjögren syndrome, sarcoidosis, tumors, 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 ophthalmoplegia. 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, 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 worsen in dry weather because the temperature is high and humidity is more minor. Dry eyes' signs include 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 osmolarity, 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 between a complete blink and the appearance of the first dry

spot in the cornea. It is examined Under the 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 average value. If the value is less than 10, 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 5x35mm 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 mild 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 Phenol 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 tear film tests:

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

4. MANAGEMENT OF DRY EYE

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

4.1 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].

4.2 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.

4.3 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].

4.4 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.

4.5 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.

4.6 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].

5. 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.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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