Review Article

Update on Surgical Interventions In Management Of Dry Eyes

V Anitha,[1] R. Meenakshi,[1] M. Vanathi[2]

[1]Department of Ophthalmology, The Institution Aravind Eye Hospital, Tirunelveli. India.
[2]Department of Ophthalmology, Dr. Rajendra Prasad Centre for Ophthalmic Sciences, New Delhi, India.

Abstract

Dry eye disease (DED) is an inflammatory disease with tear film instability and hyperosmolarity. It is also a common symptom encountered in a general ophthalmology practice. The DED symptoms range from mild, moderate to severe. The Rapid Diagnosis with non-invasive techniques are possible in the out-patient clinic itself. The management includes medical and surgical, which depends on the patients' objective symptoms, subjective complaints, and the severity of the disease. Medical treatment includes preservative-free tear substitutes, oral secretagogues, topical, and systemic anti-inflammatory therapy. The surgical modalities are the treatment options in very severe disease. The severity of the disease at the time of presentation, lifestyle modifications, compliance with the treatment is associated with a better prognosis. This review provides an update with a practical approach to surgical interventions of DED with emphasis on treatment for specific disease subtype and severity of the condition.

Delhi J Ophthalmol 2021; 31; 9-18; Doi http://dx.doi.org/10.7869/djo.650

Keywords: *Dry Eyes, Surgery For Dry Eyes, Tarsorrhaphy, Punctal Plugs*

Introduction

Dry eye disease (DED) is one of the common symptoms of presentation to ophthalmologist's office. It is a growing public health concern, causing ocular discomfort, irritation, visual disturbance and fatigue, interfering with the quality of life. The prevalence of DED varies from 3.4 – 48% [1] predominantly in postmenopausal women [2] and is more prevalent in Asian compared to western countries.[3] In 2017, the International Dry eye workshop (DEWS II) [4] report revised the definition of dry eye as "It is a multifactorial disease of the ocular surface Characterized by a loss of homeostasis of the tear film and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage and neurosensory abnormality play etiological roles". The understanding of the vicious cycle of tear film instability, hyperosmolarity and ocular surface inflammation aids in treatment for DED. The first-line therapy is medical treatment but for chronic and severe DED, surgical options play a pivotal role in management. This article reviews the advances and interventions in the surgical management of DED.

Etiopathogenesis

The appropriate understandings of the pathophysiology, risk factors and aetiology of DED have led to better treatment strategies in the last decade. Dry eye is divided into two groups,1) aqueous production deficient dry eyes 2) evaporative dry eyes. Insufficient or unstable tear film causes hyperosmolarity, key factor for release of inflammatory mediators, causes damage to DNA repair system, reduces epithelial cell volume, increases apoptosis and oxidative stress5. The inflammatory event involves release of numerous mediators such as, Matrix metalloproteinases (MMP) – MMP-9, MMP-13 and MMP-14, TNF-α, Mitogen- activated protein kinase, over expression of interleukins(IL)-1 β, IL-6, IL-17, IL-22, INF-gamma, chemokines (C-Cmotif) ligand 2 (CCL2). They are responsible for the cascade of events, leading to further ocular surface damage and lacrimal unit dysfunction (figure 1).[5,6] Management is complex due to multiple risk factors and the overlapping of etiological factors associated with DED. The risk factors for DED[6] are as follows:

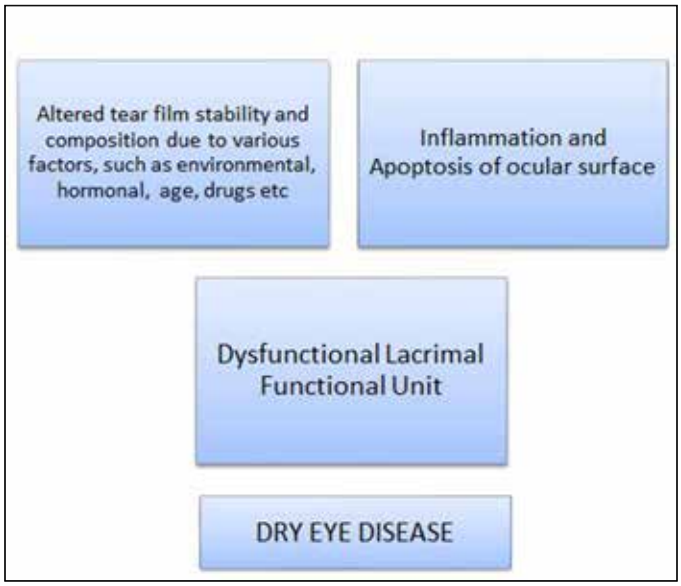


Figure 1: *Pathogenesis of DED*

1. Older age
2. Female sex
3. Sex hormones dysregulation- reduce tear secretions, causes meibomian gland (MG) dysfunction and reduce goblet cell density
4. Long term contact lens wears
5. Refractive surgeries and cataract surgery
6. Smoking
7. Diet low in omega-3 EFA and high ratio of omega 6:3 EFA
8. Low humidity conditions – office environment, air-conditioned cars, airplane cabins, extreme hot or cold weather

9. Alcohol consumption
10. Systemic drugs –Antihistamines, beta-blockers, oral Contraceptive pills
11. Chronic use of topical drops with preservatives-Antiglaucoma, anti-inflammatory etc
12. Following allogenic hematopoetic stem cell transplantation – ocular Graft versus Host Disease (oGVHD)
13. Extended visual tasking like prolonged reading, computer and television use.
14. Associated with anxiety disorders, sleep disorders and depression

The diagnosis of DED can be done in outpatient clinic. The evaluation of severity is done by the following tests:

- Tear film break-up time (TFBUT) - a measure of Tear film stability.
- Conjunctival and Corneal Staining with either rose Bengal, lissamine green or and fluorescein stains for assessment of ocular surface dessication.
- Measuring tear volume – Schirmer's test and Tear film meniscus height.
- Quality of tears is assessed by measuring osmolarity 5.

The diagnosis of DED is confirmed by the presence of subjective symptoms with OSDI score of >13 and objective DED signs in worse eye with TFBUT < 10sec, Schirmer's test < 5 mm and corneal staining grade >1. 7

The common laboratory tests are, mucus ferning test, conjunctival impression cytology, tear film interferometry, tear film osmolarity, tear lysozyme, lactoferrin levels, tear protein electrophoresis, tear glycoprotein and immunoglobulins.[7 - 10]

Management

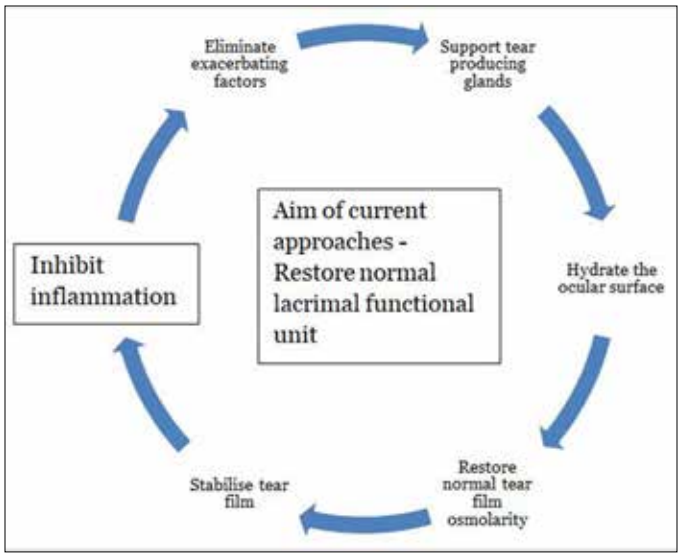
DED treatment requires multipronged approach including life style modifications, tear conservation, tear replacement, anti -inflammatory drugs and surgical approaches. The Dry eye society of Japan, proposed etiology oriented protocol known as "Tear Film – Oriented Therapy" (TFOT), which recommends replacement of deficient tears with the artificial tears accordingly (Table 1), this concept of TFOT was discussed and accepted in the meetings held by ADES (Asian Dry Eye Society) and TFOS (Tear Film and Ocular surface Society).[11]

Table 1: Tear Film- Oriented Dry eye therapy (TFOT)

Ocular surface inflammation	*cyclosporine 1% eye Steroids Rebamipide*
Lipid Layer deficiency	*Lid hygiene*
Aqueous Layer deficiency	*sodium hyaluronate Diquafosol Sodium Punctal Plugs*
Mucin Layer deficiency	*Diquafosol Sodium rebamipide*
goblet Cell Deficiency	*Auto serum Rebamipide*

The ultimate aim of treatment [12,13] (Flowchart 1)[14,15] are to:

1. Restore homeostasis of the ocular surface
2. Break the vicious cycle of inflammation
3. Ensure long term ocular surface stability



Flowchart 1: *Aim of current treatment approaches*

Although medical therapy is the mainstay of treatment, to reduce the inflammation and ocular surface damage but the chronicity, progressive nature of the disease and overlap of symptoms of different DED types, necessitates surgical options in certain scenarios.[16] The major disadvantages of medical therapy are chronic use of drugs; preservatives induced ocular surface toxicity, compliance to treatment, the economic burden due to frequent follow-up visits, medical costs involved, eye drop contamination and ocular surface infections.

The recommendations for management of DED[17] are elaborated in (Table 2). The indications for surgical interventions in DED management are severe dry eyes associated with systemic diseases, autoimmune disorders, and DED refractory to medical therapy, corneal epithelial defects, ulcerations, delayed epithelial healing, lacrimal

Table 2: Step wise treatment approach for DED

Aqueous Deficiency	Evaporative Deficiency
Tear substitutes	*Lid hygiene*
Temporary punctal Occlusion	*Topical NSAIDS / Antiseptic*
Scleral / Limbal Contact Lenses	*Systemic tetracycline and derivatives*
Minor salivary gland transplant	*Tear Substitutes*
Major salivary grand Transplant	*Stem cell Transplant*
Implantation of Dacryo Reservoir	*Lamellar Keratoplasty*
Correct excess lubrication	
Visual Rehabilitation	
OOKP (onlyin Aqueous deficient dry eyes)	

gland diseases, chronic end-stage inflammation and scarring conditions of ocular surface and dry eyes following severe chemical burns.

The various surgical approaches of DED can be considered primarily in Four groups

1) Procedures to avoid rapid loss of natural tears
2) Procedures which provides lacrimal substitutes
3) Neural stimulation of lacrimal tears
4) Miscellaneous

The various intervention procedures involved in these are detailed in the following section.[18]

1. The procedures to avoid rapid loss of natural tears include:

a) Occlusion of upper lacrimal pathways
Occlusion of upper lacrimal pathways which retains the lacrimal pool can be done by: Dacryocystectomy, Canalicular excision, Canalicular strangulation, Canalicular glavanocauterisation, Diathermy, Chemical caustication, Punctal/Canalicular plugs, Punctal patching, Punctal suturing, "Dome" Cisternoplasty.

b) Lid procedures
Tear Evaporation is delayed by Blepharoptosis, Tarsorrhaphy and AMG

2. Procedures for providing lacrimal substitutes:
   - Minor and Major salivary gland transplantations
   - Parotid duct transplant
   - Dacryoreservoirs
   - Lubricating inserts
   - Valved aqueous tube shunts

3. Lacrimal tear stimulation treatments:
   - True tears (Newer modality)
   - Tear Implants
   - Corneal Neurotisation
4. Miscellaneous: Conjunctivochalasis (CCH) excision

PUNCTAL / CANALICULAR OCCLUSION

Enhanced retention of tears on the ocular surface can be achieved by blocking the pathway for tear clearance and drainage. This is indicated in patients refractory to medical therapy, Schirmer's test < 5 mm at 5 min and positive ocular surface staining. Temporary and permanent methods are available (Table 3) and the choice depends on the severity of the disease.

Table 3: Types of punctual and canalicular occlusions

Temporary Punctal occlusion	*Permanent Punctal occlusions*	*Canalicular occlusions*
Collagen plugs	*Silicone plugs & others* *Punctal cautery* *Diathermy* *Laser Coagulation* *Incisional surgery* *Punctal patching* *Punctal Transorrhaphy*	*Canalicular occlusions* *Canalicular excision* *Canalicular ligation* *Canalicular off- set*

Punctal Plugs

The indications for punctal plug insertion in DED include dry eye syndrome[19,20], filamentary keratitis,[21] contact-lens related dry eyes,[22] chronic SJS,[23] severe trachoma,[24] neurotrophic keratopathy,[25] post penetrating epithelial defects, photorefractive procedures - PRK/LASIK.

The use of punctual plugs is beneficial in DED as they help to prevent the drainage of aqueous tears, and topical medications via the nasolacrimal drainage system, thereby beneficial in increasing effect of the medications. This is a relatively safe, out-patient procedure, and can be easily inserted, with minimal side effects and few complications.

Punctal plugs can be categorized into absorbable plugs and non-absorbable plugs.

1. Absorbable plugs are made of catgut, gelatin, hydroxyl propyl cellulose and collagen plugs, being absorbed within a short period, are effective for short term use (3 days to few weeks).
2. Non- absorbable plugs are intended for long term occlusion, with the insertion being slightly difficult. They are made of silicone, teflon, hydroxyl ethyl methacrylate (HEMA), polyethylene and PMMA. Some of the commonly used plugs include Freeman style plug, Herrick lacrimal plug and Smart plug.

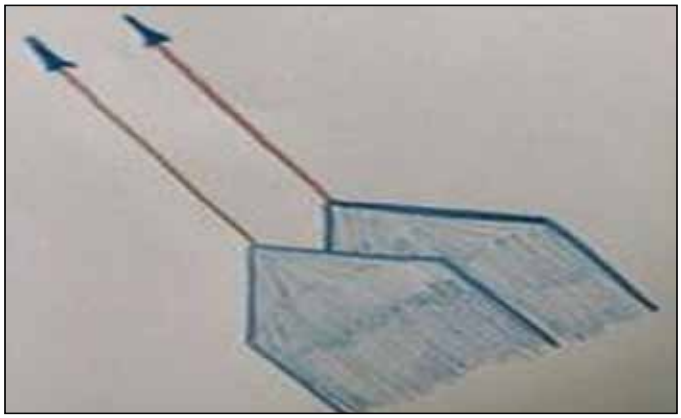


Figure 2: *Diagrammatic representation of Herrick lacrimal plugs*

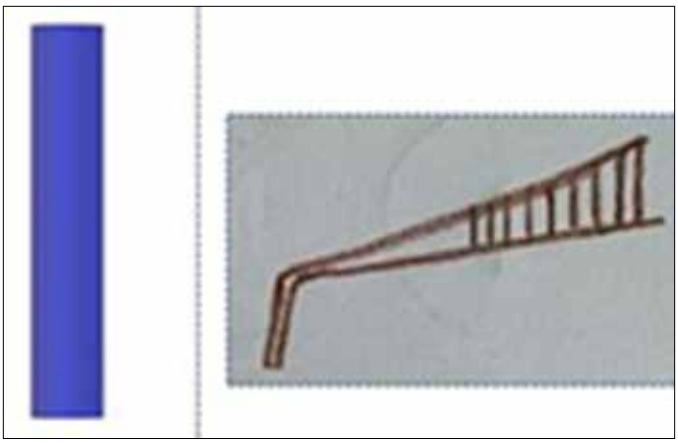


Figure 3: *Smart plug with insertion forceps*

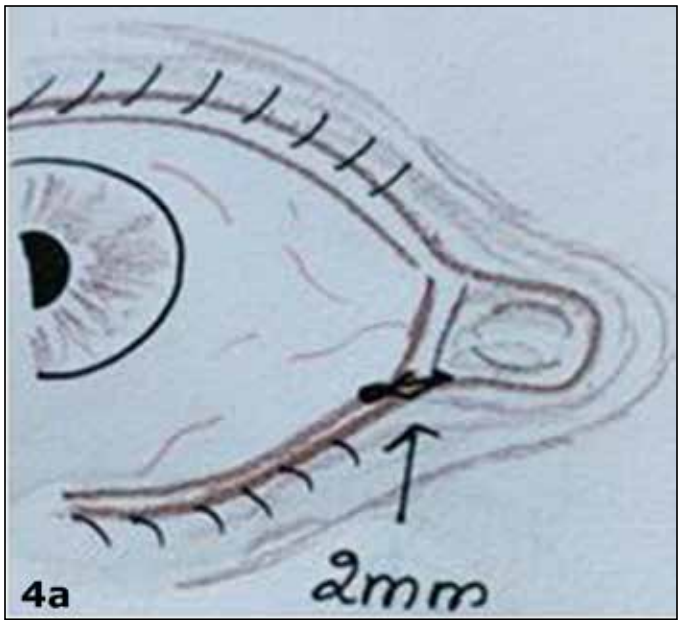


Figure 4: (a) *Full thickness incision made 2 mm nasal to the punctum and cut down vertically to divide*

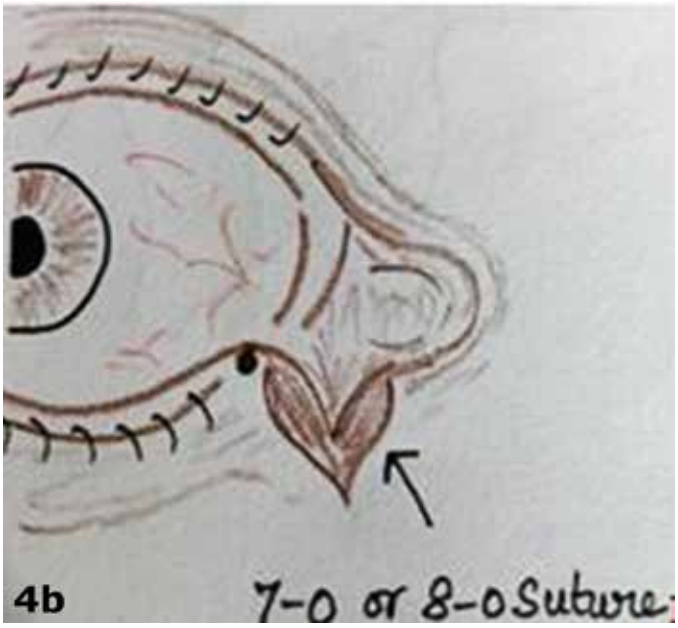


Figure 4: *(b) Proximal and distal cut ends of the canaliculus are oversewn with suture*

The method of removal is different; both smart plugs and Herrick lacrimal plugs[26] (Figure 2 & 3) can be flushed into the lacrimal passage, Freeman style plugs can be removed with the special forceps as they lie on the surface of the puncta.[27] Comparative study of punctual plug with artificial tears in trachoma patients showed improvement in signs and symptoms with the use of plugs. There are few concerns associated with non- absorbable plugs.[28] Epiphora and ocular surface irritation are common with Freeman style plugs. Epiphora necessitated removal of 5.4% of plugs among 203 eyes19. Extrusion and internal migration of Freeman style plug has been reported to be high, as they are located in the surface (extrusion rate 29-50.7 %). Internal migration is rare, and it may occasionally migrate into the

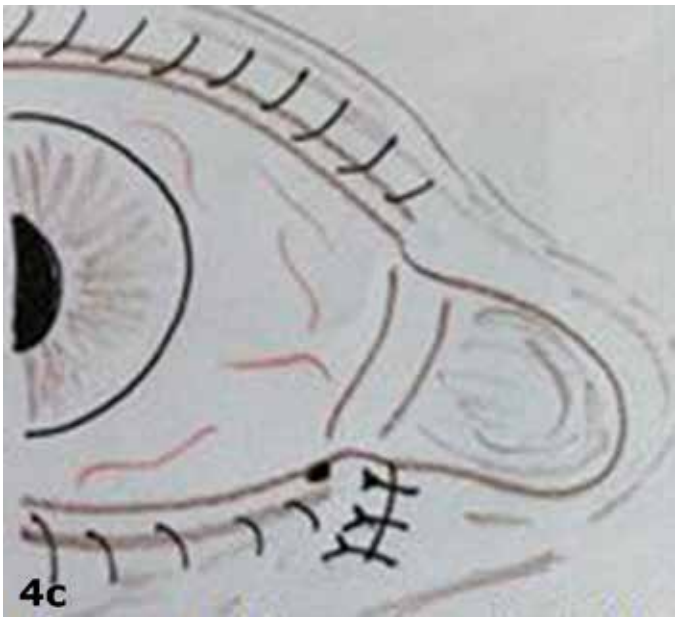


Figure 4: *(c) : Eyelid margin and skin incision is closed with 7-0 silk interrupted suture*

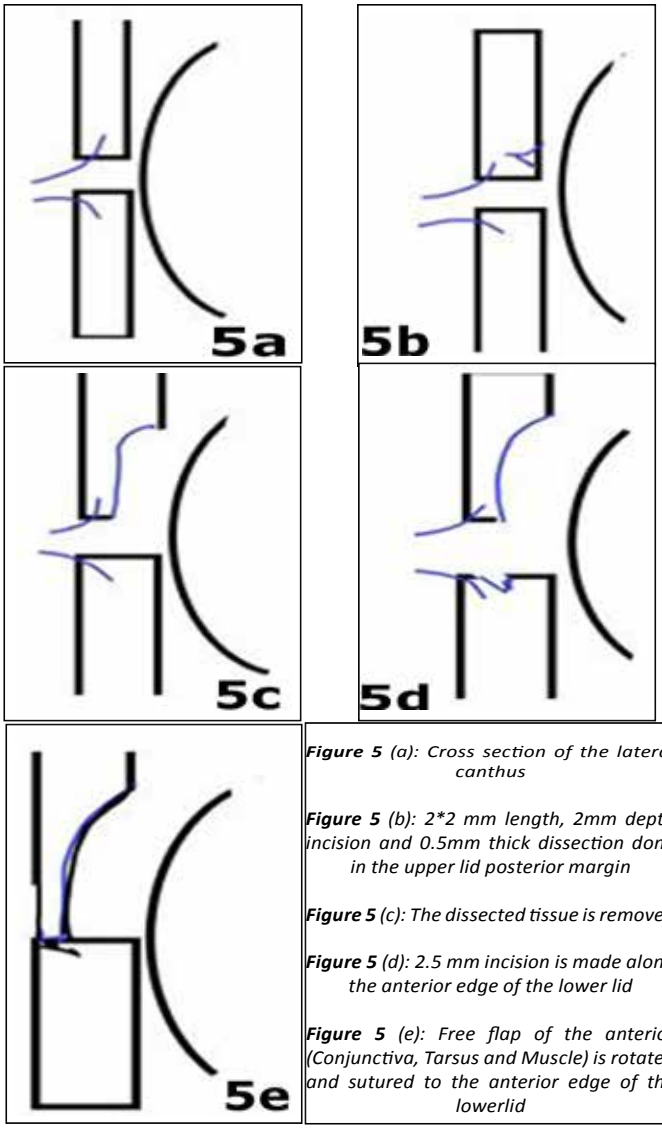


Figure 5 *(a): Cross section of the lateral canthus*

Figure 5 *(b): 2*2 mm length, 2mm depth incision and 0.5mm thick dissection done in the upper lid posterior margin*

Figure 5 *(c): The dissected tissue is removed*

Figure 5 *(d): 2.5 mm incision is made along the anterior edge of the lower lid*

Figure 5 *(e): Free flap of the anterior (Conjunctiva, Tarsus and Muscle) is rotated and sutured to the anterior edge of the lowerlid*

canaliculus, 44% of the patients have been reported to be positive for staphyloccous species with punctal plugs.[29] Bacterial colonisation can occur in the plugs with increased duration. Other uncommon complications include acute conjunctivitis, canaliculitis and dacryocystitis, pyogenic granuloma, canalicular stenosis and punctual scarring.[30-34] Decrease in tear film osmolarity has also been reported.[35] Improvement in goblet cell density with use of punctal plugs seems to be controversial.[36,37] Other permanent methods of punctual occlusions include punctal cautery, laser, diathermy and incisional surgery.

Different surgical techniques described to occlude tear drainage include canalicular ligation, canalicular off-set, canalicular excision, punctual tarsorrhaphy, Punctal patching with autologous conjunctiva, AMG, or Tenon's patch[38] and canaliculectomy.[39] Canalicular off-set[40] comprises of applying galvanocautery to the canalicular openings after dissection into the freeborder of the lid medial to punta, lid sutures applied to reappose the wound with an offset of the two openings of the lacerated canaliculus. Canalicular excision[41] involves excision of the canaliculi through the cutaneous incision over the lid 2 mm medial to the punctum, after introducing the lacrimal probe as a guide, wound sutured. Puntum closed with diathermy. Canalicular ligature is an effective and permanent method of occlusion of lacrimal pathways. The surgical steps involved in canalicular ligation are shown in (Figure 4a-4c).[42]

The canalicular surgeries are effective than the cautery due to its high (50%) failure rates and laser (86%). It is necessary to destroy the deeper part of lacrimal punctum and canaliculus for better and long term results. In patients with recurrent plugs extrusion, Yaguchi et al used high temperature disposable cautery device for punctual cauterization and observed it to be safe and effective without complication of recanalization.

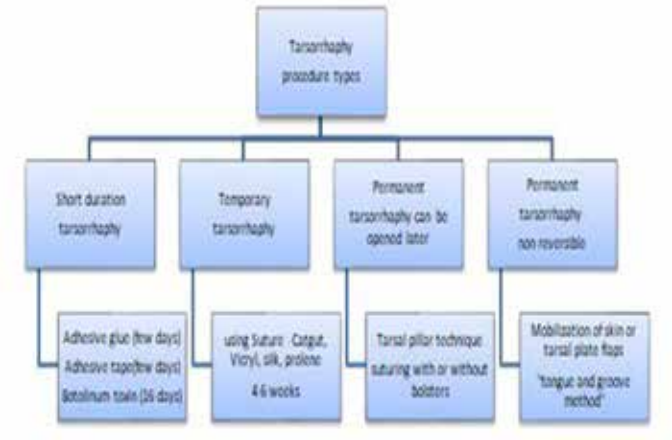


Figure 6 : *Tarsorrhaphy procedures*

Dome Cisternoplasty

Dome cisternoplasty is an easy technique to enlarge the natural lacrimal cistern.[44] This procedure does not increase the production of tears but enhances the retention and distribution of artificial tear drops thereby increasing the time interval between two instillations of artificial tears. The volume of a normal lacrimal basin is 7µl. A drop of artificial tears is 30µl and overcharges the lacrimal pool, five minutes after instilling the drop, the lacrimal pool returns to 7 ul. The Cisternoplasty procedure quadruplicates the content of the lacrimal basin and the time of retention. The surgical procedure is illustrated in the (Figure 5a-5e).

Tarsorrhaphy

Tarsorrhaphy (Figure 6) promotes healing of corneal surface in persistent epithelial defects (PED) secondary to exposure keratitis, neurotropic keratitis and DED. Tarsorrhaphy and AMT seem to have equal efficacy in management of PEDs but faster healing time has been reported with tarsorrhaphy, with a success rate of 80-100% for ocular surface healing.[45] Tarsorrhaphy decreases the evaporation rate of tears by decreasing the palpebral fissure width. The exposed cornea is in close contact with accessory lacrimal glands facilitating redistribution of tears, reducing the traumatic effect of the moving lids on the healing epithelium, promoting oxygenation and allowing instillation of eye drops with added advantage of retention of partial eye sight and examination of cornea.[46-49] Complications of tarsorrhaphy, include localised trichiasis, lid margin deficiency, suture granulomas, focal cellulitis, premature separation of tarsorrhaphy, cheese wiring of suture, distichiasis and skin breakdown.

Amniotic membrane grafts

The uncontrolled inflammation in dry eyes leads to delayed ocular surface healing, progressive tissue damage and vision threatening complications such as scarring and haze. The amniotic membrane grafting (AMG), controls inflammation and rehabilitates the ocular surface. AMG acts as a therapeutic bandage & keeps eye moist, controlling ocular surface inflammation by inducing apoptosis of neutrophils, monocytes and macrophages and promotes epithelial healing by retention of tears and regeneration of corneal nerves.[50]

There are two types of AMG 50, 51

1. Cryopreserved AMG (CAM): PROKERA (Slim, Biotissue, Miami, FL, USA) and
2. Dehydrated AMG: Amnio Disk (Katena), BioDoptix (Integra life science).

The efficacy of PROKERA for DED and neurotropic keratitis has been widely explored.[50-54] Common indications for AMG include epithelial nonhealing/persistent defects, filamentary keratitis, exposure keratitis and neurotropic keratitis. CAM was shown to effect improvement in 88 % cases in 5.4 ± 2.8 days without adverse events, with only 10% requiring repeat procedures. It was also observed to significantly increase corneal nerve density and reduce dry symptoms for 3 months [51] CAM has also been noted to be efficacious in immune mediated DED with symptomatic and visual acuity improvement.[55]

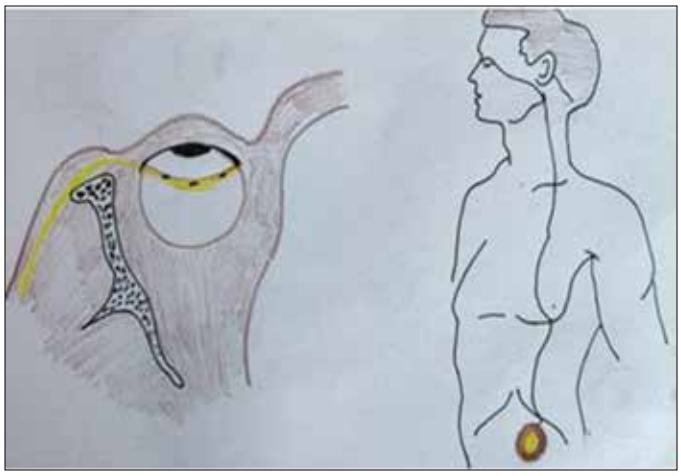


Figure 7 : *Abdominal Dacryo reservoirs*

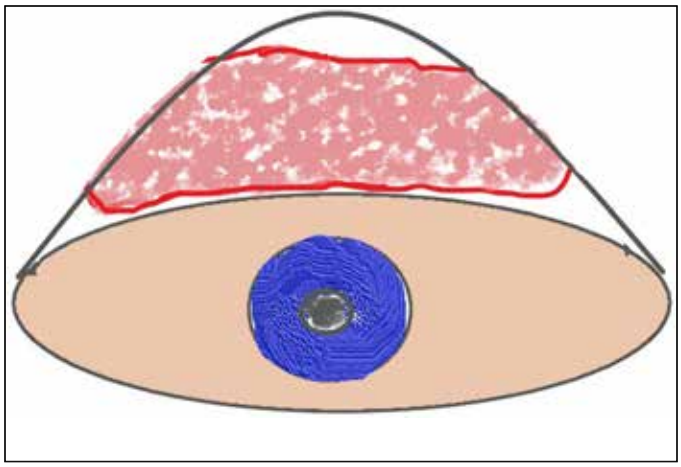


Figure 8 : *Site of placement of salivary gland under the upper lid*

Dacryo reservoirs

Dacryo reservoir, first suggested by Murube et al,[56] is a mechanical device designed to deliver artificial tears to ocular surface through interpalpebral fissure, subcutaneous tunnels in the temple and anterior abdominal wall (Figure 7), that ensures continued lubrication of ocular surface. It is useful for patients with severe dry eyes, requiring frequent instillation of eye drops every 5-10 minutes. Previously these reservoirs were attached to spectacles or placed in the pockets of patients clothes and were not in popular use, due to the associated discomfort during physical activities and frequent infections. Later these devices were placed in the subcutaneous tunnels created in the temple. Murube's abdominal pump dacryo reservoir[57] gained importance due to its increased comfort. The titanium box containing the artificial tears is fixed to the abdominal wall and delivers tears through a silicone catheter that ascends subcutaneously along the chest, neck and temple. It exteriorizes into lacrimal basin in upper conjunctival cul-de-sac and thus avoids skin penetration. Complications that can occur include skin ulceration, infections and loosening of titanium box.

Double tube Valved shunts for aqueous diversion

In chronic, end-stage inflammatory and scarring conditions of the ocular surface such as OCP, SJS, GVHD and severe chemical burns, with totally dry keratinised corneas, specially designed double–tubed valve shunt [New World Medical, Inc (Rancho Cucamongo, CA)] have been implanted to divert aqueous humour to the inferior fornix, thereby wetting the eye.[58]

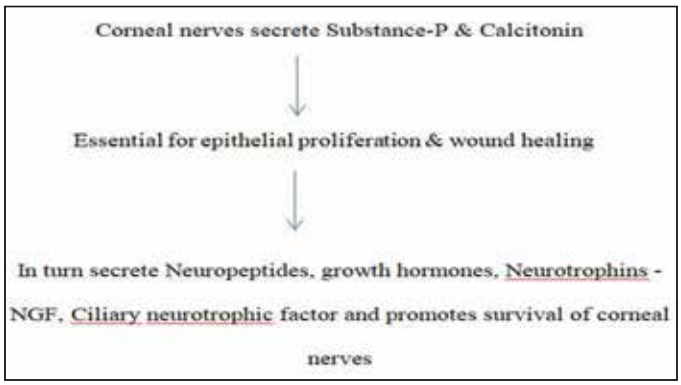
Salivary gland transplantation

The composition of saliva and tears are similar in its complexity and in several specific parameters. The albumin, immunoglobulin's, growth factors, mucins and lipids in saliva, are present in tears too. The amylase in saliva is not found to cause deleterious effect to ocular surface. The actively fluid secreting tissues such as mucosa and glands (both minor and major salivary glands) are the viable option to provide sufficient volume of substitute for lubrication. The major salivary glands are submandibular and parotid.[59,60] The minor salivary glands are labial, buccal and palatal glands.

Major salivary gland transplantation: When tear deficiency in cicatrizing ocular surface disorders such as SJS, OCP is absolute, the only beneficial option is transplantation of salivary glands. An autologous submandibular transplantation (SMGT) can be done in the temporal fossa and anastomosed to the superficial temporal artery and vein, and the excretory duct is implanted into upper conjunctival fornix (Figure 8). This enables continuous and sero-mucinous fluid lubrication which is similar to the tears. Long term (5 years) results of SMGT, shown improvement of discomfort, tear film parameters (Schirmers test), ocular surface parameters (Corneal & Conjunctival staining patterns) and decreased the need for tear substitutes.[61] The limitations include long duration of surgery, need for general anesthesia, 20% failure rates, infections, stenosis of the duct, microcystic corneal edema sometimes overproduction of tears requiring Botox injections.

The minor salivary gland transplantation (MSGT) also provides sufficient quantity of tears and for long duration and was first conceived by Murube J et al.[62] MSGT is a less cumbersome procedure which comprises of transplantation of about 12- 15 minor salivary glands from the lower labial mucosa or buccal mucosa to the upper and lower forniceal region. This enables increase in surface lubrication, moderate to significant reduction in dry eye symptoms 62 with reported graft survival rate of 90 - 97% over a follow-up ranging from

Flowchart 2: *Aim of current treatment approaches*



3 to 4.5 years.[63] The secretion is more viscous than tears with seromucinous consistency, rich in IgA, growth factors. The reported complications include ptosis and infections.[65]

Lubricating inserts

The hydroxypropyl cellulose inserts are well known devices used as once a day insert in the inferior cul-de-sac. These are sterile, preservative free, water soluble and slow-release lubricants, indicated in moderate to severe dry eyes and in patients not willing or cannot use artificial tears at frequent basis.[66] They afford good improvement with once a day dosage without any severe side effect of blurred vision14.

Corneal Neurotisation

Normal corneal sensation is essential for the maintenance of structure and function of corneal epithelium, for the normal blink reflex, for maintenance of lacrimal neural reflex for tear secretion and for wound healing (Flow chart 2).[67]

Corneal neurotisation is a revolutionary technique showing promising results for neurotrophic corneas, as almost 1.5% of the fibres exiting the trigeminal ganglion supply the cornea making it the most sensitive organ in the body.[68] The corneal sensation recovers after six months of procedure. In this procedure healthy donor nerve graft is transferred to corneo-limbal area, which re-establishes the sub-basal plexus regeneration and reverses the neurotrophic disease.[69,70] In 2009, Terzis et al reintroduced this technique with the treatment of unilateral facial nerve palsy, in which 5 out of 6 patients had improved corneal sensation after 6 months of procedure as confirmed with esthesiometry.[71] Jacinto et al in 2016 used ipsilateral supraorbital nerve for his patient with neurotic cornea following ocular surgery and photocoagulation.[72] Leyngold et al had first attempted endoscopic contralateral nerve transfer of frontal nerves, which saved the surgical time and healing time with favourable outcomes in Herpes zoster patient in 3 months duration.[73] Later, Jowett et al harvested the great auricular nerve using endoscopy.[74] The great auricular nerve was used as an interposition graft (indirect nerve transfer) as end to end anastomosis to ipsilateral supratrochlear nerve. Elbaz et al used the sural nerve to the contralateral supratrochlear or supraorbital nerve.[75] Allevi et al had used contralateral supratrochlear and supraorbital nerves for anesthetic corneas.[76]

Corneal neurotisation procedures can be considered under two headings:

1. Direct nerve transfer.
2. Indirect nerve transfer.

This procedure is gaining importance in treatment of neurotrophic corneas due to various causes such as congenital causes, herpes zoster, cerebello-pontine angle tumors, severe dry eye disease needing keratoplasty or keratoprosthesis in future.[77,78] This procedure needs a multidisciplinary approach and longer surgical time, and is a budding revolutionary technique, showing promising results for end-stage disease.

Newer treatments for stimulation of tears

The future developments in the treatment of DED aim at stimulation of lacrimal tears through neural mechanism.[79] "Onions" are known to cause reflex lacrimal tear secretions. Few devices are being made to stimulate the nasal mucosa for reflex lacrimal tear secretion. True tear is one such device, which is a hand held stimulator inserted into the nose to stimulate nerves which produces tears. US FDA has approved this device since 2017. Another device is the "Implantable Neurostimulator" devised by Michael Ackermann. A tiny wireless implant developed by Oculeve Company, sends micro-electrical pulses to lacrimal gland when implanted under the skin above the upper eyelids. It can also be placed in the nasal mucosa. This device is under clinical trial.[80]

Table 4: Differentiating features of conjunctivochalasis and DED

Conjunctivochalasis (CCH)	*Dry eyes (DED)*
Worse in the morning	*Worse in the evening*
Worse in the down gaze	*Worse in upgazg*
Worsened by blinking	*Iimproves will blinking*
Tear secretion is normal	*Tear secretions are low*
Conjunctival and corneal staining are seen	*Seen*
Staining seen in non- exposed zone	*Seen in interpalebral zone*

Table 5: Treatment options in CCH

Asymptomatic patients	*No treatment needed*
Severe cases- Medical therapy *If medical therapy is unsuccessful — Surgical treatment*	*Surface lubricants* *Topical steroids* *Antihistamines* *1)Crescent sh aped resection of conjunctiva* *2)Suture fixation of loose conjunctiva to the globe* *3) Bipolar cautery of the excess conjunctiva* *4)Conjunctivoplasty by* *a) conjunctival resection* *b) Argon green laser* *5)Paste-pinch-cut Conjunctivoplasty* *6)Conjunctivo semiperitomy with subconjunctival cautery* *7)Conjunctivoplasty with AMT*

Miscellaneous

Conjunctivochalasis (CCH) is the redundant , loose, non-edematous bulbar conjunctiva interposed between globe and eyelid. It is often bilateral, unrecognised condition, occurring in inferior bulbar conjunctiva. The prevalence rate is 44.8% in those over 60 years of age.[81] It is considered as the most important differential diagnosis and also a cause for of dry eyes. It causes tear film instability and mechanical occlusion of lower punctum by excess conjunctiva as well as delayed clearance of tears, thereby causing symptoms of dry eyes. About 50% of patients with CCH have been reported to have dry eye symptoms with reduced Schirmer's test and TBUT values It is important to diagnose and differentiate CCH

from DED (Table 4). Inflammation is the common etiological factor in both these conditions 83with elevated pro MMP-9 levels been documented in CCH 84. The association of cytokines with CCH and dry eye symptoms has been widely reported.[82 - 88] The treatment options for CCH are elaborated in (Table 5).

Role of Nerve growth factors in dry eyes

The Concept of Nerve growth factor (NGF) was introduced by Samii in 1972 .[89] It stimulates CNS to secrete acetyl choline and PS to produce substance-P, which activate tropomyosin receptor kinase A and p 75 neurotrophin receptors expressed on the corneal epithelial cells and sensory neurons. They stimulate goblet cell differentiation and mucin release. NGF/ Cenegermin,[90] is a polypeptide discovered in the early 1950 s by Levi-Montalcini. It is a naturally occurring protein responsible for the development, maintenance and survival of nerve cells. NGF originally developed for neurotrophic keratitis, also has a promising role in treatment of dry eyes. It promotes:

1. corneal epithelial healing,
2. restores sensitivity
3. increases tear production
4. increases goblet cell density
5. promotes nerve regeneration after injury 91.

Oxervate is a recombinant version of NGF, discovered by Dr Rita levi-Montalchini of Italy. It is available at 20μg/ ml and 4μg/ml concentration.[91] Both the doses have been found to be safe and effective in improvement of signs and symptoms of dry eyes in the phase IIa trials conducted in Austria.[92] Several other newer biological agents are also under trial for treatment of neurotic corneas and DED. These include epidermal growth factor, IGF-1, substance-P derived pepetide-amide, vascular endothelial growth factor, Semaphorins, Neurotrophins 3&4, Growth associated protein-43, Matrix therapy agent (RGTA).[93,94,95] Pergolide, a dopamine receptor agonist, has been evaluated for its function in promoting NGF expression, corneal wound healing and corneal nerve regeneration in cornea scratch mouse model.[96]

Conclusion

Dry eye is a multifactorial disease of tears and ocular surface. The complex pathophysiology and overlapping symptoms of DED, makes the choice of treatment difficult, although a variety of treatment modalities are available. The selection of treatment depends on the patient's subjective complaints, objective symptoms, history of systemic diseases and thorough clinical evaluation of the patient. The medical management is usually chosen for mild-moderate DED. The patient with severe symptoms and extreme ocular surface damage necessitates multiple approaches, combining both medical therapy and surgical treatment. In recent times, surgical treatment for dry eyes has improved the quality of life in many patients. The newer developments like corneal neurotisation have revolutionised the field of ophthalmology. Customised treatment for dry eyes in every patient has shown resolution of symptoms.

References

1. Janine AS. The epidemiology of dry eye disease: report of the Epidemiology Subcommittee of the International Dry Eye WorkShop (2007). Ocul Surf. 2007;5:93–107.
2. Schaumberg DA, Sullivan DA, Buring JE, Dana MR. Prevalence of dry eye syndrome among US women. Am J Ophthalmol. 2003;136:318–26.
3. Um S-B, Kim NH, Lee HK, Song JS, Kim HC. Spatial epidemiology of dry eye disease: findings from South Korea. Int J Health Geogr. 2014;13:31.
4. Jones L, Downie LE, Korb D, Benitez-Del-Castillo JM, Dana R, Deng SX, et al. TFOS DEWS II Management and Therapy Report. Ocul Surf. 2017;15:575–628.
5. Baudouin C, Aragona P, Messmer EM, Tomlinson A, Calonge M, Boboridis KG, et al. Role of hyperosmolarity in the pathogenesis and management of dry eye disease: proceedings of the OCEAN group meeting. Ocul Surf. 2013;11:246–58.
6. Bhavsar AS, Bhavsar SG, Jain SM. A review on recent advances in dry eye: Pathogenesis and management. Oman J Ophthalmol. 2011;4:50–6.
7. Messmer EM. The pathophysiology, diagnosis, and treatment of dry eye disease. Dtsch Arztebl Int. 2015;112:71–81.
8. Hashemi H, Khabazkhoob M, Kheirkhah A, Emamian MH, Mehravaran S, Shariati M, et al. Prevalence of dry eye syndrome in an adult population. Clin Experiment Ophthalmol. 2014;42:242–8.
9. Potvin R, Makari S, Rapuano CJ. Tear film osmolarity and dry eye disease: a review of the literature. Clin Ophthalmol. 2015;9:2039–47.
10. Jie Y, Xu L, Wu YY, Jonas JB. Prevalence of dry eye among adult Chinese in the Beijing Eye Study. Eye (Lond). 2009;23:688–93.
11. Tsubota K, Yokoi N, Shimazaki J, Watanabe H, Dogru M, Yamada M, et al. New Perspectives on Dry Eye Definition and Diagnosis: A Consensus Report by the Asia Dry Eye Society. Ocul Surf. 2017;15:65–76.
12. Şimşek C, Doğru M, Kojima T, Tsubota K. Current management and treatment of dry eye disease. Turkish journal of ophthalmology. 2018;48(6):309.
13. Drew VJ, Tseng C-L, Seghatchian J, Burnouf T. Reflections on Dry Eye Syndrome Treatment: Therapeutic Role of Blood Products. Front Med (Lausanne). 2018;5:33.
14. Baudouin C, Aragona P, Van Setten G, Rolando M, Irkeç M, Benítez del Castillo J, et al. Diagnosing the severity of dry eye: a clear and practical algorithm. Br J Ophthalmol. 2014;98:1168–76.
15. Stern ME, Beuerman RW, Fox RI, Gao J, Mircheff AK, Pflugfelder SC. The pathology of dry eye: the interaction between the ocular surface and lacrimal glands. Cornea. 1998;17:584–9.
16. Milner MS, Beckman KA, Luchs JI, Allen QB, Awdeh RM, Berdahl J, et al. Dysfunctional tear syndrome: dry eye disease and associated tear film disorders - new strategies for diagnosis and treatment. Curr Opin Ophthalmol. 2017;27 Suppl 1:3–47.
17. Geerling G, Raus P, Murube J. Minor salivary gland transplantation. Dev Ophthalmol. 2008;41:243–54.
18. Murube J, Murube E, Etiology and Management of Dry eyes, Samuel Boyd, Atlas and text of Ocular pathology and surgery, Panama rep of Panama, Jaypee-Highlights Medical publishers 2011,61-79
19. Tai M-C, Cosar CB, Cohen EJ, Rapuano CJ, Laibson PR. The clinical efficacy of silicone punctal plug therapy. Cornea. 2002;21:135–9.
20. Freeman JM. The punctum plug: evaluation of a new treatment for the dry eye. Trans Sect Ophthalmol Am Acad Ophthalmol Otolaryngol. 1975;79:OP874-879.
21. Albietz J, Sanfilippo P, Troutbeck R, Lenton LM. Management of filamentary keratitis associated with aqueous-deficient dry eye. Optom Vis Sci. 2003;80:420–30.
22. Giovagnoli D, Graham SJ. Inferior punctal occlusion with removable silicone punctal plugs in the treatment of dry-eye related contact lens discomfort. J Am Optom Assoc. 1992;63:481–5.

23. Kaido M, Goto E, Dogru M, Tsubota K. Punctal occlusion in the management of chronic Stevens-Johnson syndrome. Ophthalmology. 2004;111:895–900.
24. Guzey M, Ozardali I, Kilic A, Basar E, Dogan Z, Satici A, et al. The treatment of severe trachomatous dry eye with canalicular silicone plugs. Eye (Lond). 2001;15(Pt 3):297–303.
25. Baxter SA, Laibson PR. Punctal plugs in the management of dry eyes. Ocul Surf. 2004;2:255–65.
26. Jones CE, Anklesaria M, Gordon AD, Prouty RE, Rashid R, Singla RK, et al. Retrospective Safety Study of the Herrick Lacrimal Plug: A Device Used to Occlude the Lacrimal Canaliculus1. Eye & Contact Lens. 2002;28:206–210.
27. Nelson CC. Complications of Freeman plugs. Arch Ophthalmol. 1991;109:923–4.
28. Sakamoto A, Kitagawa K, Tatami A. Efficacy and retention rate of two types of silicone punctal plugs in patients with and without Sjögren syndrome. Cornea. 2004 ;23:249–54.
29. Sugita J, Yokoi N, Fullwood NJ, Quantock AJ, Takada Y, Nakamura Y, et al. The detection of bacteria and bacterial biofilms in punctal plug holes. Cornea. 2001;20:362–5.
30. John T, Kopstein AB, John OC, Lai CI, Carey RB. In vitro adherence of Staphylococcus epidermidis to silicone punctual plugs and collagen implants. J Cataract Refract Surg. 2001;27:1298–302.
31. Yokoi N, Okada K, Sugita J, Kinoshita S. Acute conjunctivitis associated with biofilm formation on a punctal plug. Jpn J Ophthalmol. 2000;44:559–60.
32. Elder MJ, Stapleton F, Evans E, Dart JK. Biofilm-related infections in ophthalmology. Eye. 1995;9:102-9.
33. Rapoza PA, Ruddat MS. Pyogenic granuloma as a complication of silicone punctal plugs. Am J Ophthalmol. 1992;113:454–5.
34. Fayet B, Koster H, Benabderrazik S, Bernard JA, Pouliquen Y. Six canalicular stenoses after 34 punctal plugs. Eur J Ophthalmol. 1991;1:154–5.
35. Gilbard JP, Rossi SR, Azar DT, Heyda KG. Effect of punctal occlusion by Freeman silicone plug insertion on tear osmolarity in dry eye disorders. CLAO J. 1989;15:216–8.
36. Willis RM, Folberg R, Krachmer JH, Holland EJ. The treatment of aqueous-deficient dry eye with removable punctal plugs: A clinical anti impression-cytologic study. Ophthalmology. 1987;94:514-8.
37. Dursun D, Ertan A, Bilezikçi B, Akova YA, Pelit A. Ocular surface changes in keratoconjunctivitis sicca with silicone punctum plug occlusion. Curr Eye Res. 2003;26:263–9.
38. Murube J, Murube E. Treatment of dry eye by blocking the lacrimal canaliculi. Surv Ophthalmol. 1996;40:463–80.
39. Putterman AM. Canaliculectomy in the treatment of keratitis sicca. Ophthalmic Surg. 1991;22:478–80.
40. Frueh BR: Exposure keratitis in Waltman SR, Keates RH, Hoyt CS, et al. Eds, Surgery of the Eye. Vol 2. New York: Churchill Livingstone; 1988:563-576.
41. Sysi B: A Suggestion for a New Method of Closing the Lachrymal Canals. Acta Ophthalmologica. 1949; 27:409–11.
42. DeMartelaere SL, Blaydon SM, Tovilla-Canales JL, Shore JW. A permanent and reversible procedure to block tear drainage for the treatment of dry eye. Ophthalmic Plast Reconstr Surg. 2006;22:352–5.
43. Yaguchi S, Ogawa Y, Kamoi M, Uchino M, Tatematsu Y, Ban Y, et al. Surgical management of lacrimal punctal cauterization in chronic GVHD-related dry eye with recurrent punctal plug extrusion. Bone Marrow Transplant. 2012;47:1465–9.
44. Murube J, Surgical management of Surfocular Dryness, Garg A. Surgical Techniques in Ophthalmology (Oculoplasty and Reconstruction Surgery) JAYPEE BROTHERS PUBLISHERS; 2010 , 231-240.
45. Dhillon HK, Bahadur H, Raj A. A comparative study of tarsorrhaphy and amniotic membrane transplantation in the healing of persistent corneal epithelial defects. Indian J Ophthalmol. 2020;68:29–33.,51
46. Cosar CB, Cohen EJ, Rapuano CJ, Maus M, Penne RP, Flanagan JC, et al. Tarsorrhaphy: clinical experience from a cornea practice. Cornea. 2001;20:787–91.
47. Hamill MB. Corneal Injury. In: Krachmer JH, Mannis MJ, Holland EJ, Eds. Cornea, Vol. II. St. Louis, Missouri: Mosby; 1997:1403-1422.
48. Pakarinen M, Tervo T, Tarkkanen A. Tarsorraphy in the treatment of persistent corneal lesions. Acta Ophthalmol Suppl. 1987;182:69–73.
49. Donnenfeld ED, Perry HD, Nelson DB. Cyanoacrylate temporary tarsorrhaphy in the management of corneal epithelial defects. Ophthalmic Surg. 1991;22:591–3.
50. McDonald MB, Sheha H, Tighe S, Janik SB, Bowden FW, Chokshi AR, et al. Treatment outcomes in the DRy Eye Amniotic Membrane (DREAM) study. Clin Ophthalmol. 2018;12:677–81.
51. John T, Tighe S, Sheha H, Hamrah P, Salem ZM, Cheng AMS, et al. Corneal Nerve Regeneration after Self-Retained Cryopreserved Amniotic Membrane in Dry Eye Disease. J Ophthalmol. 2017; 2017.
52. Rizzuti A, Goldenberg A, Lazzaro DR, Goldenberg A, Lazzaro DR. Amniotic membrane allografts: development and clinical utility in ophthalmology. Clin Ophthalmol. 2014;8:2491-9.
53. Shafer B, Fuerst NM, Massaro-Giordano M, Palladino V, Givnish T, Macchi I, Sulewski ME, Orlin SE, Bunya VY. The use of self-retained, cryopreserved amniotic membrane for the treatment of Sjögren syndrome: a case series. Digital J Ophthalmol. 2019;25:21.
54. Mead OG, Tighe S, Tseng SCG. Amniotic membrane transplantation for managing dry eye and neurotrophic keratitis. Taiwan J Ophthalmol. 2020;10:13–21.
55. Cheng AMS, Zhao D, Chen R, Yin HY, Tighe S, Sheha H, et al. Accelerated Restoration of Ocular Surface Health in Dry Eye Disease by Self-Retained Cryopreserved Amniotic Membrane. Ocul Surf. 2016;14:56–63.
56. Murube J, Geerling G. Mechanical pump dacryoreservoirs. Dev Ophthalmol. 2008;41:269–82.
57. Murube J, Murube E, ChenZhuo L, Rivas L. Subcutaneous abdominal artificial tears pump-reservoir for severe dry eye. Orbit. 2003;22:29–40.
58. Dohlman CH, Barnes SD, Ma JJK, et al : Diverting aqueous humor to distant sites in severe glaucoma: an update. Invest Ophthalmol Vis Sci 2004 (ARVO)
59. Güerrissi JO, Belmonte J. Surgical treatment of dry eye syndrome: conjunctival graft of the minor salivary gland. J Craniofac Surg. 2004;15:6–10.
60. Geerling G, Sieg P, Bastian GO, Laqua H. Transplantation of the autologous submandibular gland for most severe cases of keratoconjunctivitis sicca. Ophthalmology. 1998;105:327–35.
61. Borrelli M, Schröder C, Dart JKG, Collin JRO, Sieg P, Cree IA, et al. Long-term follow-up after submandibular gland transplantation in severe dry eyes secondary to cicatrizing conjunctivitis. Am J Ophthalmol. 2010;150:894–904.
62. Murube-del-Castillo J. Transplantation of salivary gland to the lacrimal basin. Scand J Rheumatol Suppl. 1986;61:264–7.
63. Soares EJC, França VP. [Transplantation of labial salivary glands for severe dry eye treatment]. Arq Bras Oftalmol. 2005;68:481–9.
64. Management and therapy of dry eye disease: report of the Management and Therapy Subcommittee of the International Dry Eye WorkShop (2007). Ocul Surf. 2007;5:163–78.
65. Jackson WB. Management of dysfunctional tear syndrome: a Canadian consensus. Can J Ophthalmol. 2009;44:385–94.
66. Wander AH, Koffler BH. Extending the duration of tear film protection in dry eye syndrome: review and retrospective case series study of the hydroxypropyl cellulose ophthalmic insert. Ocul Surf. 2009;7:154–62.
67. Terzis JK, Dryer MM, Bodner BI. Corneal neurotization: a novel solution to neurotrophic keratopathy. Plast Reconstr Surg. 2009;123:112–20.
68. Koaik M, Baig K. Corneal neurotization. Curr Opin Ophthalmol. 2019;30:292–8.
69. Wolkow N, Habib LA, Yoon MK, Freitag SK. Corneal Neurotization: Review of a New Surgical Approach and Its Developments. Semin Ophthalmol. 2019;34:473–87.

70. Gennaro P, Gabriele G, Aboh IV, Cascino F, Menicacci C, Mazzotta C, et al. The Second Division of Trigeminal Nerve for Corneal Neurotization: A Novel One-Stage Technique in Combination With Facial Reanimation. J Craniofac Surg. 2019;30:1252–4.
71. Terzis JK, Dryer MM, Bodner BI. Corneal neurotization: a novel technique for the anesthetic cornea. Cornea. 2010;29:812–9.
72. Jacinto F, Espana E, Padilla M, Ahmad A, Leyngold I.Ipsilateral supraorbital nerve transfer in a case of recalcitrant neurotrophic keratopathy with an intact ipsilateral frontal nerve: A novel surgical technique. Am J Ophthalmol Case Rep. 2016;4:14–17.
73. Leyngold I, Weller C, Leyngold M, et al. Endoscopic corneal neurotization: cadaver feasibility study. Ophthalmic Plast Reconstr Surg. 2018;34:213–16.
74. Jowett N, Pineda Ii R. Corneal neurotisation by great auricular nerve transfer and scleral-corneal tunnel incisions for neurotrophic keratopathy. Br J Ophthalmol. 2019;103:1235–8.
75. Elbaz U, Bains R, Zuker RM, Borschel GH, Ali A. Restoration of corneal sensation with regional nerve transfers and nerve grafts: a new approach to a difficult problem. JAMA Ophthalmol. 2014;132:1289–95.
76. Allevi F, Fogagnolo P, Rossetti L, Biglioli F. Eyelid reanimation,neurotisation, and transplantation of the cornea in a patient with facial palsy. BMJ Case Rep. 2014;2014:
77. Labetoulle M, Baudouin C, Calonge M, Merayo-Lloves J, Boboridis KG, Akova YA, et al. Role of corneal nerves in ocular surface homeostasis and disease. Acta Ophthalmol. 2019;97:137–45.
78. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. Clin Ophthalmol. 2014;8:571–9.
79. Friedman NJ, Butron K, Robledo N, Loudin J, Baba SN, Chayet A. A nonrandomized, open-label study to evaluate the effect of nasal stimulation on tear production in subjects with dry eye disease. Clin Ophthalmol. 2016;10:795–804.
80. Ackermann M. A real tear-jerker: Team creates device to alleviate dry eye. Stanford Medicine. 2015 Available from: https://med.stanford.edu/news/all-news/a-real-tear-jerker-team-creates-device-to-alleviate-dry-eye.
81. Zhang X, Li Q, Zou H, Peng J, Shi C, Zhou H, et al. Assessing the severity of conjunctivochalasis in a senile population: a community-based epidemiology study in Shanghai, China. BMC Public Health. 2011;11:198.
82. Balci O. Clinical characteristics of patients with conjunctivochalasis. Clin Ophthalmol. 2014;8:1655–60.
83. Bron AJ, de Paiva CS, Chauhan SK, Bonini S, Gabison EE, Jain S, et al. TFOS DEWS II pathophysiology report. Ocul Surf. 2017;15:438–510.
84. Acera A, Vecino E, Duran JA. Tear MMP-9 levels as a marker of ocular surface inflammation in conjunctivochalasis. Invest Ophthalmol Vis Sci. 2013;54:8285–91.
85. Li DQ, Meller D, Liu Y, Tseng SC. Overexpression of MMP-1 and MMP-3 by cultured conjunctivochalasis fibroblasts. Invest Ophthalmol Vis Sci. 2000;41:404–10.
86. Guo P, Zhang S-Z, He H, Zhu Y-T, Tseng SCG. PTX3 controls activation of matrix metalloproteinase 1 and apoptosis in conjunctivochalasis fibroblasts. Invest Ophthalmol Vis Sci. 2012;53:3414–23.
87. Zhang X, Xiang M, Wu Q, Li Q, Xu Y, Sun A. [The tear proteomics analysis of conjunctivochalasis]. Zhonghua Yan Ke Za Zhi. 2009;45:135–40.
88. Erdogan-Poyraz C, Mocan MC, Bozkurt B, Gariboglu S, Irkec M, Orhan M. Elevated tear interleukin-6 and interleukin-8 levels in patients with conjunctivochalasis. Cornea. 2009;28:189–93.
89. Müller LJ, Marfurt CF, Kruse F, Tervo TMT. Corneal nerves: structure, contents and function. Exp Eye Res. 2003;76:521–42.
90. Sheha H, Tighe S, Hashem O, Hayashida Y. Update On Cenegermin Eye Drops In The Treatment Of Neurotrophic Keratitis. Clin Ophthalmol. 2019;13:1973–80.
91. McDonald MB. Topical recombinant human nerve growth factor an innovation in ocular surface disease treatment. Ocular Surgery News. 2018 Available from: https://www.healio.com/news/ophthalmology/topical-recombinant-human-nerve-growth-factor-an-innovation-in-ocular-surface-disease-treatment.
92. Meerovitch K, Torkildsen G, Lonsdale J, Goldfarb H, Lama T, Cumberlidge G, et al. Safety and efficacy of MIM-D3 ophthalmic solutions in a randomized, placebo-controlled Phase 2 clinical trial in patients with dry eye. Clin Ophthalmol. 2013;7:1275–85.
93. Sanchez-Avila RM, Merayo-Lloves J, Riestra AC, Fernandez-Vega Cueto L, Anitua E, Begoña L, et al. Treatment of patients with neurotrophic keratitis stages 2 and 3 with plasma rich in growth factors (PRGF-Endoret) eye-drops. Int Ophthalmol. 2018;38:1193–204.
94. Nishida T, Chikama T-I, Morishige N, Yanai R, Yamada N, Saito J. Persistent epithelial defects due to neurotrophic keratopathy treated with a substance p-derived peptide and insulin-like growth factor 1. Jpn J Ophthalmol. 2007;51:442–7.
95. Seo K, Choi J, Park M, Rhee C. Angiogenesis effects of nerve growth factor (NGF) on rat corneas. J Vet Sci. 2001;2:125–30.
96. Zhang X, Muddana S, Kumar SR, Burton JN, Labroo P, Shea J, et al. Topical Pergolide Enhance Corneal Nerve Regrowth Following Induced Corneal Abrasion. Invest Ophthalmol Vis Sci. 2020 23;61:4.

Cite This Article as: Venugopal Anitha, R. Meenakshi, M. Vanathi "Update on Surgical Interventions In Management of Dry Eyes". Delhi J Ophthalmol 2021 ; 31 Vol No (4) : 9 - 18.

Acknowledgments: Nil

Conflict of interest: None declared

Source of Funding: None

Date of Submission: 10 Jun 2020
Date of Acceptance: 10 Sep 2020

Address for correspondence

Venugopal Anitha
DNB, FAICO (CORNEA), FICO
Senior Consultant, Cornea and Refractive services Aravind Eye Hospitals &Postgraduate Institute Tirunelveli, Tamil Nadu, India.
Email: aniths22@ymail.com.

Quick Response Code