



Recent development in the artificial treatment for dry eye disease

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ABSTRACT

Eyes are the most important organs of the human body. The important parts of the eyes are conjunctiva, cornea, Iris, pupil, retina, sclera. Eye is protected by eyelid from external environment. The common eye disease is kerato conjunctivitis sicca (KCS) i.e dry eyes syndrome. Tear is secreted by a lacrimal gland which lubricates the eye. The dry eyes disease syndrome commonly is caused because tears are not secreted properly by the tear duct or the tear film gets evaporated from the surface of the eye due to various factors or due to environmental changes. Dry eyes disease caused due to age, environmental factor like increase in air pollution, increase in temperature, humidity in the atmosphere, using contact lens, medication also causes dry eyes. This article reviews the causes, symptoms, and recent treatment system of dry eyes disease. Dry eyes can be treated by using medications like artificial tears, Carmellose artificial tears eye drops, Cyclosporine A, Difluprednate, Lacrisert nutritional supplements, omega-3 fatty acids, etc. The therapy like Meibomian gland expression, Intense pulsed light, Lipiflow, etc. the dry eyes disease not only affecting human eye but it also affects animals like dogs and cat.

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INTRODUCTION

Eyes are organs of the visual system. The parts of eyes are lens, retina, nerve fibre, pupil etc. The eye converts light energy to electrical impulse and send the information to brain. The exterior eye has three layers. Fibrous tunic is outer, uvea is middle layer and retina inner layers. Eye ocular surface consists of conjunctiva the outer eye and inner part of the eyelid are covered, the cornea is the clear surface

which allows light to pass through, lacrimal gland secretes tear, lacrimal drainage, and tear film. An ocular surface disease is classified as dry eyes disease and non-dry eyes disease (Craig *et al.*, 2017). Dry eye disease is classified into two types based on aqueous deficiency and evaporation of tear. Ocular discomfort caused due to change in homeostasis of the tear film leads to dry eyes disease. The insufficient tears production or increase in the rate of evaporation or change in consistency of tear leads to dry eyes (Behfar *et al.*, 2014). Inflammation of ocular surface caused due to environmental hyperosmolar in the eye. Dry eye is common in aged people and causes pain in ocular surface, a disorder that leads to systemic inflammatory diseases and eye problem. The patient with autoimmune disorder is affected by dry eyes, when compared with men, women are affected by dry eyes disease due to hormonal during post-menopause changes. The stability and tear formation in square measure is ruled by the surface chemical characteristics of the tear film system and by the right functioning of the anatomical structure. The tear film has to be secreted continuously

between blinks to fulfil its function. Improper formation will affect vision. Tears made up of aqueous, electrolytes, fatty oils, protein substances lubricate and prevent entry of bacteria, and growth factors. The tear keeps the eyes smooth and clear. Tear film thickness is $3.8\mu\text{m}$ to $6.8\mu\text{m}$ (Prydal et al., 1992). Dry eye disease was caused by lack of production of tears and increased evaporation of tear film.

MATERIALS AND METHODS

Keratitis sicca

This condition generally describes dryness and inflammation of the cornea, the improper secretion of tears, tear film instability and visual disturbance which cause harm to corneal surface.

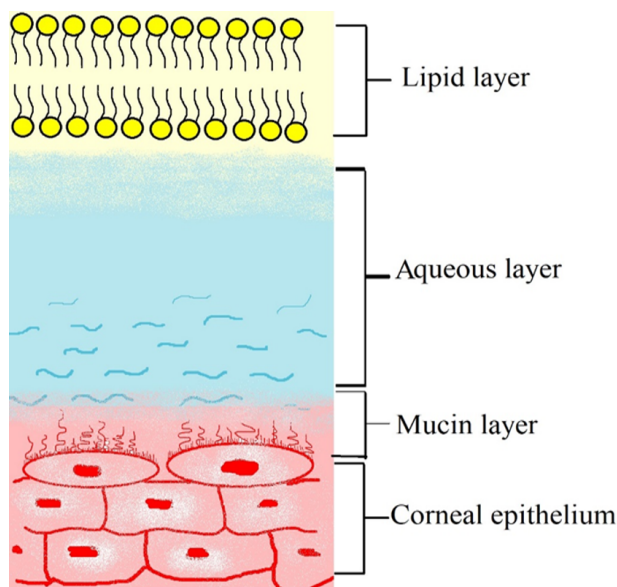


Figure 1: Layers of tear film

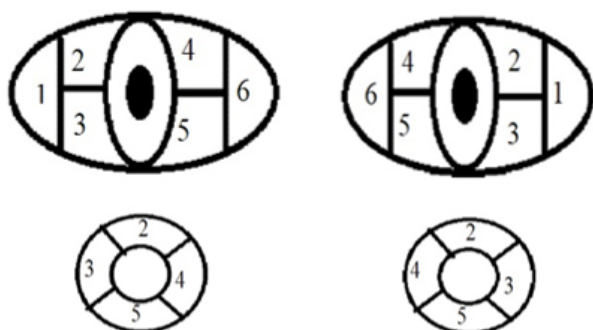


Figure 2: Corneal Fluorescein Staining

Kerato conjunctivitis sicca

In this condition less production of tear and due to rapid evaporation of tear film it affects the cornea, not closing eyes during sleeping, improper blinking

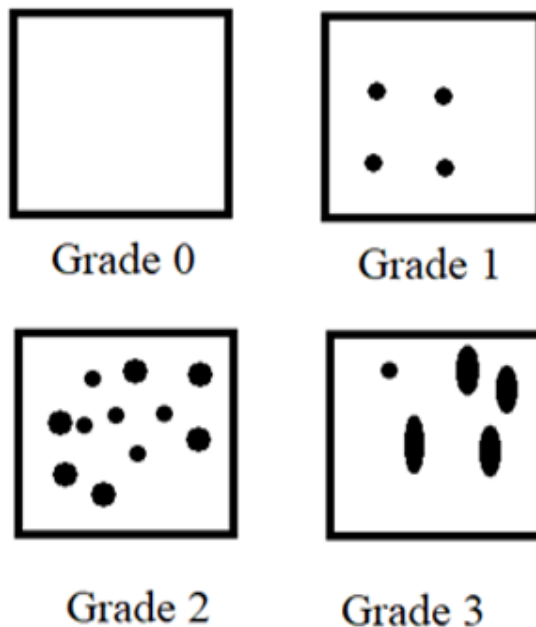


Figure 3: Corneal Straining Grade Value

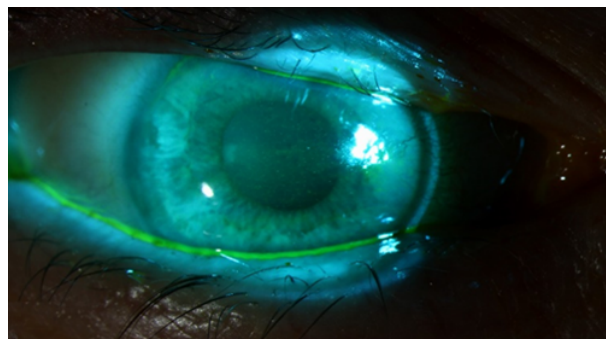


Figure 4: Fluorescein staining

of eyes which clear layers present in front of iris and pupil) and conjunctiva which covers sclera and eyelid (Kim et al., 2010).

Xerophthalmia

Is caused due to deficiency of vitamin A, which leads to dryness of cornea and the conjunctiva (Roncone D, 2006).

Dysfunctional tear syndrome

It affect ocular surface which occurs due to inadequate and change in composition of tear film (Ashraf et al., 2019).

Tear

Lacrimal gland secretes tear film and spreads it by eyelid during every blink. The cornea is $2/3^{rd}$ of the total refractory power of the eye. Tear film lubricates and protects the eye. The tear covers total area of 1 to 3 cm² and 2.7 to 11 micro m thickness

of eye (Prydal *et al.*, 1992). Stability and disorder of eye is checked by using tear film break up time as time increases image become blurred. Improper secretion of tear also causes visual problem.

Tear film layer

Tear film maintains the health and protects the eye from dust, foreign particle, removes foreign particles, keeps the surface of the eyes clear and smooth.

Tear film composed of three different layers. Figure 1,

Oil (lipid) layer

The outer oil layer is made up of lipids and fatty oil secreted by meibomian gland. Oil layer comes from edges of the eyelids outer layer whose thickness is about 0.11 μm . Outer oil spreads smoothly over the tear surface layer and reduces rate of evaporation of tear film. Inadequate oil levels cause rapid evaporation of the tear film. Dry spot is formed due to quick evaporation of tear film. Component of oil layer are cholesterol esters, wax esters, polar: (o-acyl)-u-hydroxy fatty acids, ceramides, phosphatidylcholines, lysophosphatidylcholines, sphingomyelins, phosphatidylethanolamines.

Water (aqueous) layer

Middle layer's thickness is about 7 μm . Aqueous layer is 60% of total layer. The middle aqueous layer prevent infection, removes the particles and lubricates the eye. The middle layer made up of water, salt and thickest among all layers. This layer is secreted by lacrimal glands, or tear glands. This layer cleanses the eyes and wash away irritants and particles. Instability of tear film is caused due to problem in aqueous layer. If the middle aqueous layer is too thin, the outer lipid and inner mucus layers discharge a fluid from eye.

Mucin layer

It is rich in sugar- glycosylated proteins and thickness is about 0.02-0.05 μm . Goblet cell produces mucin layer. The inner layer helps to spreads the aqueous layer and stick the tears to surface of the eye. Formation of dry patch on the cornea due to irregular mucin layer, the front surface of the eye and decreases production of tear.

Causes

Dry eyes disease is caused due to insufficient tear production or increase in rate of evaporation or improper mixing of tear.

Medication

Usage of medication like antidepressants, antihistamines, blood pressure medications, decongestants, diabetes, Parkinson's medications, neurotox-

ins, sleeping pills for rheumatoid arthritis patent and thyroid problems.

Gender

More women suffer from dry eyes disease when compare with men due to hormonal changes during pregnancy or oral contraceptive pills which leads to auto immune disorders and postmenopausal hormone therapy.

Age

Aging leads to reduction in tear quantity which leads to dryness, easily irritated and inflamed. Some of the people who fall under the age between 40 to 65 are suffering from dry eyes syndrome.

Environmental change

Indoor environment condition like usage of air conditioner and smoke. Outdoor environmental changes like air pollution, climate change, high altitude, humidity present in air and change in temperature, smoke leads to changes in tear concentration, pressure difference in airplane cabin. Dry season, higher temperatures increases evaporation of tear and low humidity are the factors affect eyes.

Deficiency

Rosacea inflammation of skin and blepharitis inflammation of outer corner of eyelids can alter the function of the meibomian glands. This gland is located in upper and lower eyelids (Rabensteiner *et al.*, 2019; Bron *et al.*, 1991). Auto-immune disorders like formation of lump sjogren's syndrome, rheumatoid arthritis scleroderma and other disorders like hyperthyroid or hypothyroid, diabetes, deficiency of vitamin A.

RESULTS AND DISCUSSION

Other factors

Regular use of contact lenses reduces thickness of tear film, radiation treatment, and seasonal allergies can contribute to dry eye, improper blinking, laser treatment for cataract surgery leads to temporary dry eye symptoms, delayed eyes blinking while using phone, increase usage of computer for long period, anxiety and high blood pressure, reading or driving a vehicle, shingles viral infection which causes rashes, bell's palsy which is facial paralysis, HIV infection, lagophthalmos, incomplete closing of eyelid and improper blinking of eyes affect spreading of tear film which leads to dry spot in tear film (Lemp M A, 2008). Ectropion is eyelid problem where lower palpebra turn outside and exposed to outer environment. Similarly, blepharitis is turning eyelid inward or outward or inflammation cause dry eyes to develop (Behfar *et al.*, 2014).

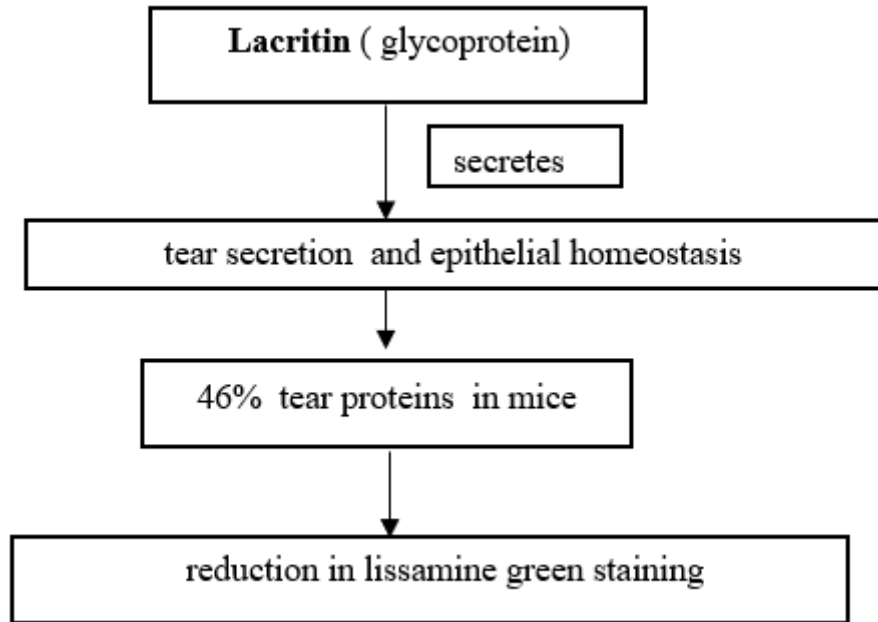


Figure 5: Mechanism of tear production by Lacritin

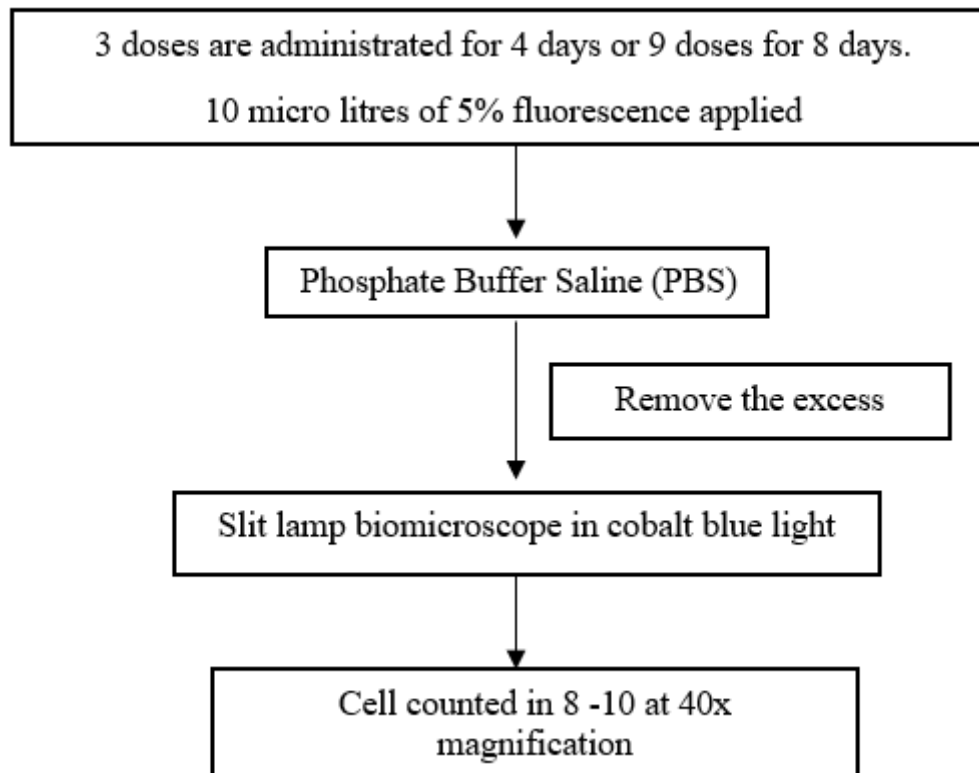


Figure 6: Measuring Meibomian gland expression

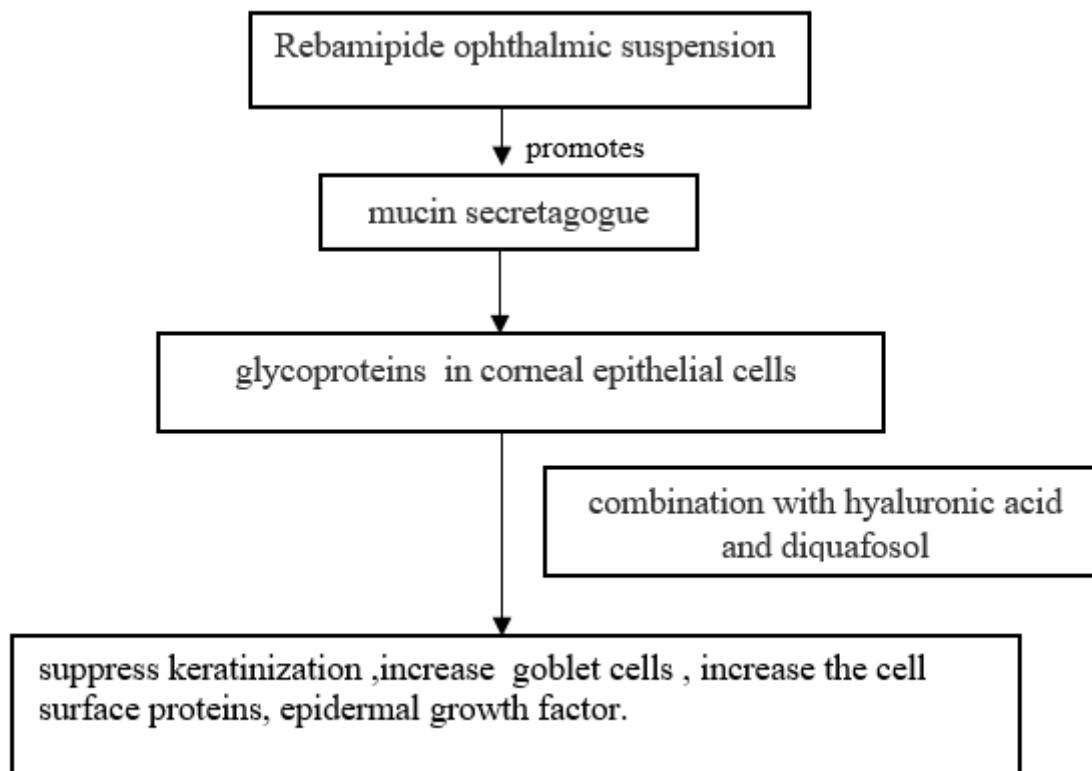


Figure 7: Mechanism of Mucin secretagogues

Symptom

Blurred vision, burning sensation, changing vision, difficulty in keeping the eyes open, deterioration of eyesight, discomfort when wearing contact lenses, dry, excess tearing, tired of eye during reading for short duration, eye sensitivity to smoke or wind, eyelids sticking together when waking up, foreign body sensation, pain, gritty feeling, Itching, redness of the eyes, photophobia, sensitivity to light, a stringy discharge stinging pain, tearing double vision, above symptoms causes anxiety, frustration that affects daily routine life (Husain I, 2020; Begley et al., 2002).

Diagnosis

Tests film test measured for quantity and the quality for dry eyes syndrome (Yokoi et al., 1996). The oxidative damage in ocular surface are clinically studied by using biomarkers like 4-hydroxynonenal and malondialdehyde, 8-hydroxy-2 deoxy guanosine, histamine green conjunctival staining score, fluorescein corneal staining score, histamine green to assess local abnormalities of the bulbar conjunctiva, levels of IL-1 beta and IL-6 in tears, questionnaire score, ocular surface disease index, Schirmer's test score, slit lamp, tear breakup time, meniscography OCT, tear osmolarity, tear fluid washing (Naga

01, 2020).

Fluorescein corneal staining score (CFS)

Measuring strain by different scale like the National Eye Institute grading system (NEI)

Baylor scale, the van Bijsterfeld scale, the Oxford scale¹⁰, etc.,

NEI SCALE is measured. (Figures 3 and 4) A plug – in circle placed and the circle is adjusted to fit cornea. Before generating a fluorescein map of the cornea is detected by a flooding algorithm. Specular reflections are excluded, as the specular reflection does not represent the true colours. The plug-in measures the RGB value of within grip for pixel and change the red green blue values to hue saturation value spacem,

$$V = \max(R, G, B)$$

Where,

R- red

G - green

B - blue

Grading value from 0 to 3 is standard value for five area of cornea. Grade 0 is used when no staining is

present, and score 15 for maximum straining (Chan and Prokopich, 2019).

Schirmer's test

A schirmer's test used to measure moisture content present in the eye. Topical anaesthesia given for preventing eye irritation. The paper strip is placed in lower eyelid of both eye at the same time to measure the amount of tear produced in the eye. Most often by keeping small piece of filter paper (inferior fornix). After keeping the strip, close the eye and wait for 5 minutes. Remove the filter strip and amount of moisture is measured (Tomlinson et al., 2006).

The schirmer test measure basic function of tear film.

Strip was moistened 15 mm for normal young person. Hypo lacrimation occurs with elderly people, 33% of normal elderly persons 10 mm in 5 minutes. Strip was moisten 5 mm in 5 minutes for sjogren's syndrome moisten less.

The schirmer's test result,

1. Normal tear secretion value ≥ 15 mm.
2. Mild tear secretion value 14-9 mm.
3. Moderate secretion value 8-4 mm.
4. Excess secretion value < 4 mm (Xue et al., 2018).

Tear film breakup time (TBUT)

TBUT is a commonly used, indirect measure of *In vivo* for dry eyes syndrome. Tear breakup time is measured for evaporative dry eye disease. A mathematical model used to measure tear film by using parameter like gravity, non-newtonian viscosity effect, osmolality, slip velocity, surface tension and van der waals forces. Fluorescein is installed in eye of patient and not blink during tear film breakup test examined by using broad beam of cobalt blue illumination. The value is calculated from last blink of eye and formation of dry spots recorded. Formation of dry spot before 10 second is abnormal in tear film breakup time and this method also indicates the Punctate Epithelial Erosions (PEE) if fluorescein stain (Figure 2) is present of erosion of ocular surface and a slit lamp examination is done to measure damage to The eye (Xue et al., 2018).

A tear protein analysis test

Protein test used to calculate the lysozyme content which is protein present in the tear. Total protein content of normal human eye ranges from 20 to 40%. The molecule Ap4A is naturally present in the tear and this is increased during ocular dryness. The Ap4A molecule in the tear can be measured using Schirmer test and the concentration of Ap4A was measured (Naga O I, 2020).

The tear Osmolarity test

The tear Osmolarity test is used to measure the tear saltiness. Compared to Schirmer Test, conjunctival staining, tear break-up time, meibomian gland grading, corneal straining, for diagnosing the eye more sensitive method is tear Osmolarity test and grading the severity of dry eye where tear film height is not constant >300 mOsm/L indicating loss of homeostasis. The value is >8 mOsm/L there is instability of the tear film. Increase in osmolarity damages the eye. As osmolarity in your tears increase ocular surface cells become damaged (Bron et al., 2014).

Treatment method

Artificial tears, carmellose artificial tears eyedrops, cyclosporine A, difluoprednate, intense pulsed light, lacrisert, lipiflow, meibomian gland expression, nutritional supplements, omega-3 fatty acids, punctal plugs, restasis, rimexolone, seawater washes (quinton[®]), steroid eye drops, voclosporin, warm compresses, xiidra, etc are used. (Begley et al., 2002).

Artificial tears solution

Common reasons for dry eyes are due to increase usage of computer, heating/air conditioning, for dry eyes include medications, reading, dry sun and wind. Drugs used in artificial tear solution are carboxymethylcellulose reduces redness, decreases inflammation of eye, prevents eye irritation, polyethylene glycol 400 polysorbate, dextran, polyvinyl alcohol, hypromellose, Glycerine or propylene glycol or povidone which keeps eye moist. (Colligris et al., 2014).

Carmellose eyedrops restasis

Restasis used to treat dry eyes disease it lubricates the eye and decreases inflammation of eyes and it helps in natural tear production on continuous usage of this drug minimum 90 days (Goldberg et al., 2019). For some patient burning sensation occurs for few days (Colligris et al., 2014).

Celluvisc

Celluvisc is used as artificial tear drops used to treat burning, dryness. It forms lubricating, moisturising, transparent film and it adheres to surface lubricate for longer duration.

Difluoprednate

6a,9a-difluoroprednisolone 17-butyrate 21-acetate is a corticosteroid reduces redness, inflammation in ocular surface. (Markoulli and A, 2019) It is mainly used after ocular surgery. Difluoprednate deacetylated in the aqueous humour to active drug from difluoprednate to difluoroprednisolone butyrate (DFB). Difluoroprednisolone butyrate is

converted by endogenous tissue esterases into inactive hydroxyfluoroprednisolone butyrate (HFB) which prevent the systemic exposure to harmful agents.

Diquafosol tetrasodium

Diquafosol tetrasodium stimulates the natural production of tear and mucin in the surface of the eye. This reduces the inflammation and increase production of goblet cells which increase corneal epithelial healing (Baudouin *et al.*, 2019). P2Y₂ receptor stimulate tear fluid, mucin secretion and activate phospholipase. P2Y₂ receptor present in goblet cells, corneal epithelium, meibomian glands and conjunctival epithelium (Markoulli and A, 2019).

Lifitegrast antagonist

Lifitegrast similar to the binding epitope. Lifitegrast act as a antagonist for the binding of icam-1 to lfa-1, it blocks the inflammatory cycle of t cell (Chan and Prokopich, 2019). It is aqueous solubility. It reduces t-cell recruitment and block lymphocyte function-associated with antigen-intracellular adhesion molecule-1 interaction. Lifitegrast ophthalmic 5% (solution is marketed as Xiidratm is used in USA for insufficient tear protein production (Tomlinson *et al.*, 2006). The drug is glycoprotein prosecretory mitogen stimulates epithelial homeostasis and basal tear secretion it reduces dry eyes caused due to using contact lens related and sjögren's syndrome. In the presence of ocular surface inflammation, lacritin is decreases tear tissue transglutaminase (Markoulli and A, 2019). Tear production mechanism is mentioned in Figure 5.

Lacrisert

Lacrisert is solid insert which contains hydroxypropyl cellulose which lubricates the eye. It dissolves and lubricates eye. Dosage in one per day. It reduces inflammation, pruritus, photo sensitivity and excess tear, refractive errors

Meibomian gland expression

Meibomian glands located along margin of eyelid. They meibum lipids are excreted by modified sebaceous holocrine glands. Insufficient oil causes dry patches. (meibum). Figure 6: Measuring Meibomian gland expression. The near base of eyelashes openings of meibomian glands is present, if pore is clogged, the oil prevent tear film from evaporating. The dry eyes causes by meibomian gland dysfunction (Bron *et al.*, 2014). Omega-3 fatty acids and omega 6 fatty acids: is also known as alpha-linolenic acid (ALA) n-3 and linolenic acid (LA) (Rashid *et al.*, 2008). the n-3 fatty acids includes alpha-linolenic acid, docosahexaenoic acid, eicosapentaenoic acid and stearidonic acid. (Bron *et al.*, 2017)

LA and ALA are essential fatty acid which not produced. Test was performed in mice with relative humidity less than 30 % airflow 15 l/min at temperature 21 to 23-degree Celsius. Scopolamine is administrated to dorsal surface of skin in 2 different ratios of 1:1 of 0.1% n-3 and 0.1% n-6; 0.2% n-3 and 0.2% n-6. Fatty acids are insoluble in water 20% of tween 80 and 2.6% of glucam E was added and formulated in the form of emulsion (Solomon *et al.*, 2001).

Mucin secretagogues

Rebamipide ophthalmic suspension promotes mucin-like glycoproteins in human corneal epithelial cells mechanism is in Figure 7, (Colligris *et al.*, 2014; Markoulli and A, 2019).

Pilocarpine

Is non-selective cholinergic agonist which Ca stimulate M3 muscarinic receptor in exocrine glands. It known to increase aqueous secretion from saliva and sweat glands and increase number of conjunctiva goblet cells (Markoulli and A, 2019)

Isolation of RNA

RNA isolated from Cornea and conjunctiva and washed with 70% ethanol for precipitation, purified and stored at -80 degree celsius. (Rath *et al.*, 2019) MCH cells is responsible for inflammation. There is no significant difference between ALA and saline treated eyes ala 37 % periphery and 42% centre; saline 21% periphery and 37% centre. In ALA treated eye there is significant difference in decrease of corneal straining. Topical application of fatty acid is alternative for intake of fatty acids (Huang *et al.*, 2018).

Rimexolone

Rimexolone is corticosteroid drug used to reduce inflammation and it is a glucocorticoid steroid which reduces allergic reaction in eye which reduces swelling, redness in the eye. It is also used for autoimmune disease like rheumatoid arthritis, psoriasis which is accumulation of skin causes skin itchy and inflammation and ulcerative colitis is inflammation of intestine. 1% Rimexolone solution is used for treatment for uveitis (Kim *et al.*, 2010).

Cyclosporines used to treat specific and nonspecific ocular inflammatory disease (Prydal *et al.*, 1992). Cyclosporine A is low aqueous solubility and low penetration. Oil are used for penetration but causes burning sensation. Cyclodextrins used to increase the corneal penetration of cyclosporine (Hyun *et al.*, 2019; Moiseev *et al.*, 2019).

Seawater washes (quinton®)

Seawater is used alternative for the internal milieu

and it is rich in elements, isotonic marine plasma, wbc, the most fragile cells of an organism, physiological fluid of living things (Kaido *et al.*, 2011).

Seawater properties

Seawater is rich in mineral supply, tissue regeneration, restore the dietary elements in like oxygen, carbon in their Natural form. Sea water administered as oral, topical dosage. The dose of seawater increases when there no adverse reaction. It can be used for cooking but it is used for hyper thyroid and high blood pressure patient. Seawater also used for ENT problems like sinus and rhinitis.

Quinton plasma is isotonic in nature which is collected from coast distance of 30 kilometre and 10 m in depth. Commercial seawater which is available in pharmacies retail shops, pharmacies. The quinton is also known as seawater plasma. Seawater dose is taken for 1 to 6 times per day. Initially a high dose of hypertonic seawater is given and reduced to isotonic and dose is maintained. Quinto plasma is also used for nasal irrigation.

Steroid eye drops

Eye drops administered in the eye as combination of Antibodies and steroids. Antibodies which prevents Infection and steroids which reduces inflammation in eyes. Ingredients used in these are hydrocortisone which act as anti-inflammatory corticosteroid /neomycin/polymyxin b(product contains neomycin and polymyxin are antibiotics prevents growth of bacteria); loteprednol reduce swelling of eye, seasonal allergy/tobramycin aminoglycoside antibiotic derived from streptomyces tenebrarius used bacterial infections, mainly gram-negative bacteria. Prednisolone reduces burning sensation, discomfort, irritation, redness, inflammation, itchiness due to histamine release (Murtagh *et al.*, 2018). Inflammation of Teareye caused due to radiation, entry of foreign particles, infection caused by bacteria allergy, chemicals, gentamycin treat bacterial infections (such as blepharitis, conjunctivitis; prednisolone/ sulfacetamide is antibiotic used to cure conjunctivitis caused by bacteria; bacitracin, hydrocortisone neomycin, polymyxin b are steroid and antibiotic eye drops prescribed to prevent or treat eye infections that are associated with inflammation. (Bron *et al.*, 2014) Topical Glucocorticoids decreases inflammation which releasing phospholipids by reduces arachidonic acid. Glucocorticoids decreases oedema, pain and vascular congestion vascular congestion, collagen deposition, edema, fibroblast proliferation, and pain. Fluorometholone, steroids dexamethasone, difluprednate ,loteprednol, prednisolone Acetate. Methylprednisolone is corticosteroid which helps to reduce inflammation,

free from preservative and toxicity level is 1% for corneal epithelium compared with other eye drops (Marsh and Pflugfelder, 1999). Using steroid-sparing agents for long-term leads immunosuppression (Yin *et al.*, 2018). T cells are inhibited by immuno suppressive drug like calcineurin (Aboud, 2018; Drew *et al.*, 2018).

CONCLUSIONS

The dry eyes disease is caused due to improper tear formation or increase in the rate of evaporation of tear film. Aging leads to reduction in tear quantity leads dryness, easily irritated. Outdoor environment changes like air pollution, climate changes, high altitude, humidity present in air and change in temperature. Auto-immune disorders like formation of lump sjogren's syndrome, rheumatoid arthritis Scleroderma, other disorders like hyperthyroid or hypothyroid, diabetes, deficiency of vitamin A. Development of new medication can decrease the dry eyes disease. Proper treatment can completely cure the disease. Drugs like diquafosol tetrasodium naturally increase the tear production on long term usage.

Conflict of Interest

None.

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