DRY EYE ASSESSMENT, DYES & STAINS AND DRY EYE TREATMENT

AUTHORS

Dr Julie McClelland: University of Ulster
Fiona Flynn Smith: Dublin Institute of Technology

PEER REVIEWER

Dr Bruce Onofrey: University of Houston

CONTENTS

This chapter includes a review of:

- Tear film
- Dry eye
- Tear film assessment
- Dry eye treatment

TEAR FILM

LAYERS OF TEAR FILM

- Outer Lipid Layer (0.1 micro m)
  - Meibomian glands and glands of Zeis
- Middle Aqueous Layer (8 micro m)
  - Lacrimal glands and accessory glands of Krause and Wolfring
- Inner Mucin Layer (0.8 micro m)
  - Goblet cells, crypts of Henle, glands of Manz

PURPOSES OF TEAR FILM LAYERS

Outer lipid layer

- To prevent evaporation of the aqueous layer.
- To increase the surface tension.
- To assist in the stability of the tear film.
- To lubricate the lids as they pass over the surface of the eye.
- To convert the epithelium to a hydrophillic surface so that it can be moistened by the aqueous component of the tear film.

Aqueous Layer

- To supply oxygen to the avascular corneal epithelium.
- To provide an antibacterial function.
- To abolish any minute irregularities of the corneal surface.
- To wash away debris.

Mucous Layer

- Allows the aqueous to easily spread over the eye.
- To create a smooth optical surface and remain moist.
- To allow the tears to stick to the surface of the eye.

DRY EYE

Causes of Dry Eye

Reduced tear flow may go unnoticed by the patient or cause a large range of problems from clinically very mild to sight threatening. It may be result of the normal aging process in which other glands function less well also, for example salivary glands. It may alternatively be a more serious ocular problem.

- Reduction of eyes ability to produce tears
- Reduction or loss of ability to blink adequately
- Meibomian gland dysfunction
    - major cause of dry eye – is associated with evaporative dry eye due to a deficient lipid layer. It can be associated with various types of blepharitis.
- Preservative
    - Preservatives can irritate eye leading to drying
- Infections
    - Infections can disrupt the corneal and tear films surface leading to dry eye.
- Contact Lens
- Medication
    - Some studies have shown that the tear film may be disrupted in patient taking the oral contraceptive pill. Anticholinergic agents can cause dryness of mucous membranes e.g. atropine, some antihistamines.

Other Conditions Leading to Dry Eye

- **Destruction of lacrimal tissues:** tumours, sarcoidosis, inflammation
- **MGD:** destabilizes tear film
- **Absence of lacrimal gland:** surgical removal or congenital (rare)
- **Blockage of ducts:** severe scarring causing destruction of goblet cells
- **Neurological lesions:** range of inherited conditions

CHRONIC DRY EYE

Keratoconjunctivitis sicca

- Pure dry eye: primarily lacrimal glands involved
- Destruction of lacrimal tissue
- Meibomian gland dysfunction
- Absence of lacrimal gland
- Blockage of excretory ducts
- Neurological lesions

Sjogren's syndrome

- Affects approximately 2% population
- Peak incidence 40-60 years of age
- Autoimmune disease
- Associated with rheumatoid arthritis (70-90%)
- Chronic disease in which white blood cells attack the moisture-producing glands.
- Affects other mucous membranes, e.g. dry mouth
- Affected patients comprise of 90% women
- Symptoms range from mild to severe (affecting Quality of life (QOL)).
- Symptoms: dry eyes, dry mouth.
- Systemic disease: may affect liver, kidneys, GI tract, lungs, CNS.
- May cause extreme fatigue and joint pain.
- One of the most prevalent autoimmune disorders

Dry Eye Syndrome

- Irritation
- Foreign body sensation
- Burning, stinging
- Mucous discharge
- Transient blurred vision
- Itching
- Photophobia

Patients may experience any number of these symptoms.

TEAR FILM ASSESSMENT

Must always attempt to determine the cause of the tear film abnormality. Diagnosis of dry eye may be based on:

- Objective Assessment
- Quantitative Assessment
- Baseline Condition

OBJECTIVE ASSESSMENT

- Tear break-up time (TBUT) with or without fluorescein
  - Measure of tear stability
  - Dependent on mucin concentration
- Rose bengal staining shows the extent of dead cells caused by lack of tears
- The Schirmer test, in which a strip of filter paper is inserted into conjuntival sac and the amount of wetting noted after 5 minutes
  - Very crude test
  - Quantity but not quality

Tear Break Up Time (TBUT) with Fluorescein

- A strip of fluorescein is placed in the lower lid fornix and then removed.
- Patient asked to blink three times and then look directly ahead, without blinking.
- The tear film is observed under cobalt-blue light of the slit-lamp.
- Time that elapsed between the last blink and appearance of the first break in the tear film is recorded. A break is seen as a dark spot.
- Less than 10 seconds is suggestive of a dry eye
- Limitation - Reflex tearing.
- Common method
- Normal tear film is continuous
- Blinking maintains the tear film continuity
- If you keep your eyes open long enough, without blinking, the tear film will start breaking up
- Your eye will feel uncomfortable forcing you to blink
- In patients with dry eyes the tear film is unstable, and breaks up faster

Non-invasive TBUT (NIBUT)

- May be assessed using keratometer, hand-held keratoscope or Tearscope.
- NIBUT measurements are longer than fluorescein break up time.
- NIBUT values of less than 15 seconds are suggestive of dry eyes.
- May encourage patient compliance due to non-invasive nature of test.
- Tear meniscus may be concave, small or absent in severe cases.
- Normal eyes: tear meniscus is convex and approximately 1mm high.

Fluorescein Sodium

- Orange-red dye
- Used as a topical stain or injection for fluorescein angiography
- Doesn’t stain tissues: colours tear film
- Normal cornea impermeable to tear film
- Disruption, eg. Abrasion or ulcer, allows tear film to gain access to deeper layers
- Green colour in areas of desquamation
- For dilute concentrations in solution light with a wavelength 485-500nm maximally absorbed
- Absorbed energy excites fluorescein molecules and emits light of lower energy and longer wavelength
- Light emitted appears green (525-530nm)

- Viewed with a Burton lamp or cobalt blue filter
- Yellow filter (Wratten 15) improves detection of staining pattern

Indications for Use

- Defects in corneal epithelium
- Contact lens fitting
- Applanation tonometry
- Assessment of naso-lacrimal duct
- Assessment of tear film
- Assessment of tear flow

Rose Bengal

- Brown-red powder, soluble in solution.
- Used as 1% solution
- Rose Bengal strips available
- Derivative of fluorescein, different staining characteristics
- Stains dead and degenerated epithelial cells and mucous
- In KCS typical RB staining: 2 triangular shapes with bases at limbus
- Corneal filaments and plaques stain with rose bengal
- Can cause ocular irritation.
- May be used with topical anaesthetic

Indications for Use

- Dendritic keratitis. Will stain ulcer but not surrounding area
- KCS: characteristic staining pattern improves diagnosis
- Pressure areas due to contact lenses

Schirmer Test

Schirmer Test measures the quantity of tears:

- Uses a 35 mm x 5 mm filter paper strip to measure the amount of tears that are produced over a period of 5 minutes.
- The strip is placed in the lower lid, between the middle and outer third.
- Normal light level.
- Patient asked to look straight ahead and blink normally during the test.
- Results: more than 10 mm wetting of the filter paper in 5 minutes suggests a normal quantity of tears.
- Results: less than 5 mm in 5 minutes suggests dry eye.
- Test results variable.
- Schirmer I or II: anaesthetic:
  - I: baseline and reflex tears
  - II: only basic
- Schirmer Test
- If tear quantity reduced: tear deficient dry eye.
- If a normal amount of tears is produced: evaporative dry eye which may be associated with MGD.

Phenol Red Thread Test

- Cotton thread impregnated with phenol red dye.
- Phenol red is pH sensitive and changes from yellow to red when soaked by tears.
- Placed in the lower conjunctival fornix.
- Colour change (mm) measured after 15 seconds - indicating the length of the thread wetted by the tears.
- Normal: 9-20mm. Less than 9mm: suggestive of dry eye.

Lissamine Green

- Available as 1% impregnated
- Similar to Rose Bengal
- Stains lipid like structures, mucous, dead or dying epithelial cells
- Better tolerated than rose bengal
- Timing important: staining observed between 1-4 minutes after instillation

QUANTITATIVE ASSESSMENT

- Patient asked a range of questions based on symptoms, general health and medication.
- Final score calculated. If over a certain number: suggested that patient may have dry eye and should be referred for further investigation.
  Example: McMonnies and Ho questionnaire.

DRY EYE TREATMENT

Conclusion of Dry eye Treatment with Ocular Lubricants and Artificial Tears

- Affects quality of life and productivity (Asbell 2006)
- Dry eye treatment should be patient specific (Asbell 2006)

CONSIDERATIONS

- Must always treat primary cause if dry eye is secondary e.g. conjunctival infection
- When considering dry eye treatment must take into account the above factors
- Before suggesting the use of artificial tears, thorough assessment of the tear film and ocular surface using dyes or stains
- May be useful to determine the patient's baseline condition
- Can be done by discontinuing drops for a day before examination
- Can help determine which product to use
- Patient preference: some artificial tears sting,
- Multi-dose vs single dose
- Preserved or unpreserved: allergy to preserved
- Patient should be advised to discontinue if allergy develops
- Regime: 1-4x day? Assistance with this.

WITHOUT ARTIFICIAL TEARS AND LUBRICATING OINTMENT

- Blinking exercises or lid hygiene and compresses. Important in treatment of blepharitis and MGD
- Treatment of inflammation: mast cell stabilizers, steroids, non steroidal
- Consideration of medication: antihistamines, oral contraceptive pill
- Punctal plugs to prevent the tears from being drained
- Nutrition: increased omega 3 fatty-acids, e.g. oily fish/supplements
- Maintain a good water intake. Avoid diuretics such as alcohol and caffeine

Recent research has shown that therapy with polyunsaturated fatty acids reduces ocular surface inflammation and improves dry eye symptoms. Increase omega-3 fatty acid intake, i.e. eat more fish. Tears Nutrition & HydroEye are oral pills that provide these supplements.

- Environmental issues: avoid air conditioning, heaters, smoke and dust.
- Use a humidifier.
- Use wraparound sunglasses or side shields.
- Visual Display Unit (VDU) issues: Keep monitor below eye level.
- Contact lens related issues: preservative in solutions etc.

Exacerbating conditions

If present, treat:
- lower lid laxity
- floppy eyelid syndrome
- inadequate eyelid closure while sleeping
- seborrheic blepharitis
- ectropion
- entropion
- trichiasis
- nasal mucosa/sinus inflammations.

WITH OCULAR LUBRICANTS AND ARTIFICIAL TEARS

Ideal Artificial Tears

Reproduce the metabolic, optical and physical characteristics of natural tears (pH, tonicity, electrolytes).

- Should not irritate the eyes
- Provide a good lubricating effect
- Have long retention time (often a prob with artificial tears – have to be instilled regularly and often)
- Obviously must not affect refractive error
- Short term benefits
- Must prevent damage to cornea long term as dry eye causes increased corneal permeability

Consensus from round table discussion:

- Increased residence/dwell time

- No blurring
- No added irritation (e.g., from preservatives)
- Protection from microbial contamination
- Symptom relief
- Increased tear breakup time (TBUT)
- Good eye-feel (comfort)
- Ease of use (easy to dispense)
- Cost-effectiveness

Viscosity

- Many dry eye sufferers have a mucin deficiency
- Mucin
  - Acts as a surface agent
  - Slows the rate of drainage
- Viscolizer to compensate

Many dry eye sufferers have a mucin deficiency. The eyes of patients having mucin deficiency often and respond by producing copious amounts of aqueous tears. Tear substitutes should contain a viscolizer to compensate for this. Mucin acts as a viscolizer and creates a hydrophillic epithelial surface. Traditionally cellulose derivatives were used and are still widely used. Also the polyvinyl alcohol (PVA) has the advantage of being a surfactant as well as a viscolizer. Viscosity can be increased to a point where the drops become gels: ocular lubricants.

- Mild symptoms – give low viscosity artificial tears
- Moderate to severe require a more viscous product

In addition to dry eye, tear substitutes may be used to (Doughty 2006):

- Reduce symptoms of grittiness, irritation, FB sensation (e.g. viral infection)
- Reduce friction (e.g. floppy eyelid syndrome)
- Stabilize tear film (e.g. roseacea keratitis)
- Protect from dessication (e.g Bell's palsy)

Artificial Tears and Ocular Lubricants

- Tear Film Deficiencies
- Simple or Complex
  - Simple artificial tears contain some salts and one or two polymers in an aqueous solution.
  - Complex artificial tears contain high concentration of certain polymers.

Formulation Considerations

Osmolarity

- Osmolarity of natural tears approximately 300mOsm/L (equivalent to 0.95% NaCl).
- Most artificial tears are iso-osmolar (250-300mOsm/L).
- Patients with aqueous deficiency have higher osmolarity causing reduced goblet cell density, epithelial defects and poor wetting.

- Require artificial tears with osmolarity 210-239mOsm/L to dilute tears.
- Ocular irritation at 75mOsm/L
- Concentration of a solution
- Lower osmolarity (conc) more water and less salt causes water to move into the aqueous deficient tears

  Example: TheraTears 181, Systane 245, Visine Tears 298, Refresh Plus 318

Hyperosmolarity

- Some dry eye experts believe that hyperosmolarity is a key feature of dry eye regardless of severity.
- Hyperosmolarity alters the behaviour of mucins causing exposure of ocular surface.
- Hyperosmolarity can result in increased inflammation (signs and symptoms of dry eye)

pH

- Normal artificial tears pH 7.4.
- Artificial tears typically 6.5-7.5.
- Some products range from pH 4-9

Preservatives

- Increase shelf life which thus has cost implications
- Preservatives used to prevent microbial growth.
- May cause allergy/hypersensitivity
- Preservative free products available (Minims etc). Single use only.
- Commonly benzalkonium chloride used – may reduce TBUT and interfere with tear stability.
- Long term use of a preservative can affect ocular surface
- Detergent or oxidative preservatives
- Detergent preservatives affect cell membrane permeability
- Oxidative preservatives penetrate cell membranes and interfere with intracellular reactions.

Polymers

A range of polymers are used in current products. More complex artificial tears may contain two polymers. This is a list of the most commonly currently used polymers.

- Hypromellose
- Hydroxyethylcellulose
- Carmellose sodium
- Polyvinyl Alcohol (PVA)
- Povidone

Hypromellose

- Hypromellose (hydroxpropyl methylcellulose HMPC) has been in use since the 1940s. More viscous than PVA and better surface wetting.

  E.g. Preserved: Hypromellose eyedrops 0.3% (P) (preservative Benzalkonium chloride)

  E.g. Unpreserved: Artelac 0.32% single use preservative free.

Hydroxyethylcellulose

- Has emolient and film forming, cohesive, properties equal to methylcelllulose.
- Less viscous and less blurring than methylcelllulose.
- Only single use available e.g. Minims artificial tears 0.44%. (P)

Carmellose sodium

- Carmellose (carboxymethylcellulose sodium). Higher molecular weight (unlikely to penetrate cornea).
- Mucoadhesive properties.
- Retention time 22mins on healthy cornea.
- E.g. Celluvisc 1% single use. (P)

Polyvinyl Alcohol

- PVA has viscolizing properties.
- Non-ionic synthetic surfactant. 1.4% low viscosity but remains in eye for 30 mins as it is absorptive. E.g. Hypotears 1%. (P) Preservative BKC.
- Liquifilm tears 1.4% (P) Single use preservative free.

Povidone

- Mixture of linear synthetic polymers of different chain lengths and molecular weights.
- Functions as a non-ionic surfactant.
- When used in a concentration of 3-5% increases viscosity of solutions.
- Used as a disinfectant in CL solns.
- E.g. Oculotect 5% single use preservative free. (P)
- Non-ionic – does not dissolve in water.

Current Multi-Use Products

Numerous products are available for management of dry eye symptoms. All multi-use bottles contain preservatives, usually benzalkonium chloride. Saline usually preserved with benzalkonium chloride. 0.004% as a preservative.

- Saline eyedrops without polymers to enhance viscosity e.g.Sodium Chloride (P)
- Hypromellose 0.3% e.g. Moisture Eyes (P), Hypromellose (P) or with dextran e.g. Tears Naturale (P)
- Hypromellose 0.5% e.g. Isopto Plain (P)
- Hydroxymethylcellulose 0.36% refresh Instant Revival Eyedrops
- Polyvinyl Alcohol 1-1.4% e.g. Hypotears (P), Liquifilm Tears (P), Sno Tears (P)

Properties

- 0.004% preservative
- Doesn’t interfere with tear film stability
- Most artificial tears have the same tonicity as tears
- 0.9% NaCl

- Some solutions have an increased osmotic pressure
- pH 7.4 usually
- Varies between 4-9 in some commercial preparations

Single-Dose Products Preservative Free

- Sodium Chloride Minims (P) 0.9%
- Hypromellose 0.32% e.g. Artelac
- Hydroxyethylcellulose 0.44% Minims (P)
- Polyvinyl Alcohol 1.4% (P) e.g. Liquifilm Tears Preservative Free
- Polyvinyl Alcohol and povidone (P) e.g. Refresh

Gels

Gels include synthetic polymers. Initially, it causes blurred vision but clears quickly.

Carbomer

- Synthetic high molecular weight polymer.
- Good water binding, forms stable tear film.
- Converts to liquid form and reformation back to gel during blinking.
- Longer retention time (7xPVA)
- Fewer doses required
- E.g. Gel tears 0.2% preservative BKC. (P)
- Carbomer is the viscoliCarbomer – high molecular weight polymer
- Carbomer is the viscoli used in gel tears

Ocular Lubricants

- No guidelines to differentiate re-wetting solutions, artificial tears and lubricants.
- Lubricants used for severe dry eye e.g. keratoconjunctivitis sicca.
- NOT used for follicular conjunctivitis
- Used with caution in toxic keratitis or vernal keratitis.
- Usually a mixture of various paraffins (relatively inert hydro-carbon chemicals).
- Liquid paraffin and yellow soft paraffin melt at ocular temperature.
- Longer retention time.
- May cause blurred vision.
- Usually used at night.
- Used when non-toxic, non-infective chronic irritation and inflammation of the conjunctiva.
- Replaces tear film with lubricating film as opposed to a simple aqueous fluid.
- Cannot improve hydration of the dry ocular surface.

    - Difficult to differentiate between artificial tears and ocular lubricants
    - All products marketed as artificial tears will provide some lubricating effect

- Lubricant as opposed to artificial tears is used for a non-infective, non-toxic irritation and inflammation of the cornea accompanied by poor traction of the lids across the globe
- Longer residency time than artificial tears
- Smeary vision after ointment is applied

True Ocular Lubricants

- Cellulose polymer 1% e.g. hypromellose (P) (Isopto Alkaline Eye Drops)
- Carbomer Gel 10g tube (GSL), Viscotears Liquid Gel 10ml (P)
- Ointments containing liquid parrafin or white parrafin e.g. Lacri-lube 3.5g tube (P)
- Lubricants used at night as will form a greasy coat on ocular surface and lid margins.
- Ointments containing yellow soft parrafin e.g. Simple Eye Ointment (P) 3.5g or 4g tubes
- Acetylcysteine eye-drops (inc. hypromellose 0.35%) e.g. Ilube Eye Drops 10ml (POM) (Mucolytic Agent)
- First aid and Health and Safety stations

Mucomimetic Agents

- Hydroxypropylguarpolysaccharide is a mucomimetic.
- Preserved with Polyquad
- Research suggests long term protection of cornea from desiccation (Ubels et al 2004).
- Effective at reducing dry eye symptoms.
- Longer retention time.
- For moderate to severe dye eye: Systane (Alcon).
- Contains 0.18% hydroxypropyl-guarpolysaccharide.
- Preserved with Polyquad.

Several research studies have demonstrated a significant reduction in symptoms when compared to cellulose control agent. There is long-term desiccation protection of intact cornea and no detrimental effect on cells (Ubels et al 2004).

New Products

Theratears

- More electrolytes added to closely match tears
- Extreme dry eye
- Using an individual's blood serum as a lubricant
- Preservative free single use products
- Mulltidose for occasional use
- Drops that are compatible with contact lenses
- Contains carboxymethylcellulose
- Electrolyte balance crucial for tears to function normally and prevent loss of goblet cells on conjunctival surface
- Using blood serum: antibodies and growth hormones
- Said to promote surface healing.

Hypotonic agents

Theory behind this is that dry eye (less aqueous) causes a higher osmotic pressure or higher salt concentration. Hypotonic agents draw salt out of solution from ocular surface into fluid/eye drops i.e. dilutes surface. Oil containing eyedrops (Refresh Endura, Soothe) may be added if meibomian gland dysfunction is present. These eyedrops will replenish the lipid layer or tear film. Warm compresses over closed eyelids for 5 minutes will also replenish the lipid layer.

Mucolytic agents

- In keratoconjunctivitis sicca thin strands of degenerated epithelial cells and mucous may become attached to the cornea
- May be possible to remove with forceps or cotton bud
- Can use mucolytic agent e.g. acetyl-cysteine
- May cause stinging
- Breaks up mucous strands
- Reduces viscosity.

Simple Ophthalmic Eyewashes

- Sterile saline solution (0.9%) buffered with phosphates e.g. Sterac Sodium Chloride (GSL)
- Foil sachets of sterile saline e.g. Normasol (P)
- Minims Sodium Chloride (P)
- First Aid stations
- Health and Safety

HYPOTONIC AGENTS

Theory behind this is that dry eye (less aqueous) causes a higher osmotic pressure or higher salt concentration. Hypotonic agents draw salt out of solution from ocular surface into fluid/eye drops i.e. dilutes surface. Oil containing eyedrops (Refresh Endura, Soothe) may be added if meibomian gland dysfunction is present. These eyedrops will replenish the lipid layer or tear film. Warm compresses over closed eyelids for 5 minutes will also replenish the lipid layer.

PUNCTUM OCCLUSION

- Plugs, sutures or thermal cautery.
- Plugs may be used in Optometric practice
- Research studies have demonstrated improvements in the aqueous component of tear film, increases goblet cell density and normalises tear film osmolarity.
- Prolongs contact time in eyes of artificial tears.
- Contra-indicated if inflammation present.
- Dissolvable or permanent.

Punctum plugs are available in a dissolvable, form lasting between three to seven days and non-absorbable forms made from polyethylene, acrylic or silicone. They may not be a permanent cure.

A helpful YouTube video link:http://www.youtube.com/watch?v=Z8mKxeBtY3Y

REFERENCES

- O'Connor Davies Ophthalmic Drugs. Hopkins and Pearson. Fourth Edition 1998
- Doughty M. Drugs, Medications and the Eye. Michael. 15th Edition. 2006.
- Kanski J. J. Clinical Ophthalmology. Third Edition. 1994
- O'Toole L. Differential Diagnosis of Ocular Disease
- The tears and lacrimal gland - Diagnosing sight and life-threatening eye disease. Optometry Today 10/03/06.
- O'Toole L . Therapeutics in practice: Disorders of the tears and lacrimal system. Optometry Today. 08 /04/05
- Heath G. Therapeutic management of dry eye Current and developing therapies. Optometry Today. 03/12/04.
- McMonnies CW, Ho A. J Am Optom Assoc. 1987 Jul;58(7):588-91. Responses to a dry eye questionnaire from a normal population.
- Ubels JL, Clousing DP, Van Haitsma TA et al. Pre-clinical of the investigation of the efficacy of an artificial tear solution containing hydroxypropylguar as a gelling agent. Current Eye Research 28;437-444.
- Asbell PA. Increasing importance of dry eye syndrome and the ideal artificial tear: consensus views from a roundtable discussion. Current Medical Research and Opinion® Vol. 22, No. 11, 2006, 2149–2157.