OSI

Ocular Surface Insight

Issue 9

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Ocular Surface Insight

"We can only see a short distance ahead, but we can see plenty there that needs to be done."

Alan Turing

Welcome to the Summer issue of **OSI**.

Welcome to the Summer issue of OSI Magazine!

Our plan was to launch this issue in the middle of May but due to the huge turmoil of Covid 19 affecting every part of life, we postponed it until now.

The OSI team have been very busy during lockdown with running a series of webinars and continued education in a "new way". To reflect the recent times of lockdown you will find some interesting Questions and Answers in this issue from Dr. Kenneth Li in Hong Kong as well as my colleagues on the editorial board in the UK.

Our last webinar before the summer break was with Sabrina Shah-Desai and Amy Gallant Sullivan, 'Safety in Beauty', discussing the many preservatives and ingredients used in cosmetics and popular cosmetic surgery procedures, which can have a real negative effect on the ocular surface and increase dry eye symptoms. This was a very timely reminder on how important it is to gather as much information as possible about patient's lifestyle and routines to help recommend the right treatment plan.

We are immensely grateful to everyone who presented, participants and our industry supporters. We have had so much great feedback that we intend to continue running webinars going forward, so keep checking our website: **www.osimag.co.uk** for news.

I am also excited to announce that OSI are going to start running a modular online course in the autumn, "Dry Eye Masterclass". This will be open to both Ophthalmologist's, and Optometrist's who want a solid foundation in how to diagnose and treat dry eye disease, based on the latest science and best practice.

Enjoy the magazine, and we hope you can join our **Dry eye masterclass,** or webinars in the autumn.

Samer Hamada

Samer Hamada,
MD, MSc, DO (hons), FRCSEd, FRCOphth

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Ocular Surface Insight

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Contents

What's in the news?

Effects of Cataract Surgery on Symptoms and Findings of Dry Eye in Subjects With and Without Pre-existing Dry Eye

The purpose of this study was to compare dry eye symptoms and findings in post cataract surgery eyes' with and without pre-existing dry eye. The design of the study was prospective, observational with case-control.

Sixty-seven eyes that had undergone cataract surgery were included; 48 were classified into group D (pre-existing dry eye) and 19 into group N (no pre-existing dry eye). No subjects received perioperative treatment for dry eye. We evaluated between-group differences in symptom scores, corrected distance visual acuity (CDVA), tear film breakup time (BUT), tear film breakup pattern (BUP), and ocular surface fluorescein staining scores, at 1 week, 1 month, and 3 months postoperatively.

Symptoms were unchanged in group N, but improved in group D ($P < .001$) postoperatively. CDVA was improved after surgery in both groups ($P < .001$). BUT was shorter preoperatively in group D than in group N although this difference was absent 1 month post-operatively. Fluorescein staining scores significantly increased at 1 month postoperatively in group N ($P = .01$), but did not change in group D. During the perioperative period, the predominant BUP was the random break pattern in both groups (≥ 85%). From 1 week to 3 months, dimple break patterns decreased in group D ($P = .007$), whereas spot break patterns increased ($P = .01$).

The authors concluded that cataract surgery has an influence on tear film stability and the ocular surface. There was either a transient improvement or worsening of ocular surface wettability in some patients without pre-existing dry eye.

Jpn J Ophthalmol. 2020 Jul;64(4):429-436.doi: 10.1007/s10384-020-00744-1.
Authors: Mikiko Shimabukuro, Naoyuki Maeda, Shizuka Koh, Keiichi Abe, Reiko Kobayashi , Kohji Nishida

The prevalence of keratoconus in children with allergic eye disease in an Egyptian population

A cross-sectional study was conducted on all children presenting with ocular allergic disease from September 2017 to September 2018. All study participants were subjected to history taking (a specially designed questionnaire), routine ophthalmological examination, and corneal tomography.
Results: A total of 79% of the study patients had vernal keratoconjunctivitis (VKC) while the remaining had perennial allergic conjunctivitis (10%), seasonal allergic conjunctivitis (9%) and atopic keratoconjunctivitis (2%). Manifest KC was seen in 7% of cases, suspect KC was found in 27% of cases, and 66% had no evidence of KC. For the manifest KC, 56% had clinical signs, while 44% were diagnosed by tomography. For the purpose of statistical analysis, the cohort was divided into group KC (manifest or suspicious KC) and group non-KC (no KC). The mean age was 11.2 years in group KC, and 9 years in group non-KC ($p < 0.001$). The mean duration of allergic symptoms was 3.75 years in group KC, and 2.5 years in group non-KC ($p = 0.001$). The mean duration of eye rubbing was 2.5 years in group KC, and 0.83 years in group non-KC ($p = 0.02$). Systemic atopy was present in 35.3% of group KC, and in 12.5% in group non-KC ($p = 0.005$).
The overall prevalence of KC was 34%. Risk factors for the development of KC in patients with ocular allergy were age, duration of symptoms specially eye rubbing, systemic atopy and VKC. Tomographic diagnosis of KC can be present in absence of clinical signs.

Eur J Ophthalmol 2020 Jul 13;1120672120942691.doi: 10.1177/1120672120942691.
Authors: Alyaa Saeed Ahmed, Mohamed-Sameh H El-Agha, Mahmoud Osama Khaled, Shireen Mostafa Shousha

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Date of last revision of Prescribing Information: 17/07/2019.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Santen UK Limited (Email medinfo@santen.co.uk or telephone: 0345 075 4863).

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2. Craig J et al. Ocul Surf 2017;15(4):802 - 812
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Date of preparation: July 2019 **Job code:** PP-IKERVI-UK-0208

What's in the news?

Symptoms of Ocular Surface Disease in Construction Workers: Comparative Study with Office Workers

The authors set out to investigate and contrast the prevalence of dry eye symptoms in construction workers and office workers using the OSDI questionnaire.

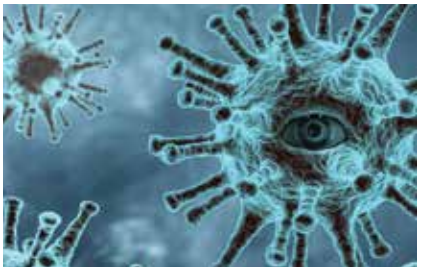
A cross-sectional, observational study was conducted using the OSDI questionnaire to evaluate dry eye symptoms and associated risk factors. Sampled size calculation with a power of 80% and a 95% degree of confidence suggested the inclusion of 298 participants.

They studied 304 subjects (149 construction workers and 155 office workers). More than half (55%) of the participants presented dry eye symptoms (OSDI > 12). The average OSDI score was 21.30 ± 22.20 points, being lower in the group of construction workers (12.45 ± 17.50) than in-office workers (28.51 ± 22.99) ($p < 0.001$). Considering participants who had moderate and severe symptoms (23 to 100 points in OSDI), office workers presented dry eye symptoms 4.15 times more frequently than construction workers (OR 4.15, 95% CI 2.52, 6.85). Women presented statistical evidence of higher OSDI scores than men (32.47 ± 23.72 vs. 14.87 ± 18.48, respectively).

The conclusion from the study was that construction workers have four times less risk of presenting dry eye symptoms than people working in the average office space. This highlights the pernicious effects on the ocular surface of the office environment, which poses a significant risk for the development or worsening of dry eye symptoms.

BMC Ophthalmol2020 Jul 9;20(1):272.doi: 10.1186/s12886-020-01548-0.
Authors: Sergio Hernandez-Llamas, Ana Karen Paz-Ramos, Patricio Marcos-Gonzalez, Francisco Amparo, Manuel Garza-Leon.

Propensity and Quantification of Aerosol and Droplet Creation During Phacoemulsification With High-Speed Shadowgraphy Amidst COVID-19 Pandemic



To study propensity of aerosol and droplet generation during phacoemulsification using high-speed shadowgraphy and quantify its spread amidst COVID-19 pandemic.
In an experimental set up, phacoemulsification was performed on enucleated goat eyes and cadaveric human corneo-scleral rims mounted on an artificial anterior chamber. Standard settings for sculpt and quadrant removal mode were used on Visalis 100 (Carl Zeiss Meditec, Germany). Microincision and standard phacoemulsification were done using titanium straight tips (2.2 and 2.8 mm in diameter). The main wound incisions were titrated equal to and larger than the sleeve size.
High speed shadowgraphy technique was used to detect the possible generation of any droplets and aerosols. The visualization and quantification of size of the aerosols and droplets along with calculation of their spread were the main outcome measures.

The results showed that in longitudinal phacoemulsification using a peristaltic pump device with a straight tip, no aerosol generation was seen in a closed chamber. In larger wounds, there was a slow leak at the main wound. The atomization of balanced salt solution was observed only when the phaco tip was completely exposed next to the ocular surface. Under this condition, the nominal size of the droplet was □ 50 µm and the maximum calculated spread was 1.3 meters.

The conclusion was that there was no visible aerosol generation during microincision or standard phacoemulsification.
Phacoemulsification is safe to perform in the COVID-19 era by taking adequate precautions against other modes of transmission.

J Cataract Refract Surg2020 Jul 6.doi: 10.1097/j.jcrs.0000000000000289.

Authors: Naren Shetty, Luci Kaweri, Pooja Khamar, Nikhil Balakrishnan, Abdur Rasheed, Prasenjit Kabi, Saptarshi Basu, Rohit Shetty, Rudy M M A Nuijts, Abhijit Sinha Roy

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A Perfect storm

by **Cian Gildea**

I don't think any eyecare professional would bat an eyelid at the claim that the incidence of dry eye disease is ever increasing. From personal experience, it is one of the most common, if not the commonest conversations I have with patients during my day in clinic. I work in a refractive surgery practice, so tears are of particular interest to us.
Performing refractive surgery on eyes with undiagnosed or missed ocular surface disease can result in refractive errors and ultimately unsatisfied patients[1,2]. This is from a clinician's perspective, looking at the impact on patients. They can develop photophobia, blurred or inconsistent vision and pain. This is just the tip of the iceberg, think about navigating through your day, dealing with some of the above symptoms and you can see why people suffering from dry eye disease often report depression[3,4]. In one study evaluating quality of life, the burden of chronic dry eye disease was similar to the impact of moderate to severe angina5,6. It is difficult to get a hard and fast figure on the prevalence of dry eye disease due to the myriad of different criteria used historically to categorize the condition. This has hopefully changed for the better now, with TFOS (Tear Film and Ocular Surface society) producing the DEWS 2 report. This has given dry eye a classification and definition, which will guide clinical studies and improve reporting.
According to the DEWS 2 report, the prevalence of dry eye disease ranged from 5 to 50% worldwide7.

So, we know from our own daily clinical experience and various reports published, that the incidence of dry eye is increasing, but what type of dry eye? We have aqueous deficient dry eye, evaporative dry eye and a combination of the two, mixed dry eye. Of these sub-types, evaporative dry eye is the most prevalent8. If we look at tear film mechanics, we know that the force of a blink expresses meibum from the gland and this spreads over our tear film. This oil is responsible for reducing the rate of evaporation of the underlying aqueous9. There are many factors that can affect the performance of the meibomian glands. Aging10, systemic medications such as Accutane11, environmental conditions and contact lens wear, have all been shown to impact the meibomian glands[9, 12, 13, 14].

Let's delve a little bit deeper into the contact lens and environmental factors. Contact lenses have been shown to reduce meibomian gland function and also affect gland morphology. Not only that, meibum quality and gland drop out are positively correlated with the duration of contact lens wear[15].
When looking at a contact lens on the eye, the tear layer splits, forming a pre-lens and post-lens tear film. Normal tear layer thickness over the central cornea is approximately 3 microns thick[16]. A contact lens will alter the integrity and stability of the tear film[17]. The pre-lens tear film is approximately one micron thinner compared to that of the pre-corneal tear film. It has been postulated that this thinner tear layer leads to more rapid destabilisation of the tear fluid. Couple this with an increase in temperature of the ocular surface by up to two degrees Celsius18 when a contact lens is worn, we can see how evaporation is a particular problem with contact lens wearers.

Now consider our modern lifestyles, many people work in air-conditioned environments. This low humidity negatively affects dry eyes by increasing tear evaporation rate[19] as well as disrupting the meibomian glands[13]. Modern lifestyle has also dictated a boom in the amount of time we spend on screens. Whether it's your smart phone, your laptop, your desktop, your games console, your television – screens are everywhere! Why is this important? Average blink rate is reported to be between 8 and 21 blinks per minute. This reduces by approximately five-fold when using a VDU20. Less blinking means less meibum secretion, leading to increased incidence of meibomian gland dysfunction[21] and tear evaporation and the circle continues ad infinitum.
One word I'm hesitant to use in the current environment is pandemic. Long before the current global pandemic of Covid-19, eyecare professionals have been trying to raise awareness of another pandemic at our doorstep. Namely, that of myopia. In 2010, an estimated 1.45 billion people were afflicted with this refractive error[21]. It doesn't stop there, estimates that 49.8% of the population will be myopic by 2050 (that's approximately 4.7 billion people). We have of course to be cognisant of all the complications associated with myopia, those of cataracts, glaucoma and myopic maculopathy[21] to name but a few. This has attracted the attention of some of the brightest minds in tackling this event horizon. So why suddenly start talking about myopia?
Research has shown that specific designs of contact lenses can reduce the progression of myopia22. If the specific design is to be worn during waking hours, they often recommend a wearing time of 8-10 hours a day, depending on design[22]. If we put all of this together, young children are being placed in contact lens wear from a young age if they are showing signs of myopia progression (-0.50DS per year). As mentioned earlier, we know contact lenses have a negative effect on meibomian glands, directly correlated to length of wear. They also affect tear film stability, increasing evaporation rates. Couple this with the destructive effect of a reduced blink rate on meibomian glands due to increased screen time and we have a perfect storm waiting for eyecare professionals that we need to be prepared for.

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Quick Q & A's with Arthur Cummings

· How did you keep in contact with your patients during lock down?
Phone, Zoom webinars, Doxy.me virtual consultations, and I saw emergencies in person.

· What worked well/didn't work so well?
Everything above worked well.

· Do you use Electronic Patient Record software, if not, is it something you would like to introduce?
Yes, we use Acuitas. We would not have been able to provide the same service without an EMR.

· How has the patient journey flow changed in out-patients?
· 1. Virtual logical history form
· 2. tech/nurse part 1 virtual consult
· 3. in-person consult for scans/optometrist/ophthalmologist exam and then
· 4. review of exam/scans/options either in person or via Doxy.me

LASIK: No big difference, simply longer intervals between cases, so the usual full day LASIK list on a Friday is now done over 2 days and clinic consults are done between cases.
Cataract: Simply reduced the numbers for the moment, with longer gaps between cases - don't have additional lists so waiting list is growing unfortunately.

· What key changes have you implemented into your clinical setting?
COVID questionnaires, temp checks, breath shields, physical glass barriers everywhere between examiner and patient, masks for everyone, gloves, sanitizer, wipe down after each patient.

· What are the most difficult aspects of seeing patients again face to face, how do you see this working?
Masks!!! Trying to reduce the consultation time.

· How have you been able to conduct consultations for Refractive surgery?
Yes - greater demand than this time last year.

· Have you seen any increase in DED, post-surgery? No.

· Have you seen any increase in DED, due to life-style changes, during lock down/ new normal? Absolutely. For patients and for us. Masks cause warm exhaled air to flow over the eyes for the whole day, so every staff member has a lubricant drop in their pocket. Patients are drier preop so spending time and efforts to rehabilitate them prior to surgery.

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Eylamdo (dorzolamide/timolol) Eye Drops Prescribing Information (please refer to the full SmPC before prescribing) Indications: Elevated intraocular pressure (IOP) in patients with open-angle glaucoma or pseudoexfoliative glaucoma when topical beta-blocker monotherapy insufficient. **Available strengths:** 20mg/ml dorzolamide + 5mg/ml timolol Eye Drops, in 5ml solution. **Dosage and method of use:** One drop in affected eye(s) twice daily. If another topical ophthalmic agent used, administer at least ten minutes apart. It is a sterile solution with no preservatives, which can be used for up to 28 days after first opening. Advise patients to wash their hands before use and avoid allowing the container tip to contact the eye. If handled improperly, contamination of ocular solutions can cause ocular infections. **Paediatrics:** Efficacy in paediatrics and safety below the age of 2 years has not been established. **Contraindications:** Patients with reactive airway disease, including bronchial asthma or a history of bronchial asthma, or severe chronic obstructive pulmonary disease (COPD), sinus bradycardia, sick sinus syndrome, sino-atrial block, second or third degree atrioventricular block not controlled with pacemaker, overt cardiac failure, cardiogenic shock, severe renal impairment (CrCl < 30ml/min) or hyperchloraemic acidosis and hypersensitivity to one or both active substances or excipients. **Special warnings and precautions for use:** Patients with cardiovascular diseases and hypotension therapy with beta-blockers should be assessed and therapy with other active substances considered. Due to its negative effect on conduction time, use with caution in patients with first degree heart block. Use with caution in patients with severe peripheral circulatory disturbance, mild/moderate COPD, hepatic impairment. Respiratory reactions, including death due to bronchospasm in patients with asthma reported following administration of some ophthalmic beta-blockers. As dorzolamide contains a sulfonamido group, which is absorbed systemically, adverse reactions can include Stevens-Johnson syndrome and toxic epidermal necrolysis. Discontinue Eylamdo if signs of serious reactions or hypersensitivity occur. When on beta-blockers, patients with history of atopy or severe anaphylactic reaction may be more reactive to repeated challenge with allergens and unresponsive to usual doses of adrenaline used to treat anaphylactic reactions. Use of two topical beta-adrenergic blocking agents not recommended. Use with oral carbonic anhydrase inhibitors not recommended. If discontinuation needed in patients with coronary heart disease, withdraw therapy gradually. Administer with caution in patients subject to spontaneous hypoglycaemia or labile diabetes, as beta-blockers may mask signs and symptoms of acute hypoglycaemia. May mask signs of hyperthyroidism so withdraw slowly to avoid worsening of symptoms. Caution in patients with corneal diseases as dryness of eyes may occur. May block systemic beta-agonist effects of adrenaline (for surgery, anaesthetist should be informed). Symptoms of myasthenia gravis may be aggravated. Patients with prior history of renal calculi may be at increased risk of urolithiasis. No studies in patients with acute angle-closure glaucoma. Use with caution in patients with pre-existing chronic corneal defects and/or a history of intraocular surgery. Choroidal detachment reported with administration of aqueous suppressant therapies after filtration procedures. Diminished responsiveness after prolonged therapy reported. Should not be used if contact hypersensitivity to silver as dispensed drops may contain traces of silver from container. No studies in patients wearing contact lenses. **Interactions:** Potential for additive effects resulting in hypotension and/or marked bradycardia when administered concomitantly with oral calcium channel blockers, catecholamine-depleting medicines or beta-adrenergic blocking agents, antiarrhythmics, digitalis glycosides, parasympathomimetics, guanethidine, narcotics, and monoamine oxidase (MAO) inhibitors. Potentiated systemic beta-blockade reported during combined treatment with CYP2D6 inhibitors. Mydriasis resulting from concomitant use with adrenaline has been reported. May increase hypoglycaemic effect of antidiabetic agents. May exacerbate rebound hypertension following withdrawal of clonidine. **Pregnancy & Lactation:** Should not be used during pregnancy or lactation. If administered until delivery, monitor neonate carefully during first days of life. **Side effects:** For full list of side effects consult SmPC. 'Very Common' 'Common' and 'Serious' side effects included. Very common (≥1/10) side effects: burning, stinging and dysgeusia. Common (≥1/100 to <1/10) side effects: headache, conjunctival injection, blurred vision, corneal erosion, ocular itching, tearing, eyelid inflammation, eyelid irritation, signs and symptoms of ocular irritation including blepharitis, keratitis, decreased corneal sensitivity, dry eyes, sinusitis, nausea, asthenia/ fatigue. Uncommon Serious (≥1/1000 to <1/100) side effects: depression, iridocyclitis, bradycardia, dyspnoea, urolithiasis. Rare Serious (≥1/10000 to <1/1000) side effects: angioedema, anaphylaxis, myasthenia gravis exacerbation, cerebrovascular accident, cerebral ischaemia, corneal oedema, congestive heart failure, cardiac arrest, heart block, Raynaud's phenomenon, respiratory failure, bronchospasm, Stevens-Johnson syndrome, toxic epidermal necrolysis, systemic lupus erythematosus, choroidal detachment following filtration surgery. Frequency not known: Serious (frequency cannot be estimated) side effects: atrioventricular block, cardiac failure, hallucinations. **MA number:** PL35533/0117 **Cost:** £13.99 for 20mg/ml dorzolamide + 5mg/ml timolol x 5ml. **MAH:** Aspire Pharma Ltd, Unit 4, Rotherbrook Court, Bedford Road, Petersfield, Hampshire, GU32 3QG. **Legal category:** POM. **Date reviewed:** April 2020. **Version number:** 1010368208 v 5.0

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Long-term follow up of Boston keratoprosthesis type one in children

by **O'Byrne C, Pilson, Qistina, O'Keefe M**

Congenital corneal opacities in children affect 3 in 100,000 newborns. With the addition of other acquired conditions and secondary corneal opacity causes, the rate is even higher (Bermejo & Martinez-Frias 1998). If left untreated, they lead to amblyopia. However, these cases are typically complicated with other conditions that also affect the final visual outcome.

Historically, penetrating keratoplasty has been the mainstay of treatment in these cases. It is however a high risk and difficult procedure in this population in the preoperative, intraoperative and the postoperative stages (Dohlman Thomas et al) making an alternative like Boston keratoprosthesis an attractive option to potentially retain the vision (Dana et al 1995). Boston keratoprosthesis type-1 was approved for use in 1992 and has been used to manage different causes of corneal opacities not suitable for penetrating keratoplasty or repeated failed corneal graft rejections. It has been successful in adult population with an improvement of visual acuity with 67% survival rate at 7 years (Srikumaran et al 2014).

Methods

This is a retrospective case series of nine children who received Boston keratoprosthesis type-1 from August 2003 to September 2016.

Patient history and examination data was available. In patients who were able to cooperate, axial length was predetermined using an IOL master. A and B scans were performed prior to surgery in those who could not cooperate. Intraocular pressure was recorded using Perkins tonometer (Haag-Streit, UK, Harlow, UK) I-care (BMB medical, Trévoux France) or digital examination. The surgery was performed in the standard manner (Zerbe et al 2006). Simultaneous lensectomy and anterior vitrectomy were performed in phakic patients. Anterior vitrectomy was also performed in aphakic patients. None of our cases had concurrent retina or glaucoma surgery at the time of implantation.

Patient number	Age at surgery	Primary diagnosis	Indication of KPRO	Past treatments	Pre op BCVA	Post op BCVA	Best postop BCVA	Follow up period (months)
1	16 years	Congenital aniridia	Subepithelial fibrosis of cornea	P, AV, Cy	CF	5/60	6/60	132
2	18 months	Peter's anomaly, isolated aniridia, congenital glaucoma	Corneal opacity	T, Cy	NA	NA	NA	52
3	6 years	Peter's anomaly, congenital aniridia, congenital cataract	Failed PK	P, PK, AV	PL	CF	CF	113
4	6 years	Peter's anomaly, congenital aniridia, congenital cataract	Failed PK	P, AV (PPV and SO)	PL	PL	PL	173
5	16 years	Congenital aniridia	Failed keratolimbal stem cell transplant	P, KLSC	HM	CF	6/60	120
6	3 years	Peter's anomaly	Failed PK	AV, PK, T	HM	3/60	3/24	127
7	3 years	Peter's anomaly	Failed PK	AV, PK, T	HM	CF	CF	124
8	9 years	Peter's anomaly, sclerocornea	Failed PK	AV, P, PK	CF	1/60	3/60	120
9	9 years	Peter's anomaly, sclerocornea	Failed PK	P, PK	PL	PL	HM	100
10	12 months	Peter's anomaly	Failed PK	PK	PL	6/60	6/60	18
11	14 months	Peter's anomaly	Failed PK	PK	PL	HM	HM	20
12	35 months	Peter's anomaly	Failed PK	PK	NPL	NPL	NPL	12
13	3 years	Congenital glaucoma	Opaque cornea	AV	PL	PL	PL	57

Table 1

Summary of general information, clinical features, visual changes and post-Boston Keratoprosthesis Type-1 outcome in our cohort.

F: Female

M: Male

PK: Penetrating keratoplasty

P: Phacoemulsification surgery

AV: Ahmed valve

KLSC: Keratolimbal stem cell transplantation

Cy: Cyclodiode

T: Trabeculotomy,

CF: Counting fingers

NA: Not available,

PL: Perception of light

HM: Hand movement

NPL: No perception of light

RPM: Retroprosthetic membrane

KPRO: Keratoprosthesis

PPV: Pars plana vitrectomy

SO: Silicone oil

A large hydrophilic contact lens (Kontur Kontact Lens, Hercules, CA, USA) was placed at the end of the surgery to prevent corneal epithelial dessication and only removed when required for cleaning.

Post-operatively, all patients were prescribed topical moxifloxacin four times daily and topical prednisolone acetate 1% six times daily and tapered as necessary. Both drops were continued indefinitely. Postoperative data collected included best corrected visual acuity, subjective measurement of IOP and appearance of the keratoprosthesis. Follow up time was defined as the length of time from keratoprosthesis implantation surgery to the last data collection. Retention failure was defined by device extrusion or removal. Any further surgical procedures and postoperative complications were recorded. Kaplan Meir was used to assess survival rate of the Boston keratoprosthesis type-1 in our cohort.

Results

Thirteen keratoprosthesis were implanted in nine patients. Surgery was done in seven male eyes (54%) and six female eyes (46%). Mean follow up was 89.38 months (range 6.0-173.0 months). Mean age was 6.1 years (range 1.0-16.0 years). Baseline features of patients were summarized in Table 1.

Indications

The most common indication for the surgery was a prior penetrating keratoplasty, failed corneal graft in nine eyes (76.9%). No child had more than one keratoplasty. One eye in a patient with aniridia (7.7%) had a failed keratolimbal stem cell transplantation procedure. The remaining three eyes (23.1%) had Boston keratoprosthesis as their primary procedure as deemed high risk for failure of keratoplasty. In this study ten (76.9%) eyes had Peters anomaly, two (15.4%) had congenital aniridia and on (7.7%) had congenital glaucoma.

Eight eyes in our cohort had had glaucoma surgeries prior to the implantation of the device including Ahmed valve implantation in 87.5% (7), trabeculotomy in 37.5% (3), goniotomy in 25% (2) and cyclodiode in 25% (2). Other procedures performed prior to keratoprosthesis surgery include phacoemulsification in 46.1% (6) and 20 gauge pars plana vitrectomy (PPV) for retinal detachment repair in 7.7% (1).

Visual outcome

Visual acuity prior to the keratoprosthesis surgery were counting fingers (CF) in two eyes, hand movement (HM) in three, seven with perception of light (PL) and we were not able to document an accurate visual acuity in one eye. 75% (9) of the eyes treated had an improvement of vision, 16.7% (2) had no change in vision and 8% (1) had worse vision on follow up.

In our group, one eye had an intraoperative complication and developed suprachoroidal haemorrhage which was noted at the end of the surgery. It was self-limited and no active management was required.
The keratoprosthesis was clear and retained until the final visit but had no visual potential with no perception of light (NPL) vision.

Complications

During the postoperative visits, the most common early complication was retroprosthetic membrane (RPM) which affected three eyes (23.1%). One (7.7%) of the eyes also developed ectasia of the ectatic keratoprosthesis and required removal. Three eyes (31%) developed retinal detachment at six and eleven years after the keratoprosthesis surgery and were managed by a Vitreoretinal surgeon using a 20-gauge pars plana vitrectomy and silicone oil insertion. None of our cases developed endophthalmitis or keratitis throughout the study (Table 2).

Kaplan-Meier analysis showed a 1 year survival rate of 92.3% and reduced to 84.6% at the 2nd year. At the final follow up, ten out of thirteen (76.9%) keratoprostheses were retained.
Only one eye developed complication associated with the keratoprosthesis procedure, which was a severe ectasia and required removal. This was repined with a subsequent tectonic penetrating keratoplasty. Another eye had a blunt trauma at home that resulted in a spontaneous extrusion but the keratoprosthesis was successfully repositioned.

Boston keratoprosthesis type-1

There are a limited number of paediatric studies on Boston keratoprosthesis type-1. The largest study to date is by (Aquavella et al. 2016) with twenty one eyes followed by (Fung et al 2018) with eleven eyes. These studies have similar primary diagnoses. Nevertheless, they show contrasting complications and retention rates.

To date, our study has the longest mean follow up for paediatric cases that received the Boston keratoprosthesis type-1 with 89.3 months in comparison with other similar studies with shorter mean follow up at nine to fifty two months. This provides a good insight into both early and late outcomes. The main aim of the procedure is to reinstate good clarity of the visual axis in these patients and to improve their vision. In our study, 69% of the eyes had an improvement of their vision especially cases 1, 5, 6, 8 and 10 which had an improvement from counting fingers, hand movement or perception of light to between 20/160 to 20/400. Some cases in our study (16%) had no change in vision before and after the Boston keratoprosthesis surgery

Table 2

Patient number	Complications	Further surgery
1	None	No
2	None	No
3	Tractional retinal detachment	No
4	Retroprosthetic membrane	Pars plana vitrectomy with silicone oil (4 times)
5	Retroprosthetic membrane	No
6	None	No
7	Tractional retinal detachment	Pars plana vitrectomy with silicone oil
8	Retroprosthetic membrane	YAG laser capsulotomy
9	Tractional retinal detachment	No
10	Ectatic keratoprosthesis	Removal of kPRO Replacement with corneal graft
11	None	No
12	Intraoperative suprachoroidal haemorrhage	No
13	Blunt trauma at home. Successfully positioned.	No

Summary of information on complications and further surgery required for Boston Keratoprosthesis Type-1 cases in our cohort.

mostly from their underlying pathology with advanced glaucoma and pre-existing optic neuropathy. However, they managed to retain clear visual axis of the keratoprosthesis. This is in an agreement with other studies where very limited visual improvement was observed in paediatric cases when comparing visual acuity before and after Boston keratoprosthesis type-1 implanatation (Table 2). Progression of glaucoma is considered a significant cause of visual loss after implantation. In our series, cases with glaucoma had Ahmed valve insertion, trabeculotomy or cyclodiode laser performed prior to implantation of the Boston keratoprosthesis. None of our cases had progression of their glaucoma.

Most of our complications were in eyes with Peters anomaly with a retroprosthetic membrane in 23.1%, which was comparable with the study by (Aquavella et al 2016) at 23.8% but significantly less compared to the study by (Fung et al 2018) at 81.8%. A study of adults with Boston keratoprosthesis by (Rudinsky et al 2016), found that aniridia and infectious keratitis had the highest risk of retroprosthetic membrane formation. The low numbers in our group could be explained due to the small number of eyes with aniridia and that may be the risk factor for development of the membrane as these eyes are profibrotic. In our series, four eyes developed retinal detachment. These occurred later and in patients with Peter's anomaly.

Stromal melt or corneal ectasia is a well-documented complication of keratoprosthesis type-1 and development in these patients can vary between 2.4% to 45.5%. Typically, this is described following infectious or non-infectious keratitis, exposure keratopathy and endophthalmitis (Chew et al 2009) (Duignan et al 2015). It was also more common in the past in cases with the polymethyl methacrylate (PMMA) keratoprosthesis system with a solid backplate as there were no perforations for nutrients to flow into the keratocytes from the aqueous humour. It still occurs but mainly due to inflammatory processes, which release collagenases and matrix metalloproteinases to the corneal surface. Management consists of non-invasive treatments depending on the causative event. In one case in our study, ectasia of the keratoprosthesis lead to device extrusion and required surgical treatment. We managed the case with a successful penetrating keratoplasty. However, (Ahmad et al 2016) in their large study on re-insertion of Boston keratoprosthesis type-1 repeated the procedure in 75% of extrusion secondary to corneal melt but found that 19% of these had a repeat extrusion.

Conclusion

The management of congenital corneal opacities remains a challenge that requires complicated surgery with guarded prognosis. A limitation of this study is that it is retrospective with small numbers of children, yet it demonstrates that in selective paediatric patients with corneal opacification, Boston keratoprosthesis type-1 could be a good option as both a primary corneal opacities and as a secondary procedure after failed keratoplasty. This device is a good alternative to improve vision in children who are otherwise not amenable to any other procedures. The visual prognosis depends on pre-existing conditions. This is in contrast to (Fung et al 2018). As a result of their higher complication rate they do not recommend the use of the keratoprosthesis in the paediatric population. We believe that management of corneal opacity with Boston Keratoprosthesis type-1 has advanced our management in these children, however, the development of retinal detachment particularly in the older children with Peters Anomaly affects the visual prognosis and raises a further surgical challenge.

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A patient's perspective

by **Shakira Elliott**

My condition was diagnosed in 2016. My journey to being diagnosed was extremely challenging. When my problems began, I started to notice that my eyes were really, really red they felt slightly dry, but I mostly noticed the redness. Then I started to have a lot of pain in my eyes. I went to an optician who was not sure what was going on and suggested that I go to see a specialist in hospital. Unfortunately, I was not seen for two months and I was in excruciating pain. I was very scared and frightened, and I did not know what was happening to me.

I eventually went for a hospital appointment and the ophthalmologist diagnosed me with meibomian gland dysfunction, possible ocular rosacea and evaporative dry eye.
At the time I did not get a full understanding of my illness, only that it was chronic.

I was sent a way with the suggestions of using an eye bag and doing hot compresses and to put drops in my eyes.

I complied with the instructions, but I did not get anywhere. In fact, I was just getting worse and worse. I then went back to hospital and this time they gave me oral doxycycline 100mg/day and cyclosporine eye drops. I started to use these, and things got a little bit better, but I was still in a lot of pain.

Then my journey to try to get better and to try to understand more started. During this time, broken as a person, I was very scared. I was unable to do anything in my life, my career and unable to use a screen. I was in a place where I did not want to go out because of what I looked like. I was in constant pain and felt like I was losing control.

I joined an online support group. There were very few patients at the time, but it has grown immensely since. I put a post-up about my condition and a lovely lady recommended that I go to see a doctor in London, and that he has a lot of knowledge about dry eye.
I found the doctor very calm and reassuring, he spent way more time with me than perhaps was even needed. I gave him as much information as possible and told him about my routine.

We decided on a course of treatment. The treatment we decided to do were gland expressions and "MiBoFlo".
He found that my glands were jampacked and had been for a very long time. This had amounted to a lot of gland loss on me, with my condition some of the glands had atrophied and no longer existed.
We started to unblock the remaining glands that were there and carried on with my Doxycycline 100mg/day, cyclosporine eye drops and preservative free ocular lubricants. I attended these treatments every 3-4 weeks, I found that at week 3 or 4 the pain would be back because the glands would be blocked again. I initially stayed away from IPL, I was concerned about my skin and skin tone and worried I would get permanent hyper pigmentation marks. However, after much consideration I decided to go ahead and try the IPL treatment and I continued to see the same doctor while having IPL. When I first started the IPL I didn't notice too much after the first two treatments, but after my third session, I started notice some improvement. It had not taken my condition away, but I noticed some improvement.

After my in-depth research on why this is helping me more than other treatments, I think it is to do with the fact that I also suffer from ocular rosacea. Before my journey started, I never knew I had ocular rosacea, but I can now see it clearly on both my upper and lower lids.

What I have learned about this other disease is that there is a lot of triggers, I am still learning them today. Anything that causes the body to have inflammation is a trigger for ocular rosacea.

With the evaporative dry eye, the triggers are hot weather, sun, wind, aircon, fans and sometimes cold weather as well. I've even had to stop doing hot compresses because the heat triggers the ocular rosacea, when my rosacea reacts my glands blocks too.
My journey is continuing with my doctor, he explains things very clearly. He also has an extremely attenuative team, they listen to me when I am in pain and when I am unable to see the doctor for a couple of weeks.

During the Covid 19 lock down, all the private clinics in London were shut and I was unable to receive my usual IPL treatment.

The condition has taken a lot from my life I grieve for my previous life, almost every day.
I can no longer wear make-up, I can no longer wear lashes, I can no longer be in the sun to get a tan, I can no longer work on a computer and have the career I used to have.
I have not got on an aeroplane since I was diagnosed five years ago, and I am only in my mid-thirties. My condition has also taken away some of my favourite hobbies which were water-skiing and horse riding. I cannot do this anymore due to the dust and water.

However, I am still feeling positive that I have good team around me that are attending to my needs and that I am able to receive my IPL and gland expression. I feel that when a doctor expresses your gland after IPL, if they really take their time and do it properly, the treatment is more successful.

My mental health has been affected by my condition with anxiety and depression. I have a real 'Image issue', as I do not want to be seen because my eyes are so red and its permanent. What I find is that when there is a doctor that really understands and really hears you, and tries to help you out of the pain, it really does make all the difference.

I do hope to continue my journey searching and being involved with as much dry eye research as I possibly can. This is a chronic condition that is not labelled as a disability in the UK, and it really should be.

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A Chance for Change

by **Nathan Little**

In the wake of the novel Coronavirus, the global health system has been starkly reminded of the current limitations of face to face patient care and for the festering need for a better and more efficient digital solutions.
It is painfully evident that the status quo healthcare within the new normal will no longer be sufficient and new, more robust, digital, economic and remote solutions are necessary.
The rapid and global spread of the Coronavirus is a direct result of our connected world and thus its digital reach will be an integral part of the solution moving forward.

UK ophthalmic numbers are a clear reminder of the need for a revolution in patient care and the addition of the Coronavirus has only escalated and exacerbated the need. The population of the UK is currently 66 million, and based on a report from 2013, 2 million live with sight loss so great their daily lives are affected which equates to roughly 3% of the total population.[1,2]
By 2030 it is estimated that 2.7 million Britons will live with some type of sight loss, by 2050 it could be as high as 4 million and in 50 years it is estimated that 8.2 million Britons will be over the age of 65, a population similar to London.[2,3] Some projections show a 10 year demand increase of 25%, 30% and 22% for cataract, medical retina and glaucoma services respectively.[4]
In 2016/2017 Ophthalmology was one of the highest ranked specialty for services in the NHS with 7.6 million hospital provider attendances per year, with a 30-40% increase in demand projected over the coming two decades.[5,6,7] To meet the demand of these growing numbers of populations an estimated 22% increase in consultant posts was required from 2018 to 2020 alone.[5]

It has clearly been established the need for eyecare in the UK is growing and the demand out ways the supply, compound on top of this numbers the inefficiencies in patient care due to Coronavirus and the existing pandemic situation and the potential outcome is alarming.
To overcome these challenges a multifaceted approach is needed, one that addresses current inefficiencies in patient care, the inability (or unwillingness) to see patients face to face and the need to manage medical eyecare through partners/co-managed care.

Firstly, Healthcare systems in both the UK and globally (either private or institutional) will need to reframe their point of view and focus on new and experimental clinical workflows that provide proper support and reimbursement for remote triage and telehealth services. A clear initiative will need to be driven to move away from “care as we know it” – face to face or in office visits, crowded waiting rooms and live referrals. The new care structure must avoid the spread of the virus to the at risk, uninfected, and vulnerable patient cohort while also providing the proper level of care remotely and in person when needed. A key element will be seeing the appropriate patient at the appropriate time via the proper method.
New processes and procedures will need to be formed to guide and inform healthcare

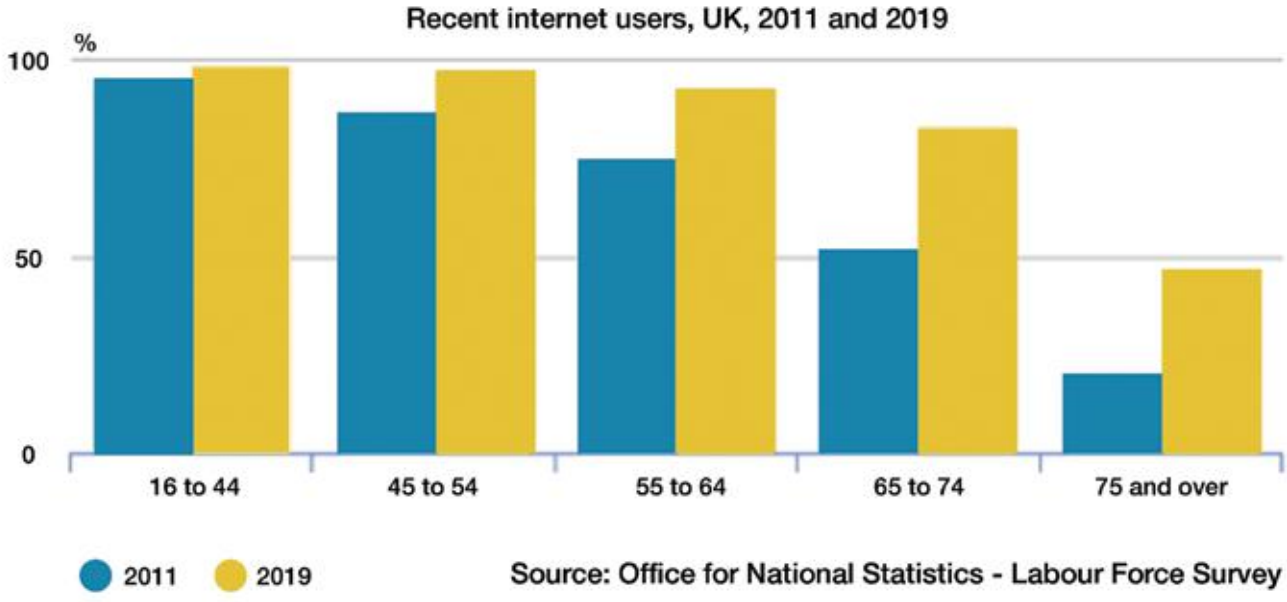
professionals based on new and innovative techniques to properly triage patients. The most recent example is CUES, Covid-19 Urgent Eyecare Service in England, which aims to minimize risk of delivering care, promote remote triage and community lead eyecare while attempting lower the burden on the NHS and GPs. This type of system is potentially the first step in a longer strategy of transitioning to a more efficient and effective care plan for minor eye conditions and ocular surface diseases.

In addition to changing the mindset and processes related to clinic workflow, new technologies will need to be rapidly adopted and implemented. This wave of new healthcare innovation adoption will be driven by necessity but will require a balance between security, safety, usability and patient reach or persistent touch. In office patient datapoints will soon be one of many that will be captured via a myriad of in office and out of office technology touch points that, if applied properly, have the ability to provide great insights into patient health. On the market today are a myriad of technologies for telemed and tele-health. The best solutions will bridge the gap between clinic and home care, offer tools to aid and inform both physician and patient, and will be simple and secure.

Patient care will need grow to be co-managed in a more efficient and effective manner. Current system inefficiencies in the in all healthcare referral systems will need to be addressed to enable better flow of pertinent patient data, images, in coming patient visit requests. Primary eyecare for patients will need to become more robust, and will need to occur outside the NHS trust via local specialty clinics, trained in eyecare that can provide pertinent information needed to decide if a secondary/consultant referral is necessary. This strategic alignment of internal and external resources for referrals will hopefully help manage the growing patient load and allow non-life or sight threating conditions to be allocated to the appropriate agent.

Lastly, it will be imperative to meet patients digitally. A recent study by the office of national statics found that 91% of adults in the UK were online.[9] Furthermore, from 2011 to 2019 internet usage increase from 52% to 83% for the 65 to 74 age group and 20% to nearly 50% for the 75 and over.[9]
The growing number of internet users of all ages is a direct result of the multi-generational reach of the web and its ability and potential to be the great equalizer. Now more than ever it is imperative to adopt and implement technologies that tap into this user base and leverage it to move healthcare forward. Eyecare providers must pivot to interact with patients digitally and a new business model must be able to support the digital interaction patients will expect. The economic downturn from the novel virus has changed the business landscape and eyecare professionals must adopt to the new normal.

Figure 1: Since 2011, the 65 to 74 years age group has seen the largest increase in recent internet use.



The key is focusing on long term and sustainable business practices, reevaluating cash flow and reallocating funds to new and innovative technologies and digital marketing techniques that can drive brand awareness. A practice's online presence is the **new front door** to the business and it is critical that the website and social media make an impact in reaching the patient cohort. A recent study by Hostingtribunal found that only 6.9% of Gen Z shoppers say they purchase products in physical stores, 55% of online readers spend less than 15 seconds on a web page and 75% of internet users never click past Google's first page.8 So, in the Covid age, how will your patients find you? And if they do find you how will you interact, treat, manage and conduct business with them online? The eyecare profession and industry have tailwinds like never before driving the digital revolution in patient care and management, how we solve the problem will be a case study for the ages.

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Ocular surface optimization in refractive surgery clinics

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INTRODUCTION

A careful preoperative assessment and optimisation of the ocular surface and tear film is absolutely imperative before performing any refractive surgery to minimises risk of adverse outcomes. Tear film is the first refractive interface of the eye with the largest change in refractive index occurring on this surface, giving tear film the greatest optical power of any ocular surface. Tear film irregularities and ocular surface disease can therefore significantly affect many aspects of refractive surgery, including preoperative measurements, refractive outcome, patient satisfaction and severity and duration of dry eyes post-surgery.

A poor tear film will result in pre-operative measurement error in keratometry, topography as well as biometry measurements. In fact, discrepancies in the various measurements, such as keratometric readings, biometry, and topography are frequently seen in these patients.

For example, keratometry or topography may show astigmatism due to tear film instability which may otherwise not be present or be of different magnitude and/or axis. These inaccuracies will lead to poor refractive outcome and decrease patient's satisfaction. In fact, Ocular surface instability is the leading cause of unhappy refractive patient and increases the chance of slow recovery and need for enhancement (3,4). A careful preoperative assessment allows us not to only identify those patients who should be excluded from refractive surgery but also enables us to identify many patients with poor ocular surface who can still be excellent candidates for refractive surgery provided the ocular surface is appropriately managed preoperatively. Optimisation of ocular surface may be achieved in matter of 2 to 3 weeks in most patients while it may take many months in other patients. This depends on severity and cause of the dry eyes as well as treatment modalities used. Optimisation is generally faster when artificial tear drops are combined with other treatment modalities. In patients where ocular surface instability continues to persist despite treatment or in patients who presents with severe dry eyes refractive surgery can be considered a contraindication.

DEFINITIONS

- **Ocular surface**: this is comprising the structures of the ocular surface and adnexa, including the tear film, lacrimal glands, Meibomian glands, cornea, conjunctiva & eyelids (1).

- **Dry eyes**: this is defined as a multifactorial disease of ocular surface due to abnormal homeostasis of the tear film, resulting in ocular symptoms and potential damage of the ocular surface. Although dry eye may have various aetiologies, hyperosmolarity of the tear and inflammation of the ocular surface are final common pathways in the pathogenesis of dry eye (1). The disease is characterised by a vicious cycle of tear film instability and hyperosmolarity which lead to increased ocular surface inflammation, damage and neurosensory abnormalities.

- **Tear film**: Traditionally the tear film has been described as having three distinct layers (mucin, aqueous and the lipid layers). However, the more recent recommendation describes tear film as a two-model phase consisting of a lipid layer overlying a muco-aqueous phase (1). The lacrimal and accessory lacrimal glands secrete the aqueous tear and its proteins, the conjunctival epithelial cells and goblet cells secrete the mucin component of tears, and the Meibomian glands produce the lipid layer of the tear film.

Risk factors for dry eyes

- Asians race, women and older patients are at increased risk of DED

- Other consistent risk factors include MGD, connective tissue disease, Sjogren syndrome, androgen deficiency, computer use, contact lens wear, certain environmental conditions (such as pollution, low humidity) and medication use (for example, antihistamines, antidepressants, anxiolytics, isotretinoin and oestrogen replacement therapy) (1)

- Probable risk factors include diabetes, rosacea, thyroid disease, psychiatric conditions, low fatty acid intake, medications (e.g. anti-cholinergic, diuretics, b-blockers)

- Any previous ocular surgery including cataract surgery, lid surgeries, botulinum toxin application and cosmetic procedures can also increase risk of dry eye

Mechanisms of postoperative dry eyes

- Disruption of corneal sensory nerves: Both intraocular surgery as well as laser refractive surgery causes disruption of corneal afferent fibres to the lacrimal unit hence decreasing the aqueous tear production. Reduced afferent stimulation can also lead to decrease blink rate and an increase in inter-blink intervals. This leads to increase exposure time of the ocular surface as well as reduces the meibum lipid components of the tear film, hence increasing evaporative dryness.

- Increase in ocular surface inflammation: There is a reduced tear clearance after laser refractive surgery (5) which may partly explain the increase osmolarity. Cytokines such as IL-1, IL-6 and IL-8, and MCP-1 are expressed by corneal fibroblasts when exposed to the excimer laser.

- Laser also lead to release of proinflammatory mediators such as neuropeptide Y, substance P, and calcitonin gene-related peptide from damaged nerves at ablation interface as well as boundaries of the flap thereby irritating and damaging ocular surface. This is called neurogenic inflammation.
  The neuropeptides have been known to lower sensory thresholds, allowing patients to perceive dry eye symptoms more readily (6, 7), and or experience neurogenic phantom type of pain even in absence of any significant dry eyes due to abnormal and excess branching of nerve endings

- Alteration of ocular surface anatomy: immobilisation of the eye via suction ring during LASIK has been shown to cause conjunctival hyperaemia, infiltration of immune cells and reduction of goblet cell density within the conjunctiva (8).

- Laser refractive surgery can cause significant alterations to the corneal curvature leading to changes in epithelial thickness and alters tear wetting as the lids move over the modified ocular surface.

- Other mechanisms such as the use of preserved eyedrops may contribute to epitheliopathy or corneal toxicity that is indistinguishable from dry eye (9). The use of povidone iodine solution preoperatively may contribute to compromised ocular surface (10). The adverse effects of iodine may be minimized by diluting the iodine solution

Incidence of postoperative dry eyes

- Based on symptoms or signs assessed at least 6 months post surgery, the incidence of post-LASIK dry eye ranges from 8.3 to 48% (11 to 16).

- There is no significant difference in either symptoms or tear function between microkeratome and femtosecond LASIK procedure (23) or between horizontal versus vertical LASIK flap hinge position (22).

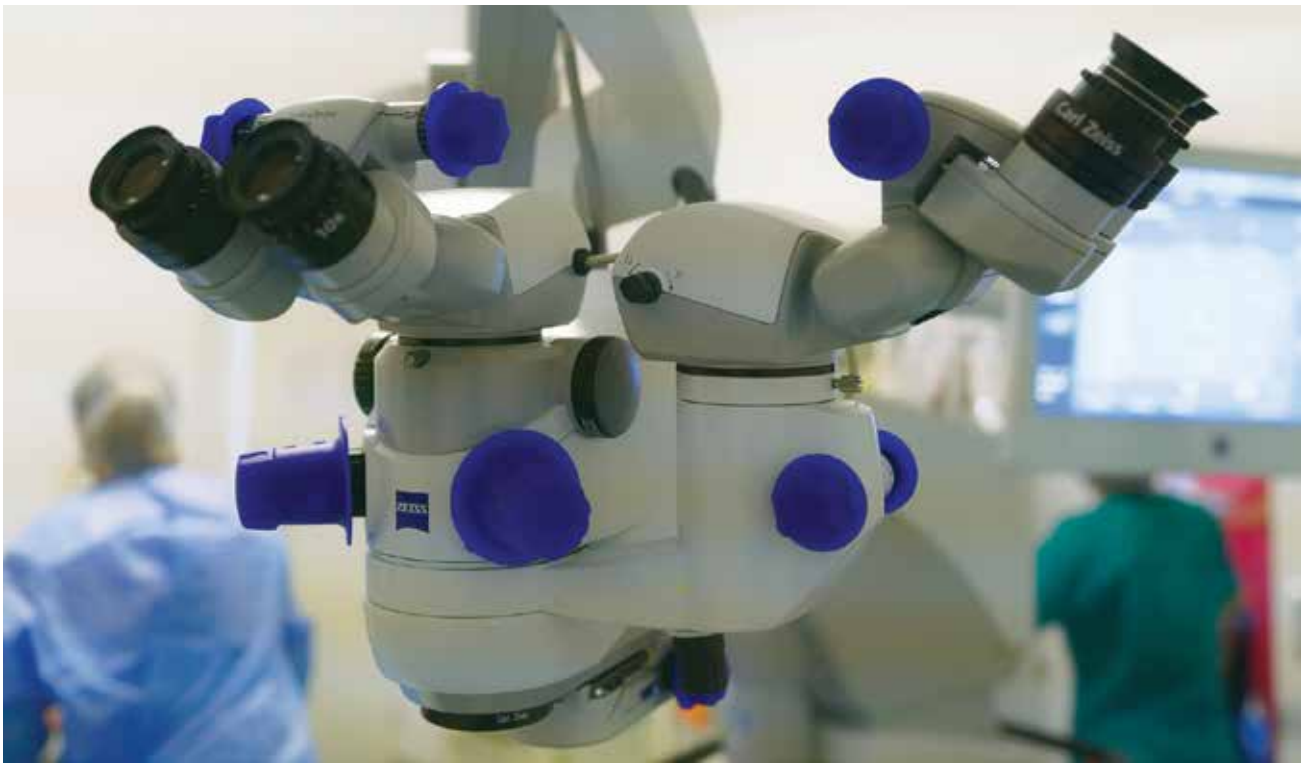
- Compared to SMILE, femtosecond LASIK is associated with significantly more dry eye symptoms and lower corneal sensitivity at 6 months post-surgery (17). However, compared with LASEK and epiLASIK, LASIK patients showed better postoperative tear secretion (20,21).

- PRK Patients have a better postoperative tear function but they suffer more severe dry eye symptoms and poorer wound healing compared to LASIK patients (18). This discrepancy between signs and symptoms may be explained by the facts that corneal sensitivity are more significantly impaired in LASIK patients compared to PRK (19) hence the LASIK patients are less sensitive to the symptoms.

- Corneal nerve regeneration occurs 3-6 months post PRK while it may take 6-12 months post LASIK. regeneration tends to be more rapid in SMILE due to retention of sensory neurones within the thicker cap.

Clinical evaluation for dry eyes

Clinical evaluation starts with a good history. Many patients seeking refractive surgery are actually dry-eye patients who become intolerant to contact lens wear and hence turn to refractive surgery for visual rehabilitation. Therefore, any mention of contact lens wear intolerance in history should raise high suspicion for pre-existing dry eyes. Also, long term contact lens wear especially the rigid lenses, can lead to decrease



corneal sensation which would have an additive effect to reduced sensitivity seen post LASIK (38).
Elicit if there is any other risk factors for dry eyes as above. Assess dry eyes symptoms using questionnaires such as the Dry Eye Questionnaire-5 (DEQ-5) (Figure 1) or Ocular Surface Disease Index (OSDI) (figure 2) is very helpful. A score of 6 or more in DEQ-5 or a score of 13 or more in OSDI is considered positive for DED symptoms. A positive score with above questionnaires should trigger a more detailed examination for clinical signs of DED. External examination should include evaluation of eyelid closure for conditions such as incomplete blink, lagophthalmos, entropion, ectropion, or eyelid notching. On slit-lamp examination, notation should be made of blepharitis, meibomitis, and tear-film quantity and quality. Ancillary testing for dry eyes include NIBUT, Osmolarity, FBUT, ocular surface staining, Lissamine green, Schirmer strip and corneal sensation which are performed in the order they appear. It is no necessary to perform all these tests but as a minimum a TBUT (NITBUT or Fluorescein TBUT), tear meniscus hight and ocular surface staining is required. When these tests are negative but dry eye still suspected additional tests can be undertaken to improve sensitivity of diagnosing DED. Below is a list of some of most commonly ancillary testing for dry eyes:

- **Non-invasive break-up time (NIBUT) test**: In this test a target such as graticules are projected onto the tear film which acts as a convex mirror. The time taken to see any discontinuity or distortion of the tear film since last complete blink is the NIBUT (figure 3). It can be measured by custom-built devices such as the Tearscope Plus (Keeler Instruments Inc, Broomall, PA, USA) or keratometry devices such as the Oculus Keratograph (Oculus Optikgeräte GmbH, Wetzlar, Germany) and the Tomey TMS-1 videokeratoscopy instrument (Tomey, Cambridge, MA, USA).

- **Tear Osmolarity**: The FDA-approved Tearlab Osmolarity System (TearLab Corporation, San Diego, CA, USA) allows point-of-care assessment of tear osmolarity. It has a sensitivity of 87–95% for severe dry eye with a specificity of 81–88% (25,27) and a lower variability (26) than other commonly-used markers of dry eye (TBUT, Schirmer, staining). An osmolarity value equal to or higher than 308 mOsm/L in either eye or a difference of 8 mOsm/L between each eye is indicative of DED.

- **Fluorescein BUT**: Use a fluorescein strip and wet it with one drop of non-preserved saline, shake off any excess fluid and gently touch the inferior tarsal conjunctiva just below the posterior margin of lower lid. Ask the patients to blink several time to spread the fluorescein over the ocular surface then ask them to stop blinking. The time between the last blink an appearance of the first break (randomly distributed dry spot or hole) in the precorneal fluorescein tear film is the TBUT. It is imperative not to instil any drops in the eye for this test as it can artificially hasten the TBUT.
The arbitrary cut off of 10 seconds appears to be quite specific in screening patients for dry eyes (28).

- **Ocular surface staining**: This is most commonly done with fluorescein dye after being applied as above. The staining can be graded using different. Other dyes such as lissamine green are less commonly used but can be useful addition to fluorescein dye in cases where fluorescein staining is negative but dry eye is still suspected. In patients with suspected dry eyes but negative fluorescein staining, it may be useful to use lissamine green dye.

- **lissamine green dye**: This stains conjunctiva better.
The amount of staining (figure 3) can be graded using different scales such as Oxford Grading Scale (figure 2).
It is important to wait at least a few minutes after application of fluorescein before examining the eye as the dry eye areas of the cornea absorb the dye slowly.

- **Schirmer test**: Schirmer test has been widely used in clinical practice for assessing tear production. The 35mm Schirmer test is folded at the notch and hooked on the lateral 1/3 of the lower eyelid for 5 minutes. It is classically performed without anaesthesia (Schirmer I). However, there are extensive criticism of the effectiveness of this technique as the invasive nature of this technique results in excessive reflex tearing, and hence a lack of sensitivity and repeat ability limits the value of the test in clinical practice (28). A cut-off value of 5.5 mm strip wetting in five minutes correctly diagnose 83% of patients with dry eyes (29). A Schirmer test of 6-10mm is considered dry eye suspect and those with over 10mm can be considered normal.

- **Corneal sensitivity**: This may be performed with a Cochet Bonnet esthesiometer at 5 location, (centrally and the four quadrants of the cornea).

- **Tear meniscus height**: When checking tear meniscus height it is important not to initiate reflex tearing as this can increase tear the tear flow rate by up to 100 times. Also avoid excessive or prolonged use of illumination which can lead to artificial drying and lower measured tear meniscus. A crude way of quantifying the tear meniscus would be graded as minimal, normal or excessive

Diagnosis of DED as per DEWS report

- First exclude other causes that account for patient's ocular symptoms or clinical signs

- A diagnosis of DED requires presence of both symptoms of dry eyes as well as demonstrable clinical sign of the disease. Symptomatic patients with no clinical signs are differentiated into pre-clinical ocular surface disease or neuropathic pain (non-ocular surface disease). Conversely, asymptomatic patients with clinical signs are differentiated into those with poor corneal sensitivity or those with prodromal signs who may be at risk of developing manifest DED with time or provocation such as ocular surgery.

- Assess symptoms using questionnaires such as the Dry Eye Questionnaire-5 (DEQ-5) (Figure 1) or Ocular Surface Disease Index (OSDI) (figure 2). A score of 6 or more in DEQ-5 or a score of 13 or more in OSDI is considered positive for DED symptoms.

- Signs of DED which indicates disrupted homeostasis. Positive symptoms combined with a positive finding in any of below test confirms the diagnosis of DED

    - Reduced non-invasive fluorescein break-up time of less than 10 seconds

    - Tear osmolarity ≥ 308 mOsm/L or disparity between two eyes of ≥ 8 mOsm/L

    - Ocular surface staining (of the cornea, conjunctiva or lid margin) in either eye (> 5 corneal spots, > 9 conjunctival spots, or lid margin staining of ≥ 2 mm in length or ≥ 25% in width of lid margin.

- Further subtype classification tests such as meibography, lipid interferometry and tear volume measurement should be conducted to determine: 1) where the DED falls on the spectrum between ADDE and EDE, and 2) the severity of DED, in order to guide treatment. A tear meniscus height of less than 0.2mm indicates a degree of ADDE.

Below are 5 main criteria which should be taken into account before proceeding with laser eye surgery.

1. Subjective assessment: Absence of symptoms of dry eyes, a score of 5 or less in DEQ-5 or a score of 12 or less in OSDI questionnaire
1. No fluorescein of lessamine green staining
2. Good TBUT of more than 10
3. good tear meniscus of 0.2mm or more
4. non injected and non inflamed ocular surface
5. Normal osmolarity of less than 308 when available

Treatment of dry eyes

Treatment options for patients with ocular surface disease (OSD)/dry eyes involves the use of non-preserved ocular lubricants and a combination of many other available modalities. These treatment options which are often prescribed in a step wise ladder includes, modification of local environment, nutritional supplements with Omega 3, lid hygiene/warm compress, application of tea tree oil to lid margin, punctual occlusion, topical or systemic antibiotics (macrolide or tetracycline), topical cyclosporin and topical steroid. For very severe dry eyes other modalities include Oral secretagogues, autologous/allogeneic serum eye drops, therapeutic contact lens wear, amniotic membrane grafts or other surgical procedures such as tarsorrhaphy may be required. The choice of these modalities depends on the cause and severity of dry eyes. Therefore, it is vital to make all the efforts to determine the main causative factor behind the DED and determine to which degree it is related to EDE, ADDE and/or other ocular surface conditions. While certain treatments may be specifically indicated for one particular aspects of an individual's condition, most patients may benefit from more than one therapy in order to treat multiple aspects of the disease. The most common risk factors for dry eye disease are listed below with appropriate treatment for each:

- Anterior blepharitis

    - Lid margin cleaning with warm water or other dedicated lid cleaning wipes twice daily

    - 50% tea tree oil if Demodex mites infestation is suspected e.g. use of tea tree oil impregnated wipes such as Cliradex

    - Use of topical antibiotics such as Fucithalmic twice daily or Chloramphenicol four time daily to lid margin for 2 weeks to decrease normal flora load such as staphylococcal.

- Posterior blepharitis

    - Warm compress with a hot flannel or using dedicated commercially available masks such as EyeBag MGD. The benefit of latter is that they tend to retain heat for longer period hence more likely to achieve a temperature that will lead to melting point of the mebomian secretion

    - Re-esterified Omega 3 Fish Oil: Omega-3 fatty acids inhibit the synthesis of lipid mediators and block the production of proinflammatory mediators such as IL-1 and TNF-alpha (30, 31). They may benefit DED by reducing inflammation and by altering the composition of Meibomian lipids. Omega-3 nutritional

supplementation has been shown to decrease tear osmolarity and inflammation as well as increase tear production (31).
SeveralOmega-3 nutritional supplements are marketed specifically for the treatment of DED which contain omega-3 EFA from flaxseed and fish oil. Commercial brands include Lagad Lacrima twice daily for 3 month or thera tears eye Nutrition.

- Doxycycline 100mg or 40mg of the modified release once daily for 3 months. An alternative to this is 5 days course of Azithromycin 500mg stat on day 1 followed by 250mg OD for another 4 days (24).
  Topical Azithromycin 1.5% has also been shown to be effective in management of chronic blepharitis. We recommend it to be used twice daily for first three days and then once at night time for the remaining of the month. Our anecdotal experience shows combining Azithromycin drop and tablets together leads to significant and fast improvement of severe MGD
- Eyedrops containing lipids such as phospholipids, triglycerides, and castor oil are effective which improves TBUT (e.g. Refresh Endura™, Allergan, Irvine, CA) (42)

• Aqueous deficiency dry eyes

- Temporary collagen plugs followed by long term silicone plugs if indicated. Patients with punctal plugs may benefit from adjunctive topical cyclosporine A due to prolonged retention of the medication on the ocular surface (40).
- punctual cautery can provide a long-term solution

• Exposure dry eyes

- This is diagnosed by a characteristic band like punctate epithelial erosions within palpebral aperture or inferior cornea
- causes include secondary to poor eye lid closure (e.g. ectropion, lagophthalmos), neurological (Bell's Palsy, hypoesthesia) or blink disorders such as reduction of blink rate during computer use
- Treat with long acting lubrications such as Clinitas Sooth and VitaPos. Some patient may require nocturnal taping of eye lids and in severe cases surgical interventions such as tarsorraphy, lateral tarsal strip or even recession of lid retractors.

• Inflammatory dry eyes

- Trial of a weak steroid drop such as Predsol 0.5% preservative free four times daily for one months. If good response patient may benefit from topical cyclosporin (e.g. Ikervis at night) for at least 3 months
- Hyperosmolarity of the tear and inflammation of the ocular surface are the final common pathways in the pathogenesis of the dry eyes and therefore many dry eye patients are likely to benefit from a short course of weak topical corticosteroid (e.g. preservative free Predsol 0.5% QDS for 2-4 weeks) or topical cyclosporine A (e.g. Ikervis Nocte for 3 months or longer).
- Topical non-steroidal anti-inflammatories are not used commonly as they may cause corneal melting (43)

• Corneal Hypoesthesia

- Diagnosed by presence of clinical signs of dry eyes such as punctate epithelial erosion in absence of symptoms
- Reduced Cochet Bonnet aesthesiometry. This allows mechanical stimulation of the cornea by a calibrated Nylon filament which applies pressure axially. As the length of the Nylon filament decrease the transmitted pressure increases. The sensitivity is assessed at the 4 quadrants on cornea as well at the centre of the cornea.
- These patients may particularly benefit from autologous/allogenic serum drops as this contain epidermal growth factors and fibronectin which play an important role in epithelial healing

• Epithelial toxicity

- Common agents are Benzalkonium Chloride, Sodium hyaluronate and Lanolin
- Diffuse microcystic epithelial changes with fluorescein
- Using preservative free drops and when sodium hyaluronate toxicity is expected switching to other preparations such as Systane.
- Consider a period of stopping all drops
- In severe cases BCL may be required

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Management of Post LASIK dry eyes

- up to 50% LASIK patients experience some degree of dry eyes lasting from one week to one year postoperatively in a small number the dry eye can be very disabling and long term which responds very poorly to treatment. Therefore, it is vital to take all preoperative cautions to minimise the risk of post LASIK dry eyes. One simple strategy is to Continue pre-operative dry eye treatment for many weeks following surgery. Topical Cyclosporin A seems to have a beneficial effect in preventing and treating post LASIK dry eyes. It has been shown to increased tear secretion, improve ocular discomfort and accelerate corneal stromal nerve regeneration (33, 34, 35) post LASIK patients. Use of cyclosporine A before LASIK continued for 3 months post LASIK combined with non-preserved artificial tear drops as needed showed improved outcomes of visual acuity and dry eye parameters. compared to tear drops alone (32). Preservative-free artificial tears are recommended in all patients post LASIK to decrease the incidence of dry eye symptoms. The use of carboxymethylcellulose artificial tears demonstrated better early postoperative tear film stability than and less ocular surface staining than hydroxypropyl methylcellulose (HPMC) artificial tears (39). Tow Particular categories of Post LASIK dry eyes are:

  - Neurotrophic epitheliopathy

    - Denervation associated with the LASIK procedure is the most significant cause of post-LASIK dry eye (37) as it leads to decreased tear production

    - This is particularly more common after hyperopic ablation where the central epithelium is thinner du to steepening in this area and epithelial decompensation

    - Responds well to bandage contact lens wear

    - Autologous serum drops may be indicated in severe cases as it promotes epithelial regeneration. Topical autologous serum has been shown to reduce corneal epithelial erosions and improve post-LASIK tear film stability more effectively than artificial tears (41)
    - In cases with significant epithelial thinning, one last resort treatment is photo ablation to central area to induce flattening of the cornea and hence leading to thicker epithelium in the area.

    - Topical cyclosporine 0.05% has beneficial effect on corneal stromal nerve regeneration and therefore recommended in this group of patients (33).

  - Aberrant nerve regeneration (Corneal neuralgia)

    - This classically causes symptoms that are disproportionate to clinical signs and in extreme cases there may be no sign of dry eyes at all despite significant patient's symptoms and pain

    - These cases typically have an elevated Cochet Bonnet aesthesiometry reading of over 50mm (normal range 35-45mm, age dependent)

    - May require oral analgesia for as per other type of neuropathic pain

    - Amitriptyline 10mg at night time for first week and then increasing to higher dose if tolerated well (typically 20mg). This inhibits presynaptic rey-take if serotonin and noradrenaline. It can lead to aqueous deficieny dry eyes

    - Gabapentin 150mg daily in 2-3 divided doses as indicated for neuropathic pain

Continued:

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Q & A's with Kenneth Li

Edited by **Vivian Ho**

Dr Kenneth Li
with
puppy guide dog **Valter**

Photographed by:
Rolan Chu

How has your work been affected by COVID 19?

Due to COVID19, we have been facing a lot of new and unforeseen challenges in our clinical service. At the beginning of this pandemic, we implemented a number of infection control measures to mitigate the transmission risk of SARS-CoV-2. This included administrative control to reduce attendance, environmental control to ensure a safe environment for patients and healthcare workers, and the use of appropriate personal protective equipment (PPE). Then we faced the prospect of an overwhelmed inpatient service, and shortage of PPE. It has been a difficult time for everyone in the team. I am particularly impressed by my team members, who have risen to the challenge. Besides addressing all the challenges mentioned, it has been my team's humble intention to share our experience and workflow, via publications and webinars, with fellow ophthalmologists worldwide to alert them to take necessary precautions for this pandemic.

In one of your recent publications, ''Stepping up infection control measures in ophthalmology during the novel coronavirus outbreak: an experience from Hong Kong." you shared some special infection control measures that were adopted by your department during the pandemic.

Does everyone get screened for fever before entering the hospital? What about COVID testing to staff or patients with COVD like symptoms?

Temperature checkpoints have been set up at the entrance of clinics since late January. This involves the use of a portable, non-contact, infrared thermometer. More recently, we have adopted the use of infrared cameras, for fever detection. In the past few months, we had staff returning to work after travelling to outbreak areas and had subsequently developed COVID symptoms. They were naturally very worried about transmitting to families, and colleagues.
Our infection control team has been extremely efficient in arranging them to undergo PCR rapid testing, either with the use of nasopharyngeal/throat swabs, or with the use of deep throat saliva. This has greatly put our staff's minds at ease. On the other hand, patients with COVID symptoms are tested and triaged at A&E Department. In order to conserve inpatient beds, only those cases tested positive on PCR test are admitted.

How did you triage your clinical patients? (did you go through all their medical records to see who needs to come for face to face consultation or it can be postponed?)

We have a daily attendance of around 500 cases in our clinics, therefore it is not practical to screen all medical records. In order to lower attendances, we have been sending out text messages using Short Message Service (SMS) at least 5 days before patients' appointments. In the text message, we ask specifically for fever, flu symptoms and offer rescheduling of appointment or drug refill via our hotline. Responded cases are then screened by our doctors who will decide whether to accept rescheduling and decide on the timing of the appointment. Out of 17,000 messages sent out in the past 2 months, we had a response rate of around 23.6%, leading to an almost 14% reduction in attendance (unpublished data). We estimated a saving of 81 working days from this initiative which could be used for implementing infection control measures and other preparations for the pandemic.

According to your paper, about 25% patient clinic attendance was reduced following the new triage pathway. Do you think it could have been reduced further?
Similar rates of non-attendance have also been observed in other public ophthalmic clinics in Hong Kong during the initial stages of the pandemic.
The figures rose significantly after we had the first death associated with COVID-19, in early February. As the COVID-19 situation in Hong Kong has been under control in the past month, we have seen a much lower non-attendance rate recently.

All elective surgeries were suspended. What about other sub-specialities such as glaucoma, cornea, VR, Oculoplastic, Paeds and medical retina?

Other than emergency surgeries, we have also been performing some semi-urgent cases, including severe diabetic tractional detachment in only eye patients, drainage procedures for refractory glaucoma, excisional biopsies for orbital and eyelid tumours. We have also been maintaining our anti-VEGF treatment throughout this pandemic, as delay or omission of treatment may lead to irreversible visual loss. We have started to gradually resume elective cataract surgeries and other subspecialty surgeries this month.

In your recent publication in the Eye journal ''Why ophthalmologists should mask: a perspective from Hong Kong" you encouraged all ophthalmologists to wear mask at work. Does everyone i.e. all hospital workers wear masks in Hong Kong? If so what type of masks do they wear? And in what settings? (clinic/theatre/ admin office?)

Under the emergency response level in our public health care system, everyone that enters hospital premises must wear a mask. Due to the shortage of PPE, we have stopped providing masks for patients. From this month, the government of Hong Kong has started providing reusable masks to all citizens. As a standard precaution, all healthcare workers (including all clinical and administrative staff) are provided with 3-ply surgical masks (>98% BFE and >98% PFE). N95 respirators are provided to HCW who work in high-risk areas and perform aerosol generating procedures. The masking rate of the general public in Hong Kong has been reported to be well over 95%, from a number of studies. We believe this is the main reason for keeping our effective reproductive number below 1.

What is happening in your workplace since the lock down has been eased off? (Clinic and theatre).

The hospital management is closely monitoring the situation of community transmission, supply of PPE and maintaining our high PCR testing capabilities. These are all essential components for deciding on the pace of overall resumption of clinical service. Within ophthalmology, we are being extremely cautious in our resumption plan. A lot of measures are still being maintained, such as universal masking, temperature checkpoints, questionnaire, regular environmental disinfection, and the use of PPE. Over the past few months, we have accumulated a substantial backlog of both outpatient and surgical cases. Due to the necessity to maintain infection control measures, our efficiency has been significantly reduced, and it is a huge challenge to tackle the backlog of cases.

What is your view on virtual clinic or video consultation? What type of patients do you think can been seen through virtual or video consultation?

We have just embarked on telemedicine, and recently conducted our first telemedicine session in ophthalmology. We are currently focusing on oculoplastic cases but are considering other cases and indications. The lack of good online visual function tests is one of the obstacles for the further advancement on virtual clinic and we are currently working in this area.

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What's in the news?

Cataract Surgery and Dry Eye Disease: A Review

The aim was for the authors to review published literature concerning cataract surgery and dry eye disease (DED).

A search was undertaken using the following: PubMed (all years), Web of Science (all years), Ovid MEDLINE(R) (1946 to 12 December 2019), Ovid MEDLINE(R) Daily Update 10 December 2019, MEDLINE and MEDLINE non-indexed items, Embase (1974-2019, week 49), Ovid MEDLINE (R) and Epub Ahead of Print, In-Process and Other Non-Indexed Citations and Daily (1946 to 12 December 2019), CENTRAL (including Cochrane Eyes and Vision Trials Register; Cochrane Library: Issue 12 of 12
December 2019), metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrial.gov)

and WHO International Clinical Trials Registry Platform (www.who.int/ictrp/search/en). Search terms included 'cataract surgery', 'phacoemulsification' and 'cataract extraction', combined with 'dry eyes' and 'ocular surface'. Relevant in-article references not returned in our searches were also considered.

Publications identified included systematic reviews, meta-analysis, randomized controlled trials, cohort studies, case series and laboratory-based studies. Published data highlighting the burden of DED both prior and following cataract surgery were reviewed as well as studies highlighting the effects of cataract surgery on the ocular surface, intra-operative measures to reduce deleterious effects on the ocular surface and current evidence on the management options of post-operative DED.

DED is common and can be exacerbated by cataract surgery. Ophthalmologists need to assess for pre-existing DED and instigate treatment before surgery; be aware of reduced accuracy of measurements for surgical planning in the presence of DED; limit intra-operative surgical factors damaging to the ocular surface; and consider management to reduce DED post-operatively.

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Authors: Khayam Naderi , Jack Gormley, David O'Brart 1

Coenzyme Q10 (CoQ10) in Corneal Health and Disease

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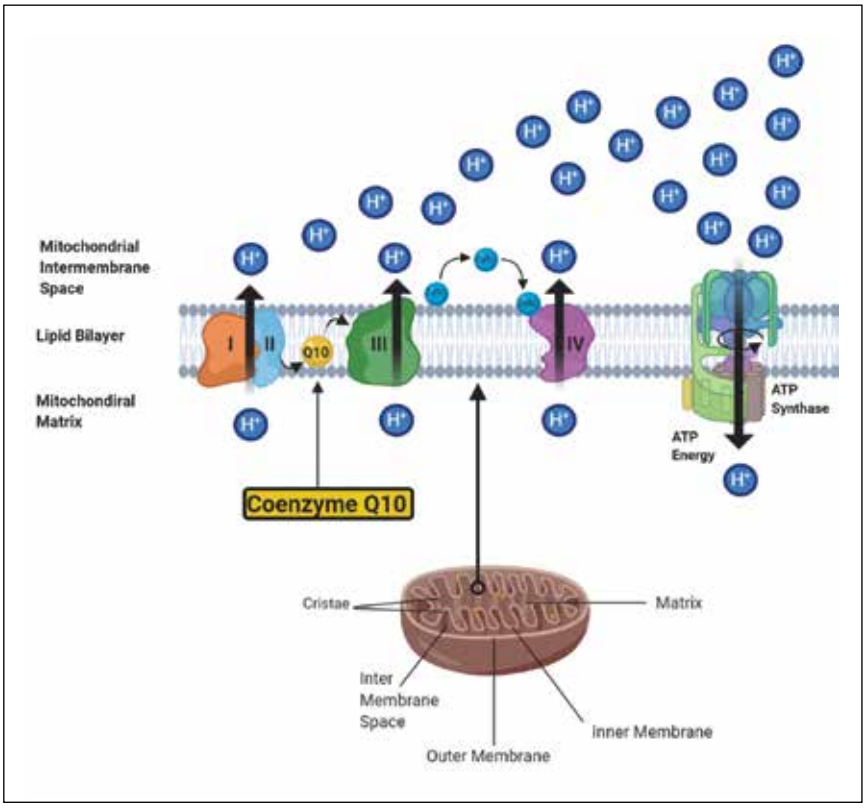
The cornea and tear film form the anterior refracting surface of eye and are essential to vision and ocular health. To maintain transparency the cornea is avascular and derives metabolic support from the tear film, the perilimbal vasculature and the aqueous humour. The unique anatomy and physiology of the cornea results in an exposure to high levels of oxidative stress[1]. Oxidative stress is an imbalance between reactive molecules (free radicals) and antioxidant defences which can lead to cellular damage and disease. Oxidative damage has been implicated in corneal and ocular surface diseases including dry eye disease, keratoconus, Fuchs' endothelial dystrophy and pterygia[1,2]. Free radicals including reactive oxygen species (ROS) and reactive nitrogen species (RNS) are generated exogenously (UV light exposure, smoking) and endogenously (mitochondria, phagocytotic cells)[3]. Antioxidant molecules counteract the effects of free radicals and include coenzyme Q10 (CoQ10), vitamins (C, E and A), carotenoids and flavonoids, glutathione and a variety of enzymes (superoxide dismutases and catalases). Oxidative stress plays a role in acute and chronic corneal diseases[1,2] and CoQ10 has been evaluated in several corneal and ocular surface conditions as a therapeutic agent.

What is CoQ10?

Coenzyme Q10 (CoQ10) or ubiquinone is a vitamin-like organic compound present in all human cells which acts as a co-enzyme in key biological processes[4]. Biochemically CoQ10 consists of a redox active quinone ring and a hydrophobic tail constructed with several isoprenoid units; CoQ10 in humans has 10 isoprene units. The hydrophobic tail makes CoQ10 lipophilic and so it associates which phospholipid bilayers within cells like the cell membrane, the mitochondrial inner membrane and Golgi apparatus. CoQ10 cycles between its three chemical forms: completely oxidised (ubiquinone), a semi-oxidised intermediate free radical (semiquinone) and a completely reduced form (ubiquinol)[5]. In humans, CoQ10 synthesis from tyrosine or phenylalanine (quinone ring) and mevalonic acid (isoprenoid side-chain units) is complex and utilises a collection of enzymes (complex Q) located in the mitochondrial matrix membrane and in the endoplasmic reticulum[4]. CoQ10 is also obtained from the diet and CoQ10 derived from dietary intake becomes more important with ageing as endogenous production decreases[6].

What is the function of CoQ10?

CoQ10 is a central component of the mitochondrial electron transport chain (ETC) located in the inner mitochondrial membrane[4,7]. CoQ10 plays a central role in mitochondrial energetics and the production of ATP (adenosine triphosphate) which the primary source of energy in cells. CoQ10 transports electrons from complexes I and II to complex III and plays a key role in oxidative phosphorylation (OXPHOS) and ATP production in mitochondria. Moving within the mitochondrial membrane allows CoQ10 to promote proton pumping at complex III helping to generate the proton motive force for ATP production[7].
Mitochondria are both the main source of ROS production though OXPHOS activity, but also paradoxically, mitochondria are a major target of ROS damage[8]. ROS have a biological role in normal physiology and cell signalling but in excess ROS can lead to cellular damage[3]. ROS damages mitochondrial DNA, lipid membranes and proteins resulting in a cycle of dysfunction of the ETC, inadequate ATP production, and further ROS production. CoQ10 is the only lipid-soluble antioxidant synthesised by the human body.
The reduced form of CoQ10 is an antioxidant which acts as a ubiquitous free radical scavenger to protect against oxidative damage to mitochondrial and lipid membranes, a process known as lipid peroxidation[5]. CoQ10 also stabilises the plasma membrane and facilitates the regeneration of ascorbate (vitamin C) and α-topopherol



(vitamin E)[5]. ROS production stimulates inflammation via the NFκB pathways and CoQ10 modulates **inflammation** via NFκB dependent gene expression and pathways9. CoQ10 has anti-inflammatory effects by reducing free radicals and ROS production, and therefore inhibiting the activation of NFκB, and so the levels of various proinflammatory cytokines and chemokines, including tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6) are reduced[10]. CoQ10 also regulates **apoptosis** or programmed cell death[11]. Mitochondria play an important role in the control of apoptosis and CoQ10 modulates the permeability transition pore (PTP), a mitochondrial inner membrane conductance channel, and so acts as a potent inhibitor of apoptotic signal transduction[11]. Opening the PTP increases the inner mitochondrial membrane permeability causing the collapse of the ETC and ATP generation which are early events in apoptosis.

What is the role of CoQ10 in the cornea and ocular surface?

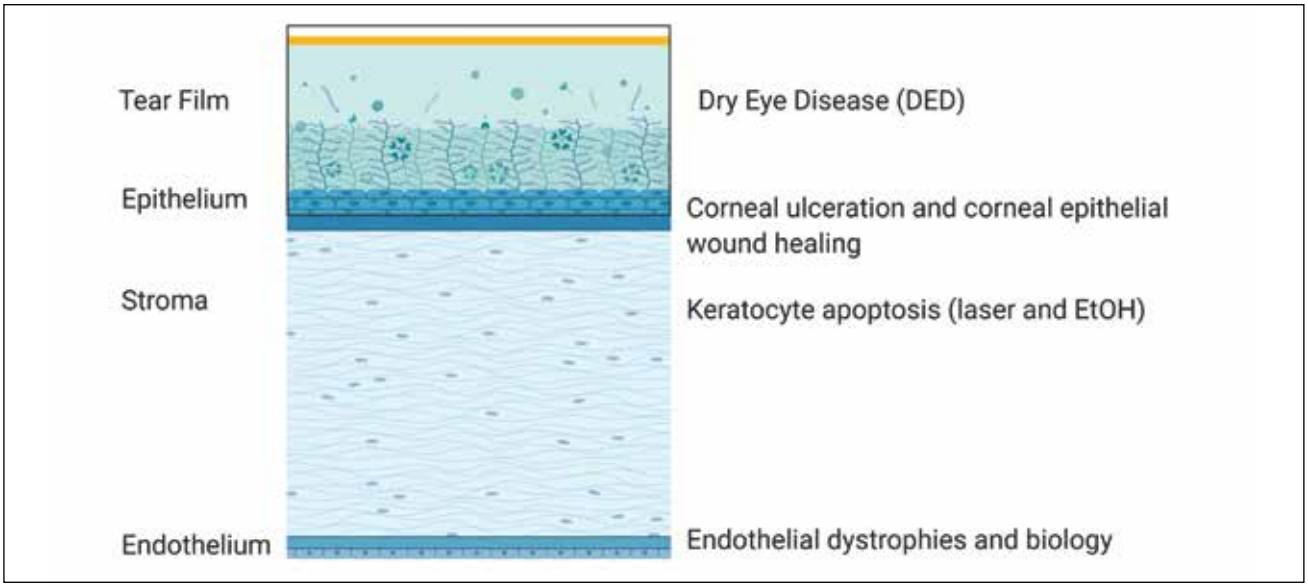
A significant reduction in the rate of CoQ10 biosynthesis occurs during ageing and age-associated diseases[10]. Multiple clinical studies have demonstrated the efficacy of CoQ10 as a therapeutic agent in cardiovascular, muscular, inflammatory, and neurodegenerative disorders[10,12]. In ocular and several neurodegenerative diseases there is an age-related decline in oxidative stress defences increasing the susceptibility to cellular damage from oxidative damage[13]. CoQ10 also plays a key role in the normal health of the cornea and ocular surface and in disease states. The cornea contains three broad populations of cells: corneal epithelial cells, stromal keratocytes and corneal endothelial cells. To function normally these cells, require energy which is supplied in the cell by ATP produced by mitochondria and protection from oxidative or free radical damage. The cornea is exposed to environmental stresses including high-tension atmospheric oxygen and sunlight/UV light which result in the generation of ROS and oxidative stress[1,2]. Mitochondrial dysfunction and oxidative stress result in corneal disease[1,2] and CoQ10 has been evaluated in several clinical scenarios.

Refractive surgery

Refractive procedures can involve the removal of the corneal epithelium using ethanol (EtOH) delamination including phototherapeutic keratectomy (PTK), laser assisted sub-epithelial keratectomy (LASEK) and 'epi-off' corneal collagen cross-lining (CXL). Excimer laser energy can induce corneal stromal keratocyte apoptosis and CoQ10 reduced the number of apoptotic corneal stromal keratocytes following excimer laser in vitro and in vivo to a greater extent than ascorbic acid or vitamin E[14,15]. There is also evidence EtOH can induce apoptosis of corneal epithelial cells and stromal keratocytes and this can be reduced in vitro with CoQ10 treatment[16,17]. The effect of pre-treatment of CoQ10 in EtOH induced corneal fibroblast apoptosis was through the inhibition of caspase 2, which when activated is an initiator caspase inducing apoptosis upstream of mitochondria[17]. CoQ10 protected rabbit corneal keratocytes in vitro from a number of apoptosis inducing agents including UVC exposure by preventing mitochondrial PTP opening, a key early event in apoptosis[11]. CoQ10 also reduced corneal damage after UVB exposure both in vitro and in vivo by supporting mitochondrial function[18]. In cultured human corneal epithelial cells exposed to UVB radiation the addition of Coq10 increased cell survival and mitochondrial function[18]. The authors demonstrated pre-treatment with CoQ10 before UVB exposure was more effective than after the insult, suggesting CoQ10 protection was a result of its free radical scavenging ability, reducing oxidative stress[18]. Depending on the corneal insult CoQ10 most likely acts in a dual role by reducing oxidative damage and inhibiting the early mechanisms of apoptosis. The effects of CoQ10 can reduce corneal stromal keratocyte apoptosis induced by laser refractive surgery and its impact on corneal epithelial wound healing, stromal haze (myofibroblast transformation) and regression of refractive correction[17,19].

Dry Eye Disease (DED)

The corneal epithelium is metabolically highly active to maintain the normal epithelial turnover and thickness. Mitochondrial damage has been implicated in dry eye disease (DED) when tear hyperosmolarity induces corneal epithelial cell apoptosis[20]. The tear film also contains antioxidants, especially ascorbate and urate, and a failure in tear film antioxidant status has been linked to ocular surface diseases, specifically DED[2]. Inflammation, oxidative stress and apoptosis play a role in dry eye disease (DED)[21]. In a double-blind trial in forty DED patients randomised to CoQ10 (plus cross-linked hyaluronic acid and vitamin E – TPGS; VisuXL®, Visufarma) versus 0.15% hyaluronic acid alone



there were significant (p=0.05) improvements in the Ocular Surface Disease Index (OSDI), corneal conjunctival fluorescein staining and meibomian gland assessment (appearance and expression)[22]. In vivo confocal microscopy demonstrated a significant reduction in epithelial cell hyperreflectivity and a more normalised epithelial structure. The authors attributed the increased clinical effectives of VisuXL® to the longer contact time of the cross-linked hyaluronic acid and the antioxidative activity of CoQ10[22]. The impact of CoQ10 on the inflammatory milieu of the ocular surface in DED should also be considered. High dose radioactive iodine (RAI) therapy for thyroid disease can impact the lacrimal gland and ocular surface. In a rodent model subjected to RAI, systemic CoQ10 reduced oxidative damage, resulting in improvements in lacrimal gland histopathology and reduction in tissue cytokine levels[23].

Corneal ulceration and wound healing
Corneal wound healing is a complex process requiring the coordinated interaction of multiple cellular, extracellular matrix, growth factor, immunological and metabolic factors[24]. Multiple aetiological agents can perturb these factors resulting in non-healing corneal epithelial defects and ulceration with subsequent neovascularisation, scarring and visual impairment[24]. CoQ10 has been evaluated in corneal wound healing and both its role as a **free radical scavenger** and as an anti-apoptotic agent have been implicated in its beneficial effects[18]. CoQ10 administration promoted corneal wound healing after corneal epithelial removal in vivo18. In a rodent model of corneal epithelial injury topical CoQ10 treatment resulted in a significantly reduced epithelial defect size at 12 hours post injury which was maintained up to 48 hours[18]. The finding that pre-treatment with CoQ10 ophthalmic solution was more effective that post-insult treatment was suggested as supporting a free radical scavenger role for CoQ10 in early phases of corneal injury[18]. The free radical scavenging ability and **antioxidant** activity of CoQ10 were assessed in nitrogen mustard-induced ocular injury in a rodent model and demonstrated improved macroscopic and histological findings[25]. In an observational clinical case series of refractory corneal ulceration (n=6), CoQ10 promoted epithelial closure in all cases[26]. The clinical cases had a mixed aetiology (neurotrophic keratitis, postinfectious corneal ulcers and Stevens-Johnson syndrome) and received CoQ10 twice or four times per day (CoQ10 100mg, vitamin E-TPGS 500mg and hypromellose 0.2%) and the modal time to healing was 4 - 8 weeks[26]. CoQ10 (combined with vitamin E-TPGS) has been proposed to improve corneal sub-basal nerves following cataract surgery[27] and the authors suggested this may be the mechanism of improved corneal epithelial closure with topical CoQ10 in neurotrophic keratopathy[26].

Endothelial biology

The corneal endothelium is a postmitotic structure which is highly metabolically active and contains a large number of mitochondria for ATP production. The corneal endothelium is packed with mitochondria to maintain the metabolic demands of its functional role of ATPase pumping of water. Corneal endothelial dysfunction can occur in the background of inherited mitochondrial disorders[1,28,29]. Kearns-Sayre syndrome (KSS) is a rare mitochondrial genetic disorder characterised by retinitis pigmentosa, external ophthalmoplegia and cardiac conduction defects. In KSS systemic administration of Q10 resulted in improvement in corneal function in two cases[29]. The authors proposed that CoQ10 may have a role in ameliorating oxidative stress in Fuchs' endothelial corneal dystrophy (FECD)[29]. FECD is an ageing disorder of the corneal endothelium which results from genetic and environmental factors[30]. It affects approximately 5% of the population over 40 years of age and is a leading reason for corneal transplantation[30]. There is evidence that oxidative stress damages mitochondria in the corneal endothelium. The corneal endothelium is prone to oxidative stress as it has a lifelong exposure to UV light, high oxygen demand and metabolic activity to continually pump ions using by Na+K+ATPases, and post-mitotic arrest[1,30].

Summary

There are an increasing number of antioxidant and mitochondrial therapies for corneal and ocular surface diseases[1,2]. CoQ10 is a coenzyme with essential roles in: (1) **mitochondrial energetics** and the production of ATP, (2) the defence against oxidative damage as an antioxidant and free radical scavenger, (3) inhibiting inflammation and (4) protecting cells from apoptosis. Mitochondrial dysfunction and oxidative damage are seen in several corneal and ocular surface diseases[1,2]. CoQ10 has shown beneficial therapeutic effects in preventing corneal stromal keratocyte apoptosis in refractive surgery, improving corneal epithelial wound healing and reducing the ocular surface impact of dry eye disease. CoQ10 may also have a role in supporting corneal endothelial biology. Oxidative stress and mitochondrial dysfunction play a role in other corneal diseases like keratoconus31 and further studies are required to look at the impact of CoQ10 in other clinical scenarios.

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A conjunctival makeover

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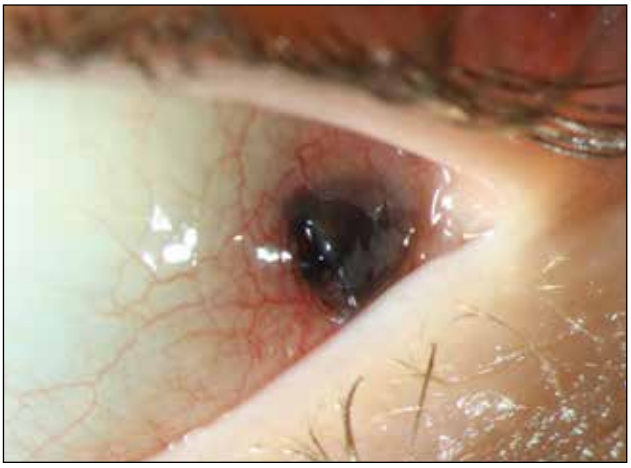
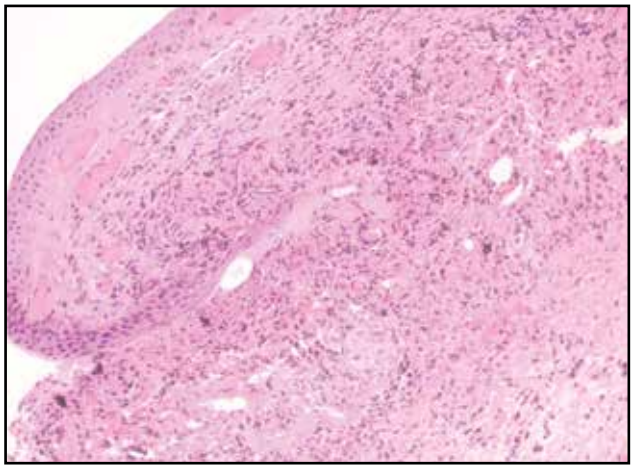
Case report

A 10 year old girl presented to the Eye emergency clinic with a recent onset dark/pigmented lesion involving temporal aspect of the left eye bulbar conjunctiva (Figure 1).



The pigmented lesion appeared to be a possible conjunctival melanoma, however, due to the unusual presentation and the age of the patient, all alternative possibilities were kept in mind. A detailed history revealed a recent visit to a makeup party and trying out Mascara. It appeared that while applying mascara, the girl may have been poked or had a small self inflicted injury. This might have led to the mascara been deposited in the conjunctiva and the subconjunctival tissue. It also raised concern regarding the fact that conjunctiva/tenons mascara may cause permanent 'tattooing' of conjunctiva and sclera. Slit lamp photos were taken and localised resection of conjunctiva along with pigmented deposits was performed under general anaesthesia. Conjunctiva was closed with absorbable 8/0 vicryl sutures. At the postoperative visit, no conjunctival or scleral tattooing was seen (Figure 2).

The histopathology report of the lesion was also compatible with clinical history of deposits of mascara in the conjunctival epithelium, sub epithelial tissue and in the subconjunctival space (Figure 3).



Discussion

Eye cosmetics such as mascara and eyeliner can cause ocular side effects. Mascara is a widely worn cosmetic. It is a pigment used to darken the eyelashes. It has previously been implicated in eyelid pathologies including blepharitis, contact dermatitis, allergic conjunctivitis, and conjunctival pigmentation. It has even been documented to collect to form a mascara-laden dacryolith.
A conjunctival mass associated with mascara use is described as a 'mascaroma' (1) (2) (3) (4) (5).
As far as the authors are aware, this is the first case of a 'mascaroma' described in a child. Ophthalmologists should be aware of mascara associated eye problems even in children. In this particular case, we were unsure of the particular brand of the mascara. The specific ingredients of mascara can vary between products. It is believed that conjunctival pigmentation due to exogenous material occurs when macrophages ingest pigmented material that then settles within the substantia propria of the epithelium (1). Since specific ingredients in mascara products may cause permanent tattooing of ocular surfaces which can become a cosmetic issue, timely intervention is necessary.
Ophthalmologists are usually the first individuals to identify potentially harmful eye cosmetic products. In unusual cases like these, it is important to take history of exposure to any eye cosmetic products. Timely diagnosis and surgical removal can prevent permanent cosmetic disfigurement of ocular surfaces.

Disclosure

Ethical issues have been completely observed by the authors.
We have obtained signed consent from the parent of the child to use the ocular images. No conflict of interest has been presented.
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TDU 059 JANUARY 2020

Creating 'staying power' in ocular lubricants

by **Professor Christine Purslow** PhD, MCOptom, FBCLA
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It's often the case that patients and professionals use different phrases to mean the same thing, and for dry eye drops this is no different. Patients talk about 'how long drops their last' (or don't), marketing campaigns talk about 'long lasting relief', and scientists talk about 'residence or contact time'. But we all seek the same thing: an effective lubricant that stays on the eye as long as possible, even when we blink. This is slightly different to a drug delivery goal, where it is more of a 'deposit and run' scenario.

I'm also choosing the word 'lubricant' for this form of dry eye treatment deliberately here. It serves as a reminder of the inherent (bio) engineering challenge - rapidly moving eyelids with variable load, fluctuating production and drainage of the tear fluid, and biological surfaces exposed to the environment. The ideal lubricant logically needs to:

- Supplement the tear film to hydrate and lubricate the ocular surface
- Behave in a similar way to the tear film
- Be non-toxic towards ocular tissues
- Have a long residence time to withstand blinking
- Protect the ocular surface

This 'wish' list also explains the evolution that has occurred in lubricants for dry eye treatment. I frequently meet health care professionals, especially those in primary care, who think that 'all dry eye drops are the same', and nothing much has changed since the conception of simple eye ointment and hypromellose. To challenge this perception, I refer them to parallel evolutions in other over-the-counter treatments such as indigestion, where Milk of Magnesia continues to sit alongside Proton Pump Inhibitors on the shelf – this parallel can also be a useful way to communicate with patients about differences between treatments, too.

The first generation of dry eye drops includes basic lubricants such as hypromellose and other cellulose derivatives, simple carbomer, polyvinyl alcohol: these are all still widely available and inexpensive. They are generally non-toxic for the ocular surface (unless preserved[1]), and their purpose is to add bulk to the tear film. They bring symptomatic relief but it will not last long due to relatively short residence time[2], and patients will have to re-apply frequently throughout the day.

The second generation of dry eye drops provides a big leap forward in residence time, due to the commercialisation of ingredients which simulate important characteristics of the natural tear film, namely viscoelastic (pseudoplastic or Non-Newtonian, thixotropic) behaviours, water retention and mucoadhesion. Sodium hyaluronate (commonly referred to as Hyaluronic Acid or HA), which is a polysaccharide, is the key ingredient in this category. HA is viscous at rest but transforms to a less viscous fluid at high shear rates, such as in human blinking. The ability of HA to retain water is remarkable: more than 2-3000x its own weight when hydrated[3]. The great ability of HA to be water binding also makes it muco-mimetic and improve wettability of the ocular surface[4]. HA treatment periods of three months have been shown to improve epithelial cell viability following ocular surface damage[5]. Tear film stability improves with HA[6], and residence time is significantly longer when compared to saline[7], CMC[8], HPMC and polyvinyl alcohol[2]. In one study of glaucoma patients with ocular surface disease, 0.18% HA demonstrated significant superiority for improving symptoms and signs, over a 0.3% HPMC/Dextran combination[9].

The third (and latest) generation of dry eye drops go further: they combine HA with another ingredient which may be:

- An oil component such as glycerin to supplement the tear film lipid layer
- Added carbomer or CMC - there seems to be a synergistic increase in just low shear viscosity in particular when CMC and HA are combined[10], avoiding the stickiness and blur when blinking; such drops are even superior to CMC alone for wetting contact lenses[11].
- A further saccharide such as Trehalose (bioprotection for epithelial cells[12.13] and longer residence time[14]) or Tamarind Seed polysaccharide (increased mucomimetic behaviour[15.16])

It is this third generation of synergistic polymer eye drops for dry eye relief that really challenges the intuitive idea that solutions have to be highly viscous to improve residence time, or treat a more severe case. For example, in one study where tear film thickness was measured over a four hour period, a single drop of HA+Trehalose was detectable for 6x longer than a single drop of HA solution[14], even though the viscosities of both solutions were similar. (See Figure 1 on next page).

Viscous dry eye drops (gels, ointments) still have their place however. Some patients prefer the sensation from their application, which will be cooling for longer than a liquid drop – simple heat transfer. These products can also benefit at night time when the eyes are closed, and retention time will increase.

And finally, what about real world evidence?

During educational talks on dry eye I refer to a British study[17] by Bhojwani et al, which investigated this anecdotal association of 'thicker' products being more effective. Over a thousand members of the British Sjögren's Syndrome Association completed a questionnaire regarding their physical condition and the use of lubricant eye drops. Visco-analysis was performed on each of the products used by at least 50 respondents and their responses compared. Interestingly, they did not find a significant correlation between viscosity and frequency of use or duration of relief felt.

In conclusion, staying power for an ocular lubricant is not simply about viscosity any more – modern dry eye drops are working at a synergistic and molecular level.

In lay terms, it's not about drops being 'thicker', just like it's not about using a thicker oil in a high performance car – it's about choosing the modern lubricant.

Residence time in fact depends on several things, and viscosity is just one (Figure 1).

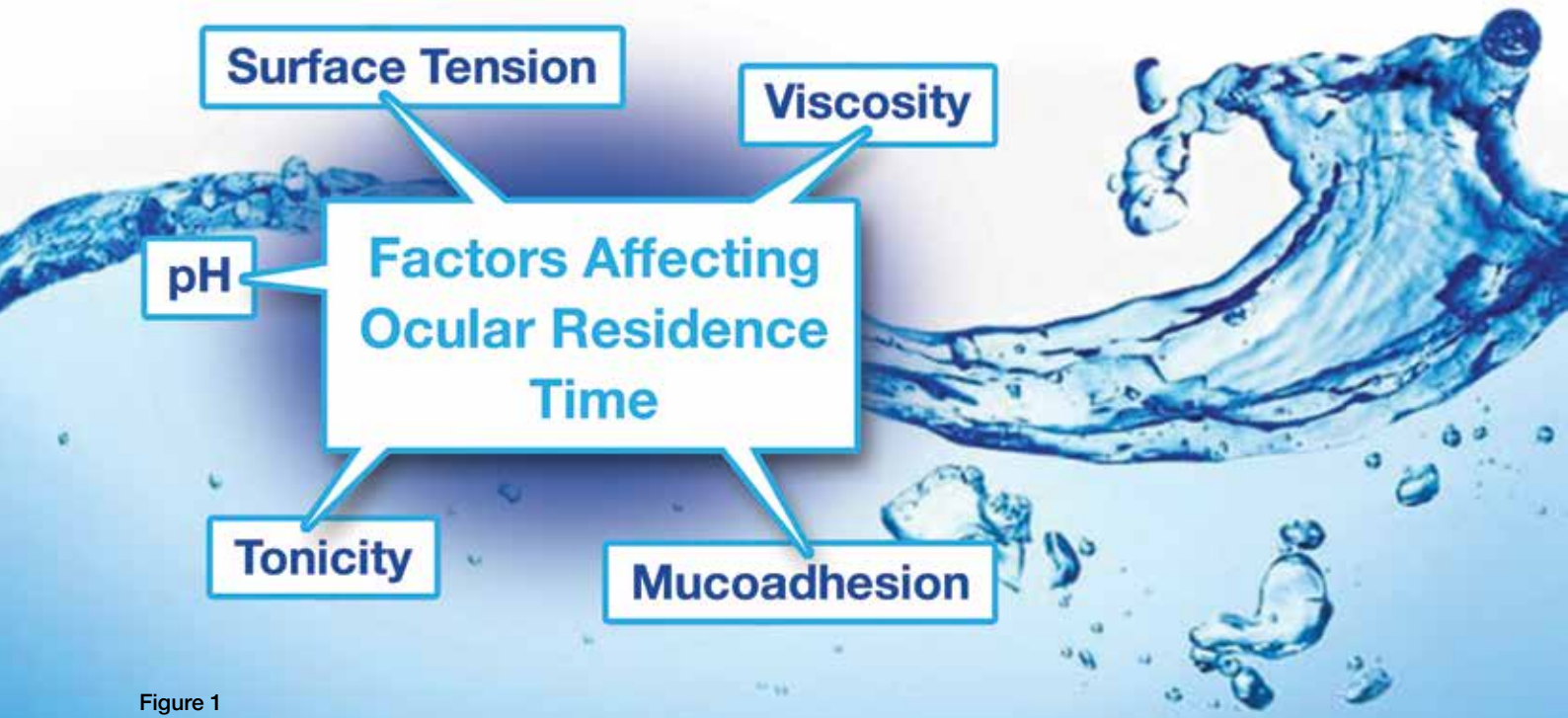

Figure 1
Mucoadhesion and surface tension properties can give modern eye drops staying power without viscosity, which also means avoiding blurry vision and stickiness. In fact, when you think about the viscosity of human tears, most of the time they are similar to water. And when we prescribe a viscous dry eye treatment to patients we often warn them that their vision will blur but slowly clear over a few minutes. This tells us that natural blinking will seek to restore the equilibrium for viscosity that the ocular surface requires; in other words excess viscosity may serve no purpose in humans that blink every few seconds. Indeed, many ocular residence time studies are conducted on rodents that blink very infrequently – something to bear in mind when you are presented with animal data on dry eye drops!

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