Amniotic Membrane – Preservation Techniques

Five Rare Cases of Central Toxic Keratopathy post Cross linking

Dry eye disease - how to manage it at home
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Welcome to the Winter issue of OSI.

Welcome to the winter issue of OSI Magazine!
Our second Symposium in London is approaching fast, and I look forward to welcoming excellent colleagues and speakers to participate in the symposium.

I would also like to take the opportunity to thank our industry colleagues for supporting this meeting. We understand it is a busy schedule with meetings and congresses throughout the year, but we believe there is a need and interest for a meeting that is completely dedicated to the ocular surface.

It’s that time a year again to get ready for the pollen season, if you plan to prescribe Mast-cell stabilisers know is the time to start loading, as it normally takes up to a month to reach its full benefit.

We will cover more on allergic conditions in the spring issue which will be out in time for the Royal College of Ophthalmology annual meeting in Birmingham.

We have many exciting articles in this issue, and I will mention a few: We kick off with a very interesting article about Amniotic Membrane preservation techniques. Then we have a hands-on simple guide shared by Arthur Cummings how we as clinicians can guide our patients to manage their dry eye disease at home with simple pointers to improve compliance.

Also my colleague from Jordan, Nancy Al Raqqad presents five intriguing rare cases of central toxic keratopathy post cross linking.

Enjoy the magazine and hope to see you at the OSI Symposium on the 12th of March.

Samer Hamada
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If you are interested in submitting an article, please get in touch by emailing: articles@visionduo.com
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What’s in the news?

Long-term visual outcomes of the Boston type I keratoprosthesis in Canada

The aim of this study was to evaluate long-term visual outcomes of Boston type I keratoprosthesis (KPro) surgery and identify risk factors for visual failure.

The method used was a single surgeon retrospective cohort study including 85 eyes of 74 patients who underwent KPro implantation to treat severe ocular surface disease, including limbal stem cell deficiency, postinfectious keratitis, aniridia and chemical burns. Procedures were performed at the Centre hospitalier de l’Université de Montréal from October 2008 to May 2012. All patients with at least 5 years of follow-up were included in the analysis, including eyes with repeated KPro. Main outcome measures were visual acuity (VA), visual failure, defined as a sustained worse than preoperative VA, postoperative complications, and device retention.

The mean follow-up was 7.2±1.3 years (±SD). Mean VA was 2.1±0.7 (logarithm of minimal angle resolution) preoperatively and 1.9±1.2 at last follow-up. There were 2.4% of patients with VA better than 20/200 preoperatively and 36.5% at last follow-up. Maintenance of improved postoperative VA was seen in 61.8% of eyes at 7 years. Preoperative factors associated with visual failure were known history of glaucoma (HR=2.7 (1.2 to 5.9), p=0.02) and Stevens-Johnson syndrome (HR=7.3 (2.5 to 21.4) p<0.01). Cumulative 8-year complication rates were 38.8% retroprosthetic membrane formation, 25.9% new onset glaucoma, 23.5% hypotony, 23.5% retinal detachment, 8.2% device extrusion and 5.9% endophthalmitis. The majority (91.8%) of eyes retained the device 8 years after implantation.

The conclusion showed almost two-thirds of patients had improved VA 7 years after KPro implantation. Preoperative risk factors for visual failure were known glaucoma and Stevens-Johnson syndrome.

Authors: Szigiato AA, Bostan C, Nayman T, Harissi-Dagher M.

Role of Oral Vitamin C on astigmatic errors in phacoemulsification

The purpose of the study was to evaluate the role of oral vitamin C on postoperative astigmatism in phacoemulsification and to assess its effect on postoperative symptoms. This was a prospective randomised double-blind study, the 400 consecutive patients of cataract were randomized into two groups consisting of 200 patients each. Group “A” patients were started on Oral Vitamin C (1500 mg per day in three divided doses) from first postoperative day and Group “B” patients were given routine postoperative medications along with placebo. The Keratometry of both the groups were done preoperatively and post operatively at 2, 4 and 6 weeks. All patients underwent temporal clear corneal phacoemulsification by same surgeon.

The results showed a mean difference of astigmatism preoperatively in right eye of Group ‘A’ patients was 1.049±0.971 which reduced to 0.680±0.554 at 6 weeks postoperatively, (p-value 0.0018) whereas in Group B it changed to 1.141±0.771 at 6 weeks from 1.116±0.566 of preoperatively (p-value 0.759). In left eye of Group ‘A’ patients its value was 0.995±0.899 which changed to 0.574±0.528 at 6 weeks (p-value 0.0001) which was highly significant whereas that in Group “B” patients it was 0.733±0.440 preoperatively which modified to 0.877±0.581 at 6 weeks (p-value 0.004). In Group “A” 0.5% patients had pain, foreign body sensation and photophobia at 6 weeks whereas in Group “B” patients 5% had pain, 1.5% had foreign body sensation, 1% had photophobia and 0.5% had watering.

The authors concluded that Oral Vitamin C may play a beneficial role in decreasing the postoperative astigmatism. It also enhances patients’ comfort levels and ensures faster recovery after phacoemulsification.

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\textbf{Undesirable Effects:} Consult SmPC for full details. The most common adverse reactions in clinical studies were eye pain, dryness, irritation, lacrimation, ocular hyperaemia and eyelid erythema. Other common adverse reactions observed were visual blurred, eyelid oedema, conjunctival hyperaemia, and irritation site pain, irritation, erythema, lacrimation. Patients receiving immunomodulatory therapies including ciclosporin are at increased risk of infections.

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\textbf{Date of preparation:} July 2019 \textbf{Job code:} PF-IKERV-UK-0208
What’s in the news?

Ocular pain response to treatment in dry eye patients

Pain is a frequently reported symptom in dry eye disease (DED). We examine the factors associated with ocular pain severity and patient-reported improvement in ocular pain to commonly used dry eye and pain treatments.

Cross-sectional study of patients presenting for dry eye management. Demographics, ocular and medical history, OSDI, numeric pain scale, pain descriptors, and subjective response to tried eye drop, systemic, and non-pharmacologic treatments were collected. Statistical analysis was performed to identify differential treatment response in patients with various pain levels using the non-parametric test for trend.

144 patients were categorised into 4 groups according to reported pain severity. Increasing pain was significantly associated with younger age, history of refractive surgery, higher OSDI score, and less likelihood of corneal staining. Patients with higher pain intensity were more likely to report a history of fibromyalgia, depression, anxiety, and migraine. Patients with greater pain severity were less responsive to treatment with artificial tears ($p < 0.001$), lubricating ointment ($p = 0.002$), steroid eye drops ($p = 0.03$), cyclosporine $0.05\%$ ($p = 0.03$), $20\%$ autologous serum tears ($p = 0.01$), hot compresses ($p = 0.04$), lid hygiene ($p = 0.002$) and punctal occlusion ($p = 0.03$).

Dry eye patients with severe ocular pain often have associated psychological and systemic pain conditions. Treating the underlying DED is beneficial in reducing ocular pain, however the low rate of a satisfactory response highlights the need for further investigation of effective therapies. Cross-sectional studies can provide guidance in the treatment of patients with dry eye-related ocular pain and guide future prospective studies on potentially effective therapies.

Economic impact of dry eye disease in Spain: A multicentre retrospective insurance claims database analysis

The purpose of this analysis was to analyse the occurrence and cost of dry eye disease in Spain in the recent years.

A cross-sectional analysis based on anonymised data from an insurance claims database that includes data from 1997 to 2015 from public and private hospitals and healthcare centres; 36,081 patients were eligible for the study after duplicate elimination. Five ICD9 codes associated with dry eye were used for patient selection, including vitamin A deficiency with xerophthalmic scars of cornea, xerophthalmia due to vitamin A deficiency, keratoconjunctivitis sicca not specified as Sjögren’s, dry eye syndrome and keratoconjunctivitis sicca Sjögren’s disease.

Over 88% of the patients were female, and the mean age was 66 years. Patients with keratoconjunctivitis sicca Sjögren’s disease represented more than 89% of all patients and had the highest percentage of women. Both the annual number of patients and the number of admissions have increased exponentially since 1997 raising from 1079 to 3097 and from 1344 to 5938, respectively. The in-hospital length of stay was 9.6 (standard deviation = 11.6) days where more than 65% of the admissions were due to emergencies. Total costs were found to increase from €4.9 to €30.3 million during the study period; in parallel, there was an increase in the mean annual cost per patient, which was on average €7379.

The authors concluded that disease incidence is likely to increase due to the influence of modern-day workplace, and it is important to take into account the high economic burden and the large decrease in quality of life in regard to Spanish society and health policies.

Authors: Siedlecki AN, Smith SD, Siedlecki AR, Hayek SM, Sayegh RR.
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Amniotic Membrane – Preservation Techniques; Transplantation Methodologies and the Growth of In-Clinic Sutureless Application in Ophthalmology.

by Andrew Hopkinson, PhD1,2; Tonicha Spencer, MChem2

INTRODUCTION

Amniotic membrane (amnion) is the innermost avascular, immune-privileged layer of the placental sac surrounding the baby during pregnancy. Human amnion is reprocessed into a transplant material for use in tissue reconstruction and wound healing therapy1, 2. This was developed in the early 1940’s, but clinical adoption of amnion transplantation (AMT) in ophthalmology significantly expanded in the late 1990’s3.

Though research into the mechanism of action continues, AMT is known to possess anti-inflammatory; anti-fibrotic and anti-angiogenic properties4 resulting from an interplay between the complex bioactive composition of the devitalised tissue. The structure, composition, and organisation of amnion provides a scaffold (substrate) for cells to interact, promoting epithelial regeneration5. Amnion is enriched with important semi-soluble proteins such as hyaluronic acid and multiple proteoglycans that contribute to its therapeutic action. Amnion’s matrix and epithelial layers are also interspersed with a multitude of soluble trophic proteins, including growth factors, cytokines, neurotrophic substances, and protease inhibitors which supports wound healing6. The net result, and ultimate clinical objective, is promoting epithelial recovery and increasing rate of wound healing6. Reduction of pain; increased oxygen permeation, and protection of the wound from the external environment and eyelid friction are additional benefits7.

MODES ON AMNION APPLICATION

Ophthalmic surgeons take advantage of the physical and biological properties of amnion in three main modes of transplantation (Table 1).

Table 1. Application Methods of Amniotic Membrane.

<table>
<thead>
<tr>
<th>Application Method</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inlay Graft</td>
<td>Inlay-AMT is grafted into the damaged ocular surface and utilises amnions physical structure to replace defective or lost tissue. Applied epithelial side up, the replacement amnion basement membrane acts as substrate for epithelial regeneration. Whilst the biochemical composition reduces inflammation and fibrosis and accelerates wound healing. An inlay-AMT is permanently incorporated and remodelled over time into the ocular matrix.</td>
</tr>
<tr>
<td>Overlay Graft (Patch)</td>
<td>Overlay-AMT is a temporary biological dressing used to protect and nurture an underlying superficial defect to facilitate wound healing. Placed epithelial side down on the compromised surface, the protective patch serves as physical barrier against further environmental or physical insult; prevents formation of detrimental symblepharon or ankyloblepharon and eliminates infiltrating immune cells to reduce inflammation and tissue degradation. Structural, semi-soluble and soluble proteins then interact with the superficial wound to reduce inflammation, neovascularisation and fibrosis, providing an environment conducive to accelerated epithelial regeneration. Overlay-AMT is applied to stabilise and heal superficial defects; to overcome inflammatory situations and protect iatrogenic insults. An overlay graft significantly reduces pain and improves patient comfort, remaining in situ until it is removed, or falls away due to degradation.</td>
</tr>
<tr>
<td>Inlay and Onlay (Combined) Graft</td>
<td>Utilising a combined-AMT benefits from the advantages of both modes of application to accelerate wound healing and improve the clinical outcome of a procedure.</td>
</tr>
</tbody>
</table>
The most widely accepted mode of AMT is an inlay graft as a substrate, which is reflected in the wide range of clinical indications. Amnion provides a protective substrate for conjunctival regeneration in glaucoma surgery\(^8\); following removal of ocular surface tumours\(^9\) and pterygium\(^10\), and in ocuoplastic procedures, where large areas of the sclera remain exposed and regenerating conjunctiva requires a healthy basement membrane.

The clinical success of AMT in these procedures is reported to be variable but this may be explained by differences in the amnion technology (detailed below); variation in surgical techniques, and the robustness of study design. Inlay-AMT must be secured using sutures or bio-adhesives, thus requires surgical intervention.

Amnion has been shown to be particularly beneficial in the surgical treatment of superficial corneal disease. In a recent study, Schuerch et al 2019\(^1\), demonstrated a combined-AMT healed 70% of non-healing corneal ulcers refractory to standard of care. Neurotrophic, bacterial and herpetic ulcers had the fastest rate of wound healing. A recent meta-analysis by Lui et al\(^2\) studied the effectiveness of cryopreserved AMT in the treatment of corneal ulcers. Their study confirmed inlay-AMT and combined-AMT are effective in the treatment of corneal ulceration, improving both the rate of epithelial wound healing and visual acuity, whilst reducing inflammation and post-operative complications\(^2\).

Lui et al excluded the analysis of overlay-AMT due to the lack of available data\(^2\) illustrating overlay-AMT for superficial disease is not routinely considered most likely due to associated surgical costs. Instead, overlay-AMT is reserved for severe conditions such as cicatrizating conjunctivitis, following Chemical Burns\(^3\) or Steven’s Johnson Syndrome\(^4\).

Tabatabaei et al 2017\(^5\) demonstrated how overlay-AMT in acute (2-5 days) bacterial keratitis significantly improves vision and reduces scarring and neovascularisation at six months. In England alone, an estimated 37,000 keratitis and 70,000 persistent epithelial defect episodes are recorded annually (Hospital Episode Statistical Data – NHS Digital 2017-18). In addition to this, severe Dry Eye Disease (DED) affects around 500,000 patients in the UK. Due to the chronic nature of DED, these patients may repeatedly attend out-patient appointments over many months, even indefinitely, but are excluded from the benefits of AMT. AMT is recognised as a potential treatment option for DED, but due to the need for surgical grafting, it is currently listed in Stage 4 of disease management, as defined by the Report of the International Dry Eye Workshop (DEWS)\(^6\).

Recent technological advancements in amnion preservation and application have introduced in-clinic ‘sutureless’ AMT (sAMT) opening up new therapy options. The ability to access AMT without surgery has potential to have a significant impact on patient care pathways and health beneficiaries by increasing the availability of AMT.

### ADVANCES IN AMniOTIC MEMBRANE PRESERVATION TECHNIQUES

Several methods for preserving amnion are commercially available, all of which compromise tissue integrity in some way, rendering the tissue none-viable. The manufacturing challenge is to minimise tissue damage which may reduce product quality, biological activity and clinical benefit.

The most widely used method for preserving amnion involves deep-freezing amnion at -80°C, typically in storage medium such as Dulbecco’s Modified Eagle’s Medium (DMEM) containing a cryoprotectant such as glycerol (50% v/v). An example being the CryoTek\(^\text{®}\) (PCT US2010/046675) procedure, used to produce AmnioGraft\(^\text{®}\) and ProKera\(^\text{®}\) (BioTissue, USA). This is often referred to as ‘cryopreserved’ amnion, though it does not preserve living cells. Cryopreservation aims to minimise tissue-damage caused by unregulated enzymatic reactions, leading to degradation of its biological state. Without true cryopreservation steps, ice crystal formation unavoidably compromises cellular integrity. Thawing and preparation for transplantation has been shown result in significant reduction of important soluble and semi-soluble wound-healing proteins, potentially reducing the clinical benefit of amnion preserved in this manner\(^7\). Cryopreserved amnion is also restricted to cold-chain storage and logistics, precluding routine access in an outpatient setting where it is most needed.

Dehydrated amnion can be stored long-term and easily shipped at room temperature without deterioration, thus, overcoming cryopreservation limitations. Freeze-dried, or lyophilised, amnion, such as VISIO AMTRIX\(^\text{®}\) (TBF, France), utilises sublimation of water from frozen amnion. This involves pre-freezing amnion at -80°C, introducing ice crystal-damage, resulting in considerable protein loss\(^8\). In the lyophilised state, amnion can be friable, challenging to handle and difficult to effectively rehydrate. Dehydration via heat, such as the Purin\(^\text{®}\) process (MiMedx, US 8,323,701) used to manufacture AmbioDisk\(^\text{®}\) (Katena, USA), eliminates potential freeze-damage but the drying process can be difficult to standardise, which reduces the biological activity of the amnion, compared to cryopreserved amnion\(^9\). Conventional dehydration techniques also rely on a final radiation-stabilisation step, which can further compromise the biological function and quality of tissues.

The Tereo\(^\text{®}\) process is a modern dehydration technique developed by the University of Nottingham, exclusively licenced to NuVision Biotherapies for the manufacture of Omnigen\(^\text{®}\). Tereo overcomes issues with freeze- and heat- drying, by utilising a sugar protectant and low temperature vacuum evaporation preservation to delicately dehydrate amnion, preserving important tissue integrity, biochemistry and wound-healing potential of amnion\(^10\). Low temperature vacuum evaporation allows for the amnion to be directly applied to the wound for rapid and effective in-vivo rehydration. Omnigen is the only amnion easily accessible at the point of care in the U.K.

### THE IN-CLINIC TRANSPLANTATION OF AMNIOTIC MEMBRANE

In-clinic application of amnion has been developed due to the introduction of sutureless AMT (sAMT) methodologies. Due to the out-patient setting, sAMT is required to be easily accessible at the point of care; simple to apply and effective within the patient care pathway. Allowing the treatment to deliver service improvements to the hospital (reduced cost, time and care pathway).

In 2018, McDonald et al\(^11\), made significant progress in sAMT by demonstrating cryopreserved amnion retained on a plastic ring (ProKera, BioTissue), successfully treated
moderate to severe DED patients in clinic. An average treatment of 5.4±2.8 days (range 2–11 days) significantly reduced DEWS score, patient discomfort and corneal surface instability over 3 months. A supporting study demonstrated significant corneal nerve regeneration and reduced pain score over 1 month\(^{20}\). Prior to recent withdrawal, ProKera sAMT was limited to the treatment of severe ocular surface diseases, such as: ocular burns and persistent epithelial defects, with less penetration within the DED market in the U.K. Logistic, storage and access at the point of care challenges greatly limited the widespread adoption of ProKera throughout the sAMT market. In the US, AmbioDisk exploits the natural adhesive properties of exposed corneal stromal to temporally self-adhere (3-5 days) amnion to defects > 3mm diameter. Overlying a commercial bandage contact lens is recommended, however it is hypothesised that without specialised parameters retention of the amnion will be poor.

Advancing sAMT, NuVision Biotherapies in conjunction with Menicon U.K, have recently developed, OmniLenz\(^{7}\), a bespoke bandage contact lens specifically designed to apply Omnigen. Adapted from the Menicon 72, an everyday contact lens, OmniLenz allows easy delivery and comfortable retention of Omnigen at the ocular surface (Figure 1, A and B), in a simple 5-minute procedure. Due to the ease of application, non-surgical healthcare professionals can be trained to apply OmniLenz ‘in the office’ and the specification of OmniLenz is compatible with around 80% of patients. OmniLenz protects the ocular surface and Omnigen, whilst effective wound-healing is delivered. The accelerated wound healing benefits of OmniLenz sAMT (Figure 1, C-F) in corneal defects has been reported at several national and international meetings, reporting >70% success in hard to heal defects.

**Figure 1.** Images showing Omnigen applied via OmniLenz (A); Omnigen held in situ with Omnigen at the ocular surface (B); Diffuse view (C) and fluorescein stained view (D) of non-healing (4 months) neurotrophic keratopathy refractory to standard care. Ulcer is centrally located on the cornea, involving the visual axis and affected vision. Extensive inflammation can be seen; diffuse view of OmniLenz in situ over the ulcer 2-weeks after application (E). The outline of the Omnigen disc can be seen covering the epithelial defect, though it is slightly displaced up and out; and, fluorescein stain following a 2-week treatment and removal of OmniLenz showing the epithelial defect fully healed and pooling of dye along the edge. Extensive inflammation can be seen; diffuse view of OmniLenz in situ over the ulcer 2-weeks after application (E). The outline of the Omnigen disc can be seen covering the epithelial defect, though it is slightly displaced up and out; and, fluorescein stain following a 2-week treatment and removal of OmniLenz showing the epithelial defect fully healed and pooling of dye along the edge.

**REFERENCES**


**SUMMARY**

Surgical AMT is an accepted procedure for providing anti-inflammatory, anti-scarring, anti-fibrotic and anti-angiogenesis benefits, and delivering effective wound healing. Increasingly, the priority is now focusing on delivering similar therapeutic benefits ‘in the clinic’. New sAMT techniques, and innovative dehydrated amnion technologies, developed through a University-industry-NHS tri-partnership has allowed for amnion to be successfully accessed where it was previously precluded without surgical intervention.

The development of OmniLenz application for Omnigen delivers an ‘off-the-shell’ and comfortable sAMT technique, which is easily accessible in the clinic. Thus, for the first time, thousands of patients suffering from indications such: persistent epithelial defects, corneal ulcers\(^{12}\), keratitis\(^{13}\), and dry eye disease\(^{19}\) are able to gain access to amnion’s therapeutic benefit prior to reaching surgical intervention in the treatment pathway.
Dry Eye Disease - how to manage it at home

SYMPTOMS
Dry eye has a wide variety of symptoms. People often don’t realise that their eyes are dry. Symptoms can include painful, sore, gritty or burning eyes, blurred vision, eyes feel tired or fatigued and eyes that water a lot.

TREATMENT OPTIONS
Treatment options will vary depending on the type of dry eye that you have. If there is a shortage of water production, it is necessary to increase the supply of water in the tear layer. If there is sufficient water but there is excessive evaporation of the tear layer, then the tears will also be lacking due to them being exposed to the outside world and it is necessary to improve the oil/ lipid layer to reduce evaporation.

If the problem is due to lack of water:
1. Every time that you blink, whether it is a complete blink or an incomplete blink (the eyelids don’t touch each other during the blink), you produce a water drop. So, remember to blink!
2. Make sure to drink enough water during the day
3. Avoid consuming too much coffee and tea
4. Avoid/reduce intake of medications that reduce the water component or find an alternative medication that does not reduce the water layer of the tear-film: antihistamine tablets for allergies, cold and flu medications/ decongestants, some blood pressure medications (please do not stop any medications prescribed by your G.P. without checking that it is ok for your general health to do this)
5. Use lubricating eye drops that assist the water layer such as drops containing Sodium Hyaluronate 0.2% or even 0.4% for particularly dry eyes. There are also drops specifically for use at night-time. You can use any drop that you prefer. The only strong recommendation is that you use a drop that is preservative-free. It is advised to use drops 4 times per day as a general guideline but drops can be used as often as required. There is no limit to the number of drops that can be used daily.

If the problem is due to lack of oil:
1. You only produce oil when the eyelids touch one another during the blink process. When the eyelids touch each other, the Meibomian glands express a drop of oil much like a toothpaste tube would express toothpaste. The blink therefore needs to be COMPLETE i.e. the eyelids must touch during the blink action. Train yourself to blink properly e.g. while working on a laptop or computer, squeeze the eyelids tightly every time that you press the Enter key. This creates an association and over time, your blinking will become more effective.
2. Drops for use at night contain oil and help add to the oil component of the tear film overnight.
3. Some eyedrops contain some oil too and these can be used during the day.

Dry Eye Disease (DED) is mostly due to one of two things and often both:
1. Lack of water in the tear film
2. Lack of oil on the surface of the tear film protecting the water layer from evaporating.
3. In 86% of DED cases, the lack of the protective oil is the biggest issue.

THE TEAR FILM IS COMPOSED OF THREE DIFFERENT LAYERS

1. A lipid layer. This is an oily layer on the outer most surface of the tears. This layer stops your tears from evaporating. The lipid layer is secreted by meibomian glands which are located along both the upper and lower eyelid margin.
2. An aqueous or water layer. This is the largest component of the tear film and makes up the bulk of the tears. Aqueous is produced by the lacrimal gland.
3. The mucin layer is the inner most layer of the tear film. It is contact with the surface cells of the cornea. It is responsible for binding the tears to the surface of the eye.
4. Do warm compresses: this softens the oil, opens the glands and when you squeeze them, the thicker, older oil can be expressed and newer, fresher oil can be loaded into the gland from the blood stream. There are a number of videos on the internet that demonstrate the use of an eye bag and doing warm compresses with a hot cloth. Doing them with a hot cloth is hard work and most times people tend to give up on this method of hot compresses within a couple of weeks. With an eye bag that heats in a microwave or oven, better outcomes are achieved thanks to improved compliance.

HOW TO DO WARM COMPRESSES:

• Place an eye bag or microwaveable heat pad into the microwave as per instructions on bag
• Be sure to check the temperature of the compress on the back of your hand or on your cheek, making sure it’s not too hot.
• Find a comfortable place to sit down where you can recline your head. Place the compress over the eyes for at least 10 minutes. The heat tends to make the meibum secretions softer and dilate the glands slightly thereby facilitating the expression of the oily meibum. This should ideally be followed by meibomian gland expression which is explained below.

5. Do Meibomian Gland (MG) expression using a Q-tip/earbud/cotton-tipped applicator to apply pressure to the Meibomian Glands and get the thicker oils to evacuate the glands. Once the warm compress has been done, it is best to express the glands by massaging them with a Q-tip/cotton bud. This takes about one minute per eye lid. It can be performed on both lids but is generally only performed on the lower lid. When this material is expressed into the tear film it may be very uncomfortable as the material is old and possibly inflamed. Within a few days to weeks however, once the older oils have been expressed, the new healthy oils will start moving through the glands and the comfort levels will increase significantly.

6. Ensure that you get enough omega-3 oils in your diet. In recent years fish oil has been suggested as a possible remedy for dry eyes. Fish oil contains two omega-3 fatty acids called docosahexaenoic acid, or DHA, and eicosapentaenoic acid, or EPA. Research studies looking into the benefits of omega-3 fatty acid supplements have found fewer dry eye symptoms in people who take the supplement. The omega-3 fatty acids are indicated to improve the eye’s oil film that is produced by the Meibomian Glands. There are alternatives to omega-3 like flaxseed oil and krill oil but they need to contain the same amount of EPA and DHA as omega-3 to be as effective at improving the tear film.

7. If you go through all the above treatment options and have success at opening the MGs and getting them returned to producing oil, if you are NOT blinking properly and keeping the oil moving through the glands, they will clog up again. If you are not blinking properly, you will need to continue with warm compresses and MG expression to keep the oil moving through the MGs.

8. The “perfect solution” is once the MGs have been rehabilitated and the tear film is healthy, that this status is maintained by proper blinking where the eyelids touch during the blink process.

ALTERNATIVE TREATMENTS (IN CLINIC)

If the MGs are completely blocked, an attempt can be made to open them by means of MG probing. This procedure is done in a treatment room where the MGs are individually probed and opened under the operating microscope. This often leads to an improvement in the condition if the glands were blocked and there is oil in the glands. If the MGs have atrophied completely (died/disappeared), then these treatments will not be of help and the only treatment is putting in artificial tear gel every night. If the MGs are viable but these conservative measures are not helping, then treatments such as IPL often help. These are performed in ophthalmologists treatment rooms and clinics.

<table>
<thead>
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<th>Genre</th>
<th>Use</th>
<th>Type</th>
<th>Dosage</th>
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</thead>
<tbody>
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<td>Mild to moderate dry eye</td>
<td>Sodium Hyaluronate 0.2%</td>
<td>As necessary</td>
</tr>
<tr>
<td>Lubricant Drops</td>
<td>Moderate to severe dry eye</td>
<td>Sodium Hyaluronate 0.4%</td>
<td>As necessary</td>
</tr>
<tr>
<td>Lubricant Gels &amp; Ointments</td>
<td>Night-time use</td>
<td>Typically Liquid Paraffin</td>
<td>At night</td>
</tr>
<tr>
<td>Omega 3s</td>
<td></td>
<td>Omega 3 dietary supplements</td>
<td>As per product instructions</td>
</tr>
<tr>
<td>Warm Compresses</td>
<td>To help unblock Meibomian Glands</td>
<td>Eye bag, eye wipes</td>
<td>10 minutes per day</td>
</tr>
<tr>
<td>Q-tip expression</td>
<td></td>
<td>Lower lid</td>
<td>1 minute per eyelid</td>
</tr>
</tbody>
</table>
SODIUM HYALURONATE 0.4%, TS POLYSACCHARIDE 0.2%

On the NHS Drug Tariff from 1st May 2020.

10 ml - £6.92 - PIP code: 413-5315
30 x 0.5ml - £6.92 - PIP code: 413-5794

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A bi-polymer of two synergistic ingredients
Improves tear film and ocular surface damage

Implements mucin stability and distribution
Supports conjunctival goblet cell preservation

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Five Rare Cases of Central Toxic Keratopathy post Cross linking

by Nancy Al Raqqad1 FRCS, AlYarabi Mohammed1,2, MD and Mohammad Al Tarawneh3 MRCS

Purpose:
To report 5 cases of Central Toxic Keratopathy post cross linking and one case after PRK reviewed and followed up at King Hussein Medical Center in Jordan.

Methods:
We describe a retrospective observational cases series of central toxic keratopathy CTK in 5 cases.
(4 cases post cross linking and one case post PRK). Three local cases and 2 referred cases outside King Hussein Medical Center Jordan were seen within a two-months period and followed up to 6 months.
Post-surgical corneal infection was excluded. Details of the procedure performed were reviewed. Cases that were crosslinked at KHMC underwent epi off accelerated CXL mode with density of 5.4 J/Cm2, intensity of 9 mW/Cm2, over 8 mm for 10 minutes. The Riboflavin used is Ricrolin (Sooft, Italia) Figure 1. Lightlink-CXL device was used in all patients (Figure 2). All affected patients were examined, treated and followed up at 1 week, 1 month, 3 months and 6 months. Data collected included: visual acuity, BCVA, refraction, slit lamp biomicroscopy, pentacam topography (Oculus), and anterior segment optical coherence tomography OCT. Clinical findings of central corneal haze, thinning and stria were documented serially.

Case No.1:
Twenty years old lady with keratoconus, underwent accelerated mode CXL (Epi off/Isotonic Riboflavin) at local private ophthalmic center outside KHMC. She started to complain on the 3rd day post operatively of pain associated with photophobia and blurry vision. She was referred to our service 3 weeks post operatively. Pre-operative visual acuity was 0.1 LOGMAR in both eyes according to old records, and her central corneal thickness as seen on pentacam was 460um in her right eye and 473um in her left eye. Visual acuity on day 20 post-operatively was 0.8 OD/ 0.5 OS. Central pachymetry recorded at her post-operative visit was 317um OD/ 336um OS. Slit lamp examination showed central corneal haze, thinning, striation and flattening. Her postoperative refraction showed hypermetropic changes.

Table 1.
Case No. 2:
Thirty one years old lady, with Forme-frust keratoconus, underwent accelerated CXL (Epi off) for her left eye. Her right eye didn’t show signs of progression or ectasia and was not cross linked. She developed pain on the third day post operatively that was associated with mild haze. Pre operatively her UOVA in the left eye was 0.1, BCVA -0.25/-0.5 x170= 0.0 LOG MAR with corneal thickness 457 um and K max of 48.1. One week post operatively her visual acuity deteriorated to 0.7 and her cornea showed thinning with central pachymetry of 300um. She was suspected and managed initially as bacterial keratitis with antibiotics and no steroids were used initially. As haze increased over the first few days and striation started to appear we started her with a high dose of topical steroids prednisolone acetate every two hours for 48 hours tapered gradually to QID (Pred Forte , Allergan). She started to show signs of improvement over the next few weeks and haze and striation started to decrease. One month post operatively her vision was 0.2 LOG MAR.

Case No. 3:
Thirty years old male patient underwent surface laser ablation PRK at a private center. We have no records of the patient being cross linked after his PRK. He developed corneal haze on the third day post operatively in his left eye. He was managed initially as microbial keratitis. His preoperative refraction was -3.0/-1.75X28 =0.0 OD, and 0.7 improved with -2.0/-1.0X30=0.1 OS. Pre-operative corneal thickness was 510um. He presented to our service three weeks post PRK with bilateral central corneal scarring, striation and flattening with the central pachymetry being 343 um.

Case No. 4:
Twenty-two years old male with keratoconus. He underwent bilateral accelerated cross linking (Epi Off). He developed left corneal scar and stria on the 4th day post operatively. His pre-operative visual acuity was 0.1 OD LOG MAR, with left central pachymetry 474um, his right eye was normal, with no Keratoconus and vision was 0.0 with normal parameters. First week post cross linking his visual acuity was 0.7 OS with central pachymetry of 255um.
Case No. 5:

Twenty-three years old male, underwent bilateral accelerated Epi Off CXL at KHMC. He developed right central corneal haze in the first week post operatively. His right corneal central pachymetry before treatment was 449um. Post operatively his right eye central thickness was 318um with signs of striation and flattening.

Figure 7 - showing right corneal thinning and flattenning. Pentacam showing irregular cornea.

Results:

All reported cases developed typical signs of CTK within three to four days post procedure. All patients underwent epithelial debridement and received high dose of topical steroid drops prednisolone acetate (Pred Forte, Allergan) once toxic keratopathy was suspected. Patients who were identified early as case no.2 responded quickly and showed best response in terms of decrease in haze and decrease of corneal striation. Visual acuity profile (Table 1 and graph1) shows worsening of the visual acuity over the first week that progresses for 1-2 months post op, then starts to improve for the next 4 months, with some reaching pre-operative baseline BCVA. Similarly, the corneal scar faded minimally over time but disproportionate to improvement in visual acuity. The central corneal thickness (table and graph 3) showed progressive thinning over the first 6 weeks in average, then it increased slowly over 6 months. The corresponding K max( table and graph4) decreased over 2-3 months then improved. However visual symptoms started to disappear in all cases from 2 months onward. In all cases no specific triggering factor was identified.

Discussion:

Central toxic keratopathy CTK refers to a condition of very rare, non-inflammatory, central corneal thinning, flattening, scarring and striation associated with photophobia, reduced visual acuity, and hypermetropic shift.1.2. It is a self-limiting condition and has a good prognosis over 18 months (6-18 months).2. CTK been linked with refractive surgeries like PRK, LASIK, and CXL as well. The inciting factor for CTK is still not yet explained. 1.2.3. However, few attributed factors were hypothesized, these include the use of povidone iodine, blepharitis, sensitizing gloves powder. These factors can acutely trigger keratocyte apoptosis leading to thinning, stria formation, haze and hypermetropic shift.4. CTK occurs acutely on the first week post corneal procedures.5.6. Authors also reported CTK cases post contact lens wear and corneal mechanical debridement procedures.7. It can resemble Type 4 deep lamellar keratitis DLK described post LASIK, however this entity is purely inflammatory condition in comparison to CTK. Interestingly, the interface pathology between the contact lens and ablated cornea post op can mimic DLK.8

In our case series we found that initial treatment with steroid drops decreased the duration of corneal changes and this opposes the non-inflammatory theory behind CTK. Nevertheless the thinning, striation, quiet conjunctiva and hypermetropic shift all follow with the diagnosis of CTK.

We did not find any reported cases of CTK after cross linking although one case reported CTK post PRK with cross linking.8 Whether the removal of the epithelium plays a role in the development of CTK in these cases should be further assessed.

We investigated the method of treatment, the riboflavin material used, the protocol adopted in each one of those patients and did not conclude to any unusual inciting factor.

Conclusion:

CTK is an acute rare complication of corneal refractive as well as corneal debridement procedures like CXL. It is a self-limiting condition. Meticulous precautions regarding the use of antiseptic, latex free gloves and preop lid margin treatment may reduce its prevalence. The use of accelerated mode could probably have a related issue that needs to be studied further. Initial steroid treatment can play a role in decreasing the sequelae of this condition. Further studies needed to highlight the specific causes.
Table 1: refractive profile.

<table>
<thead>
<tr>
<th>Case#</th>
<th>Preop Refraction</th>
<th>1 week Postop refraction</th>
<th>1 month Post op refraction</th>
<th>2 months Post op refraction</th>
<th>3 months Post op refraction</th>
<th>6 months Post op refraction</th>
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Table 1: Visual Acuity Profile (LOG MAR)

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<td>5 RT</td>
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Table 2: Refraction Profile

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Table 3: Thickness Profile

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#### Thickness Profile:

![Thickness Profile Diagram](image)

References:


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3 Co-author: ALTarawneh Mohammed (Mat20005@yahoo.com). Royal Jordan Medical services, King Hussein Medical/Ophthalmology center, Amman.
It is predicted that by 2050, half of the world will become Myopic. Increasing prevalence of Myopia is continuously buzzing that Myopia is a 21st century public health concern. The mission of the conference is to cover and present new findings from a wide range of research areas including experimental myopia, environmental factors, genetic analysis, ophthalmological optics and pathologic myopia. We also hope to encourage researchers from around the world to deepen mutual relationships and to broadcast a new global message with respect to the future of myopia research.

Dr Amir Ali Chaudhary Conference Convener

KEY NOTE SPEAKERS

- Dr Malcolm Sameul
  Medical Director, Optimax & Ultrasense Group, UK
- Special Session by Dr Kate Gifford
  Myopia Profile, Australia
- Prof Christopher Liu
  (OBE Award) Tongdean Eye Clinic, UK
- Dr Lisa A Ostrin
  University of Houston, USA
- Prof Dr Asad Aslam
  Khan King Edward Medical University, Pakistan
- Dr Amer Awan
  Shifa International Hospital, Pakistan
- Dr Hashim Ali Khan
  SEHAT Foundation, Pakistan
- Dr Ali Minto
  Nain Suih Hospital, Pakistan
- Dr Faisal Rasheed
  Sheikh Zayed Medical College, Pakistan
- Prof Dr Qasim Lateef
  Lahore Medicare, Pakistan

Abstract Submission: 31st January, 2020
Early Bird Registration: 9th March, 2020
Pre-Conference Workshops: 20th March, 2020

For Information & Registration

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2nd-international-conference-on-myopia-in-Pakistan
username: ICM2020
Ocular surface diseases (OSD) can affect patient’s quality of life in the same degree as severe angina, renal dialysis or hip fracture (Buchholz P, et al). Evidence support that hematic derivates eye drops such as serum eye drops (SED), platelet rich plasma drops (PRP), plasma rich in growth factor (PRGF) and umbilical cord blood serum (UCBS), are a very effective treatment for OSD because their similar composition with natural tears (Rauu) in terms of pH, osmolarity and functional proteins such as growth factors, vitamins, immunoglobulins, neuropeptides and anti-inflammatory molecules.

**SERUM EYE DROPS (SED)**

Autologous serum and plasma were first used to treat a patient with chemical burns in 1975(Ralph). The first report of SED use in a patient with Sjögren’s syndrome related dry eye was in 1984 (Fox) and since then their use as been increasing, despite the elevated production costs, different preparation techniques and controversies among its efficacy. A Cochrane review published in 2017 reports that SED may improve patient reported symptoms in the short term but there is no evidence over a longer period (Pan). Nonetheless, we think there is enough evidence to support their use in a variety of ocular surface diseases such as dry eye and Sjögren’s syndrome related dry eye (Tananuvat, Noble, Kojima, Urzua, Celebi, Shtein), Stevens-Johnson syndrome (Tsubota 1 and 2), persistent epithelial defects (Lekhanont, Chiang et al, Harritshej et al, Shtein), graft-versus-host disease (Na), recurrent corneal erosion (Ziakas), neurotrophic keratitis (Matsumoto), post refractive surgery (Noda-Tsuruya) and aniridia patients (Lopez-Garcia). More RCT with longer follow-up, measuring objective (e.g. TBUT, Schirmer, Osmolarity, MMP-9 level) and subjective (e.g. OSI score) are needed. Another important issue with SED reports is the significant variations in elaboration, storage and treatment protocols. This makes that the efficacy of SED varies substantially between studies.

In the U.K. the NHS provide SED treatment since 2003 in the form of auto-SED (obtained from the same patient’s blood) or allo-SED (from blood donors) in case of patients younger than 16, unable to donate blood or with neoplastic or autoinflammatory disease where the presence of antibodies or immunocomplex on patient’s blood can affect the ocular surface homeostasis. The blood suppliers are tested for hepatitis B and C, HIV, HTLV and syphilis before obtaining the blood unit, which can produce 150 small units of SED at 50% dilution with a duration of 12 months in the fridge.

Blood derived eyedrops, when is the right time to use them?

by Osvaldo Berger - Senior Fellow in Cornea and Anterior Segment - MD, MSc
OTHER BLOOD DROPS, WHY THEY MAY BE BETTER THAN SED?

SED also contain some of the pro-inflammatory cells and their cytokines of blood (Pflugfelder, Yoon 2007b). This together with the presence of immunoglobulins and complement may be detrimental for the ocular surface, especially in those patients with immunological diseases such as graft versus host diseases, Sjögren syndrome, Steven Johnson’s syndrome, and ocular cicatricial pemphigoid.

On their alpha granules, platelets contain a large pool of healing and growth factors (PDGF, TGF-β, VEGF, IGF-I, HGF among others)(Acta 2015 Anitura). Platelets are not part of SED. Plasma rich in growth factors (PRGF) consist of a limited volume of plasma enriched in platelets from the patient, without the presence of red and white cells. Once the platelet concentrate is activated, a fibrin scaffold is formed and a combination of growth factors and proteins are released from the platelets, contributing to the acceleration of wound healing and tissue repair (anitura 2004). PRGF has been shown to be an effective treatment in cases of dry eye (Alio et al. 2007b; Lopez-Plandolit et al. 2011, Garcia-Conca et al.), graft-versus-host disease, (Pezzotta et al. (2012, Sanchez-Avila et al, Anitura 2016) Sjögren’s syndrome (Lopez-Plandolit et al. 2011), persistent epithelial defect (Lopez-Plandolit et al. 2010, Kim et al. 2012 Alizadeh S) corneal ulcers (Alio et al. 2007), post LASIK chronic ocular syndrome (Alio 2017) recurrent corneal erosion with better results than SED (Lee) and chemical injuries (Panda et al). Among SED, PRP and PRGF, the latter has a greater effect on the corneal epithelial cell proliferation, suggesting that platelet degranulation is an important step for the concentration of growth factors and other healing proteins. The same study observed that PRGF produced an over-expression of some genes involved in cell communication and differentiation (Freire).

However, there are not many studies comparing SED vs PRP or PRGF. One study showed that the cicatrization rate in patients with persistent epithelial defects is significantly higher when treated with PRGF instead of SED (Kim). Another study compared the use of PRGF vs SED in patients with graft-versus-host disease showing PRGF to be a more effective treatment. Finally, there is a report by Lee which shows that in patients with recurrent corneal erosion, PRP is more effective than SED (Lee).

For UCBS, blood is collected from the umbilical vein after fetal delivery. UCBS has a bacteriostatic effect due to IgG, lysozyme, and complement and is known to contains more growth factors than other blood derived preparations, with higher levels of EGF, TGF-, NGF and VEGF (Versura P), but lower levels of IGF-1 and vitamin A compared to peripheral blood serum. [Versura P2]. UCBS induces faster healing of persistent corneal epithelial defects compared to SED [Vajpayee RB, Erdem E, Yoon KC2] and also was found to be more effective in treating severe dry eye syndrome, particularly secondary to GVHD (Yoon KCb) and Sjögren’s syndrome (Yoon KCb). It is also more effective than SED in treating chemical burns (Sharma N). UCBS has also been used with good results to treat recurrent corneal erosions (Yoon c), neurotrophic keratitis (Yoon d), and post LASIK patients (Yoon e).

EARLIER USE OF BLOOD DERIVED DROPS

Current Royal College of Ophthalmologist, U.K guideline recommend using SED in severe cases and when conventional treatment has already failed. The following guidance scoring for when to start SED is proposed by the RCOphth:
- Persistent corneal surface symptoms for more than 1 year.
- Patient severity score: Visual Analogue Score more than 8 or Ocular surface diseases index (OSDI) more than 33.
- Tear film Break Up Time less than 3 seconds.
- Staining domains: Van Bجسترفيلد score 8 to 9, Ocular Surface Staining Score 9 to 12 or Oxford Staining Score 11 to 15.
- Persistent epithelial defect unresponsive to the standard treatment.

The TFOS Dry Eye Workshop II of 2017 also recommend SED use as a tertiary strategy, wen previous treatment have already failed (Jones).

The above citeria entailising plasma drops when there is already a considerable amount of inflammation and damage to the ocular surface. We think that with an earlier use, most of the inflammation can be controlled at an early stage due to the anti-inflammatory properties of blood derived drops; and the consequent damage in the ocular surface can be reduced or avoided. In the study by Panda et al, patients with chemical eye injury were divided into two groups: one was treated initially with PRP while the other group was treated with standard drops. The first group showed a significant faster reepithelization (Panda). This supports an early use of blood derived products in the management of active ocular surface inflammation.

Summary

While the majority of the reports described using blood derived products only in severe cases of OSD or when conventional treatment is ineffective or when the degree of inflammation and damage is high, we believe that early use of these products should be considered at allow the full benefit of anti-inflammatory properties of blood derived products. More studies comparing the use of hemoderivates as an initial treatment are needed.
Impact of Ocular Surface Disease Treatment in Patients with Glaucoma

Chronic topical treatment for glaucoma may lead to Ocular Surface Disease (OSD). This study aimed to evaluate: (1) the prevalence of OSD in glaucoma patients under topical treatment, quantifying symptoms and objective ocular surface parameters and (2) the impact of ocular surface treatment on OSD and IOP control. Patients with primary open angle or primary angle closure glaucoma under topical treatment for at least 6 months were enrolled in the study. Patients underwent symptom screening with the ocular surface disease index (OSDI) questionnaire, assessment of objective ocular surface parameters, ocular surface staining and Schirmer test. A treatment for OSD with eyelid hygiene, fluorometholone acetate 0.1%, preservative-free lubricants, free-acid supplementation and oral tetracyclin derivate was started, and the same evaluation was performed. In the study sample (n=19), 73.68% of the patients reported severe symptoms of dry eye disease, with OSDI scores higher than 33 at baseline. Tear film instability was found in 50% of patients, while 23.53% had severe meibomian gland abnormalities. Fluorescein and lissamine green stainings were abnormal in 88.24% and 82.35% of patients, respectively. After ocular surface treatment, statistically significant improvement was found in best-corrected visual acuity (p=0.0003), OSDI score (p<0.0001), bulbar redness (p=0.0196) and fluorescein staining (p<0.0001.) Mean IOP following OSD treatment reduced -1.59 mmHg from baseline in the left eye (p=0.0510).

The prevalence of OSD signs and symptoms was high in glaucoma patients under medical treatment. Short-term OSD treatment may improve ocular surface disease and IOP control, with no need to discontinue glaucoma medications.

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The cornea is the most richly innervated surface in the body making it 400 times more sensitive than the skin. It is densely supplied by unmyelinated sensory nerves (derived from the ophthalmic branch of the trigeminal nerve) and to a lesser extent by autonomic nerve fibers (arise from the superior cervical ganglion). Our knowledge about the complete corneal nerves architecture and functions remain very limited despite extensive laboratory investigations and research in the field. The interest in corneal nerves has accelerated in the recent years largely due to concerns about loss or disorganisation of corneal nerves after cornea laser vision correction. More recently, the role of corneal nerves dysfunction in the pathophysiology of dry eye disease is becoming widely discussed.

The use of in vivo confocal microscopy examination (IVCM) is revolutionary, however it only allows a detailed examination of a small central area of the cornea not of the entire cornea. Nerves were found to enter the corneal limbus from all quadrants in equal distribution moving towards the central cornea. They travel anteriorly and pass through Bowman’s membrane forming terminal bulbs from which the sub-basal nerves originate, which in turn innervates the corneal epithelium. There is no preferential concentration of nerve bundles in the 3 and 9 o’clock meridians. In clinical practice moving the LASIK flap hinge should therefore, opposite what is believed, make no difference to the degree to corneal nerve damage or speed of nerve recovery.

The corneal nerves have sensory and reflex functions, but also have important trophic effects on the cornea. They play a significant role in the maintenance of a healthy ocular surface through the stimulation of corneal wound healing after corneal injuries. Damage or dysfunction of the corneal sensory innervation produces a degenerative condition known as neurotrophic keratitis characterised by decreased epithelial thickness, varying degrees of epithelial degradation, decreased epithelial cell mitosis, and impaired wound healing after corneal injuries. Several experimental and clinical studies have shown that there is a bidirectional control of corneal epithelium proliferation. Sensory neurotransmitters enhance epithelial cell mitosis, while sympathetic mediators, epinephrine and norepinephrine, decrease epithelial cell mitosis. Corneal pain sensation can be triggered by mechanical, thermal or chemical stimulation.

Neurotrophic keratopathy is caused by damage to corneal nerves. The damage could be central, peripheral or both as in some congenital or systemic diseases.
Corneal Innervation after surgical interventions:

Corneal nerves are routinely damaged following modern refractive surgery. It has been reported that procedures like radial keratotomy, photorefractive keratectomy, and Laser In situ Keratomileusis (LASIK) produce localised injury of thick stromal nerves and the sub-basal plexus. This results in transient mild to severe epithelial changes with neurotrophic and/or dry eye features. Damaged corneal nerves may never restore its anatomical architecture or physiological functions. In one long term follow-up study, there has been incomplete regeneration of the sub-basal nerves for up to 5 years following LASIK. Furthermore, there is a significant reduction in the sub-basal nerve diameter and density following LASEK and these do not recover to pre-operative states even 6 months after surgery.

There is no direct association between the sub-basal nerve regeneration and central corneal sensitivity. This might be due to the inability of the current confocal microscopes to detect tiny regenerating nerves that are responsible for restoration of the corneal sensitivity after surgery or that there is substantial redundancy in corneal innervation and the density of nerves required for normal sensitivity is much less than what the cornea is endowed with. It could also mean that the present techniques to measure corneal sensitivity (Cochet Bonnett) are crude and are unable to pick up subtle loss of sensations.
Corneal Innervation in common eye diseases:

One of the most common causes of neurotrophic keratopathy is acute and chronic herpes simplex virus keratitis (HSVK). A profound reduction in the sub-basal nerve plexus is found and strongly correlates with loss of corneal sensation in those cases. Unexpectedly, the contralateral, clinically unaffected eye might also show a diminishment of sub-basal nerve plexus, suggesting bilateral nerve alteration in a clinically unilateral disease.

It is well known that Sjogren’s syndrome is associated with increased prevalence of peripheral and cranial neuropathy. In addition, a relation has been suggested between corneal innervation and aqueous tear production. The results were inconsistent with regard to the effect of dry eye on sub-basal nerve density. While some studies reported a significantly reduced sub-basal nerve density in both Sjogren’s and non-Sjogren’s syndrome dry eyes disease, others observed no significant differences in the density. One of the interesting findings on confocal microscopy (IVCM) was sub-basal nerve tortuosity in Sjogren’s syndrome which was believed to be secondary to the release of nerve growth factors in response to the inflammatory process. Although associated with reduced corneal sensation, long term contact lens wear does not appear to affect the morphology, distribution or number of corneal nerves. Non-structural functional nerve changes have been attributed to the decreased corneal sensitivity in these subjects.

Mapping of the sub-basal nerve plexus in keratoconus has revealed abnormal architecture with a tortuous network of nerve fiber bundles at the apex of the cone; many of these bundles formed closed loops. At the topographic base of the cone, nerve fiber bundles appeared to follow the contour of the base, with many of the bundles running concentrically in this region.

REFERENCES:
In the UK, ophthalmology training lasts for a total of seven years. Once you have been awarded with fellowship of the Royal College of Ophthalmologists, some would go on and become general ophthalmologists while others, wishing to pursue a career in subspecialty, would look for fellowship opportunities.

I did not know what subspecialty I wanted to pursue until towards the end of my training. Eventually, it was the elegant surgical techniques and immediate outcome I see in refractive and ocular surface surgeries won me over.

I was fortunate enough to have worked with some of the best and most respected corneal surgeons, such as Prof Stephen Kaye, Prof David O’Brart and Mr Samer Hamada, who are just a few such individuals that have taught, motivated and inspired me during my training years and fellowship. They all have tremendous surgical skills and wealth of knowledge (very much like a walking Wikipedia) but it was their immense hardwork and the willingness to share their knowledge with me that is truly inspiring.

Most people would seek for 1 or 2 years of fellowship experience. I am currently on my second corneal fellowship. My typical week as a corneal fellow involves 5-6 specialist clinics, 2-3 theatre sessions and 2 research sessions, where I work with all the consultants and 2 other corneal fellows. We are expected to attend and participate in our departmental teaching and audit meetings regularly, and to take part in teaching. Specialist clinics are the chances where we further our diagnosis and medical knowledge in conditions such as dry eyes, autoimmune conditions, allergies, dystrophies and degenerations. We obtain our ‘hands on’ surgical experience in theatres in surgeries e.g. penetrating keratoplasty, endothelial keratoplasty, ocular surface reconstruction (inc. stem cell transplant, amniotic membrane), trauma as well as cataract surgery. Surgical opportunities in femto- and excimer- (LASIK, PRK, PTK) refractive surgery are becoming more and more available in several surgical centres in the UK and I am fortunate to be able to perform some of these surgeries as a fellow at my current unit. We also participate in on call duty covering cornea referrals from other hospitals; reviewing and sometimes admitting patients with severe cornea pathologies, whom may require intensive treatment or emergency surgery to the hospital. During our research sessions, we are strongly encouraged to take up research or audit projects and to attend national/international meetings. This allows us to enhance our knowledge of the diseases and stay up-to-date with some of the latest developed clinical and surgical treatments. After work, it would usually be time to study cases I see in clinics or to go through the surgical steps I learn in theatre by watching videos and making notes.

Fellowship year should be a time where you gain most of the knowledge and skills you require to become a competent surgeon and a consultant. It should also provide you with ample opportunities to take part in research, audit and teaching. Seek a fellowship and mentor who is best fit for your career goal. Location is also important. Most overseas’ fellowship applications start 1 or 2 years in advance before the start of placement. Working visa also takes time to apply so good planning and organization are needed for those considering a fellowship abroad. If finance and the lengthy application process is not an issue for you, then an international fellowship can be extremely rewarding, as you would get to experience a new way of life and move out of your comfort zone, it also helps to broaden your experience with different care models with different ethnic populations. Many international fellowships can offer a much higher surgical volume compared with the UKs, likely due to the difference in health care systems they provide. Best way to find out which is best option for you is by visiting the department and talking to the fellows or trainees who work there.

The main differences between a trainee and a fellow is you would require to have a different set of mind when it comes to making management plan for your patients as if you are the acting consultant. This would come easier as your knowledge and experience build up. You would also have added responsibility to support your colleagues and take lead especially when consultants are not available. This would help to make you an effective leader as well as being able to cope under stress whilst still deliver safe and effective care for your patients.

Fellowship should be an exciting time in your career as it gives you the knowledge you need to step up as a consultant. It is only then - the beginning of a rewarding career truly begins that will hopefully last for a good few decades!
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2 - Below the surface: The corneal nerves
   - What do we know?
   - Neuropathic cornea
   - Neurotrophic cornea
   - Post LASIK corneal neuropathy

3 - Keratoconus: It is not the same anymore!
   - Can we prevent it?
   - How about children?
   - What is new and innovative in contact lenses fitting

4 - Ocular surface neoplasia: What to look for and when to refer?

5 - Interesting and innovative
   - Surgery to repair damaged ocular surface
   - What is in the pipeline!

Each session will cover:
- Best available evidence
- Current practices
- Future innovations
- Panel discussion

Speakers:
Mr Samer Hamada
Prof. Michael O’Keeffe
Mr Damian Lake
Dr Gordon Hay
Mr Damien Gatine
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