OSI

Ocular Surface Insight

Issue 5

Booby Traps on the Road to Refractive Surgery

MIGS: A potential solution to sparing the ocular surface in glaucomatous eyes?

Why does the topic of Dry Eye seem to surface so often?

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Ocular Surface Insight

"If you change the way you look at things, the things you look at change"

Wayne Dyer

Welcome to this new edition of Ocular Surface Insight!

This issue covers a variety of topics, some of which are related to your day-to-day practice, and others which will highlight some of the available therapies in complex ocular surface and cornea diseases.

The widespread use of MIGS, has brought huge advantages to patients and surgeons. Dealing with the paucity of preservative free anti glaucoma medications, the limitations of available products, the ocular surface toxicity (active inflammation and ongoing damage to the conjunctiva and cornea) are some of the challenges that are faced by today's glaucoma and ocular surface specialists.

It is often too late to reverse the damage that has happened already to the eye. The paper by Dr. Ike Ahmed's group, discusses why MIGS is probably one of the most important innovations in managing glaucomatous eyes.

A common question we are often asked by patients: does CXL have any visual benefits? Although the answer is, in general possibly not, there is a great deal of work showing who might benefit visually from CXL. This is important information that will guide you during CXL consultation, with your patients.

The forthcoming OSI symposia will be unlike any other cornea and ocular surface meeting. We will focus on aspects related to ocular surface, which will both interest and benefit cornea and non-cornea specialists. Short presentations will be followed by round table discussions, with the experts themselves.

We will discuss dry eye diagnosis and management which is relevant to every ophthalmologist and optometrist, not just for cornea and ocular Surface specialists: DEWS II for everyone! We will also cover allergic eye disease which although common, there is no standardised agreement on approaching, diagnosing, and treating allergic eye disease.

We will have a very interesting session on Today-Tomorrow innovations, where some of the very new innovations will be presented for the first time. More importantly we will be discussing real life cases, with the experts. CPD points have been applied for and we expect it to be an unforgettable event.

Samer Hamada

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Mr. Allon Barsam - *London*

Ocular Surface Insight are looking for contributors to supply exciting articles of interest. If you would be interested in submitting an article, please get in touch by emailing: articles@visionduo.com

Contents

What's in the news?

Patient stratification in clinical glaucoma trials using the individual tear proteome

Glaucoma patients are prone to concomitant ocular surface diseases; however, switching from preserved to preservative-free medication can often alleviate these symptoms. Nättinen et al objective of this study was to examine how the adverse effects and tear proteome change for glaucoma patients (n = 28) during a 12-month drug switch from preserved latanoprost (Xalatan) to preservative-free tafluprost (Taflotan). They hypothesized that patient stratification could help identify novel recovery patterns in both tear proteomics and clinical data. In order to accomplish patient stratification, they implemented sequential window acquisition of all theoretical mass spectrometry (SWATH-MS) as a tool for quantitative analysis of individual tear protein profiles. During each visit (baseline and four follow-up visits), the patients' tears were sampled and the state of their ocular surface was evaluated clinically. Altogether 785 proteins were quantified from each tear sample using SWATH strategy and as these protein expression levels were compared between baseline and 12-month follow-up, three distinct patient groups were identified. They evaluated how these patient groups differed in their protein expression levels at baseline and discovered that the patients with increased levels of pro-inflammatory proteins and decreased levels of protective proteins benefited most from the medication switch.

Nättinen J, Jylhä A, Aapola U, Parkkari M, Mikhailova A, Beuerman RW, Uusitalo H.

Sci Rep. 2018 Aug 13;8(1):12038. doi: 10.1038/s41598-018-30369-x.

Blue light phototoxicity toward human corneal and conjunctival epithelial cells

The ocular surface is the very first barrier between the visual system and external environment. It protects the eye from the exposure to various light sources that significantly emit in blue spectrum. However, the impact of blue light on the ocular surface has been poorly explored so far. In this study, Marek et al investigated in vitro the phototoxicity of blue light illumination in human epithelial cells of the ocular surface. They worked either in basal conditions or under hyperosmolar stress, in order to mimic dry eye disease (DED) that is the most common disease involving the ocular surface.

The results showed that corneal and conjunctival epithelial cells suffered the most from violet-blue light but also from longer-wave blue light. Exposure to blue wavebands significantly decreased cellular viability, impacted on cellular morphology and provoked reactive oxygen species (ROS) over-production. Conjunctival epithelial cell line had a greater photosensitivity than the corneal epithelial one. Hyperosmolar stress potentiated the blue light phototoxicity, increasing inflammation, altering mitochondrial membrane potential, and triggering the glutathione-based antioxidant system.

In human epithelial corneal and conjunctival cells of the ocular surface, the study demonstrated the harmful impact of blue light on viability, redox state and inflammation processes, which was modified by hyperosmolarity.

Blue light induced cell death and significant ROS production, and altered the expression of inflammatory genes and operation of the cellular defensive system. This study established for the first time that hyperosmolar stress impacted phototoxicity, further suggesting that DED patients might be more sensitive to blue light ocular toxicity.

Marek V, Mélik-Parsadaniantz S, Villette T, Montoya F, Baudouin C, Brignole-Baudouin F, Denoyer A.

Free Radic Biol Med. 2018 Jul 21;126:27-40. doi: 10.1016/j.freeradbiomed.2018.07.012.

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Job code: STN 0418 IKV 00004c

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1. Baudouin C et al. Br J Ophthalmol 2014;98:1168-1176
2. DEWS (International Dry Eye Workshop). Ocul Surf 2007;5(2):65-204
3. Leonardi A et al. Eur J Ophthalmol 2016;26(4):287-296.

Date of preparation: December 2017
Job code: PP-IKERVI-UK-0054

What's in the news?

Changes in ocular surface status after phacoemulsification in patients with senile cataract

The aim of this study was to evaluate the signs and symptoms of dry eye after phacoemulsification; effects on the status of ocular surface using impression cytology; and associated risk factors.

The prospective study included 50 eyes (50 patients) with no dry eye signs or symptoms, who underwent clear corneal phacoemulsification for senile cataract. Dry eye indices used included Ocular Surface Disease Index scoring, Schirmer I test, tear break up time, tear meniscus height, corneal fluorescein staining, lissamine green staining and goblet cell density (GCD) with the help of impression cytology. Primary outcome measures included post-operative changes in the dry eye indices. Secondary outcome measures included correlation of the dry eye signs and symptoms with various risk factors.

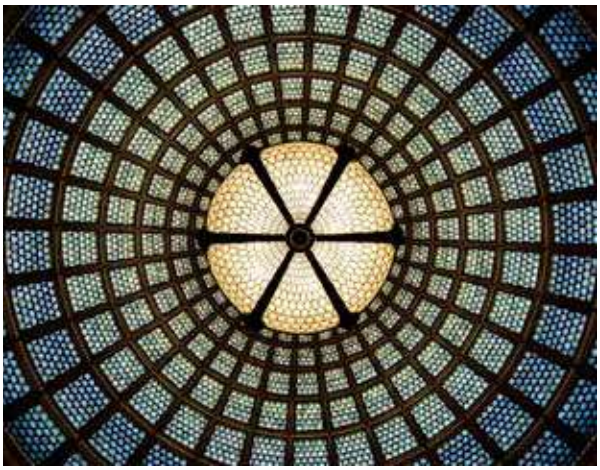
The results showed aggravation of both the signs and symptoms of dry eye were noted in immediate post-operative period. The sharp deterioration was followed by a recovering trend towards the end of sixth week. A decrease in Granular corneal dystrophy (GCD) was also noted. Risk factors for deterioration include age, duration of exposure to microscope light and effective phacoemulsification time. Diabetic status, socio-economic status and site of incision did not have any effect on dry eye status.

Kohli et al concluded that there is a transient deterioration of "dry eye" status post-phacoemulsification. The patients should be carefully counselled about the evanescent nature of the disease. Incision can be given at the site of high corneal curvature to neutralize astigmatism without any fear of inducing dry eye. Minimum light exposure and ultrasound energy should be used during the surgery.

Kohli P, Arya SK, Raj A, Handa U.

Int Ophthalmol. 2018 Jun 20. doi: 10.1007/s10792-018-0953-8.

Ophthalmic community perception of new medication needs



Stewart et al aim was to survey ophthalmologists (who have participated previously in clinical research) and ophthalmic industry professionals (who have been involved in ocular research and development) to indicate perceived needs for new pharmaceuticals in various ophthalmic sub-specialities.

A prospective, industry-based survey was sent to ophthalmologists and ophthalmic industry professionals about the perceived needs for new pharmaceutical products.

The survey was sent to 559 ophthalmic pharma professionals and ophthalmologists. They received 82 (15%) responses. The results showed that the most commonly perceived need for new pharmaceuticals among ophthalmic pharma professionals and ophthalmologists were dry and wet age-related macular degeneration, glaucoma, diabetic macular edema and dry eye.

Stewart WC, Stewart JA, Nelson LA.

Int J Ophthalmol. 2018 May 18;11(5):848-851. doi: 10.18240/ijo.2018.05.22. ECollection 2018.

Antimicrobial activity of a new Aloe Vera formulation for the hygiene of the periocular Area

The aim of this study was to evaluate the antimicrobial activity of a novel preservative-free lid wipe formulation containing Aloe vera gel and hyaluronic acid that is commercialised for the hygiene of the periocular area.

In vitro susceptibility testing of the solution contained in wipes against bacteria and fungi commonly colonizing the periocular area, both reference strains and multidrug-resistant (MDR) clinical isolates, was assessed following the CLSI M07-A9 and M27-A3 broth methods, respectively. The solution was 2-fold serially diluted in broth from 25 µL (25% v/v) to 0.012 µL (0.012% v/v) in microtiter plates. Plates were incubated and minimal inhibitory concentrations (MICs) were read visually. The antimicrobial effectiveness test was performed by inoculating the wipe solution with microbial suspensions at the initial concentration of 105-106 CFU/mL, as recommended by the international Pharmacopoeias. At different time intervals, samples were tested for microbial count.

The results demonstrated that the MIC value of the solution ranged from 25% to 12.5% for bacteria and was 6.25% for Candida albicans. The MIC for MDR isolates was 12.5%. By assessing antimicrobial effectiveness, we found that the solution meets the criteria reported by the European Pharmacopoeia and United States Pharmacopeia for its preservative effect.

This study concluded that the novel wipes they tested possess antimicrobial activity against bacteria and yeast commonly found in the periocular area, and against MDR clinical isolates. The microbial death curves obtained following deliberate contamination of the wipe solution revealed potent bactericidal and fungicidal activity of the formulation.

Vecchione A, Celandroni F, Lupetti A, Favuzza E, Mencucci R, Ghelardi E.

J Ocul Pharmacol Ther. 2018 Aug 10. doi: 10.1089/jop.2018.0011.

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REFERENCES: 1. iStent *inject*® Trabecular Micro-Bypass System: Directions for Use, Part #45-0176. **2.** Hengerer FH. Personal experience with second-generation trabecular micro-bypass stents in combination with cataract surgery in patients with glaucoma: 3-year follow-up. ASCRS 2018 Presentation.

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MIGS:

A potential solution to sparing the ocular surface in glaucomatous eyes?

by Fady Sedarous MD[1,2], Jeb Alden Ong MD[1,2], Iqbal Ike K. Ahmed MD[1,2]

Ocular surface disease (OSD) is one of the most common pathologies associated with glaucoma. Not only do OSD and glaucoma frequently co-exist, but often glaucoma treatment may lead to the initiation or exacerbation of OSD. One of the most common examples of ocular surface irritants causing OSD is the continual use of glaucoma drops. Traditional glaucoma filtration surgery, which has typically been reserved for those failing maximal tolerable medical therapy, has also been known to have detrimental effects to the ocular surface, leading to OSD.[1] The recent developments and continual evolution of microinvasive glaucoma surgery (MIGS) have seen its emerging role in the glaucoma treatment algorithm. MIGS may prove to be a unique option for adequate treatment, both for glaucoma patients who have pre-existing OSD, and in decreasing the incidence of OSD development as an ocular surface sparing remedy of glaucoma.

Topical medications are typically considered first line therapy in glaucoma management. However, roughly half of patients using topical glaucoma medications have OSD symptoms.[2] These symptoms can negatively impact patients' quality of life and cause significant visual symptoms in addition to the progressive visual loss caused by glaucoma. Furthermore, the presence of pre-existing OSD and poor tolerability to topical medications have both been noted to decrease drop regimen adherence, which in turn increases risk of glaucomatous progression.[3,4] Preservatives in topical glaucoma medications can cause toxicity and inflammation. The most common preservative contained in most topical glaucoma medications is benzalkonium chloride (BAK), which non-selectively destroys the cell membranes of microorganisms including normal cells.[5] This toxicity and inflammation with repeated use leads to dryness and OSD. This correlation is further demonstrated as an increase in the number of prescribed topical glaucoma drops leads to increased prevalence of OSD in glaucoma.[6] Continual use can also lead to alteration in the composition and distribution of the tear film, leading to damage to the structures of the ocular surface.[5] The use of preservative-free topical glaucoma medications can be an option to consider as they are often less irritating to patients and increase medication adherence. However, beyond preservatives, the base molecule of topical glaucoma drops has also been implicated in ocular surface derangement. Additionally, these medications are not currently as widely available in all medication classes, are more costly to patients and do not overcome the challenges of patient adherence to treatment. MIGS can potentially lessen reliance on topical glaucoma medications, leading to improvement of the ocular surface.

MIGS offers intraocular pressure-lowering (IOP) with minimal trauma and tissue manipulation, resulting in high safety profiles and rapid recovery. MIGS can be divided into internal and

subconjunctival MIGS depending on outflow pathway targeted. Internal MIGS target either Schlemm's canal or create non-conventional outflow pathways through the suprachoroidal space, and subconjunctival MIGS target outflow pathways into the scleral or subconjunctival space leading to the creation of filtering blebs. The goal of MIGS implantation is not necessarily to reduce IOP to below-normal range but often reduce medication burden while achieving modest IOP targets. Reducing the medication burden leads to less toxicity and inflammatory mediator response that can typically cause or exacerbate OSD. Although traditional glaucoma filtration surgery such as trabeculectomy may decrease the medication burden, they have not been shown to decrease dry eye features when compared to chronically medicated glaucoma patients.[1,7] More work needs to be done to determine the potential beneficial effects of MIGS in patients with OSD from glaucoma drops. The advancement of less invasive surgical treatments have also allowed physicians to be more proactive in the treatment of glaucoma, offering earlier surgical intervention along the glaucoma treatment algorithm. This is in contrast to the traditional treatment paradigm of using a step-wise approach with more aggressive therapy only being used after failure of maximal tolerable medical therapy due to its risks and invasiveness. The early treatment offered by MIGS may also lead to prevention of progression or sparing of OSD.

In contrast to traditional filtration surgeries, MIGS offers quicker recovery time, less inflammation, and avoidance of incising conjunctiva, theoretically leading to decreased likelihood of developing OSD. It is worth noting that bleb forming procedures have been reported to be associated with OSD as they disrupt the tear film.[5] However,

"MIGS can potentially lessen reliance on topical glaucoma medications, leading to improvement of the ocular surface..."

blebs formed following MIGS procedures are typically more posterior and diffuse than those resulting from trabeculectomy, and therefore may potentially be less likely to have a negative effect on OSD.[8] When comparing between different MIGS devices, internal MIGS have less impact on the ocular surface and may play a more prominent role as OSD-sparing procedures than subconjunctival MIGS, given that the latter tend to be bleb-forming procedures. However, internal MIGS are less likely to render a patient on multiple drops to be medication free, which is the ideal state for patients with OSD, while subconjunctival MIGS are more likely to. Furthermore, selective laser trabeculoplasty (SLT) used in conjunction with MIGS may have beneficial cumulative effects in the treatment of glaucoma and prevention of OSD. SLT is widely used with a well-established efficacy and safety profile, which has led many physicians to adopt it as first line therapy.[9] Similar to MIGS, SLT may further reduce medication burden, allowing less disruption of tear film and the ocular surface to improve. Future advances such as intraocular sustained drug delivery may have a role as well in improving OSD in glaucoma patients.

In summation, dealing with OSD in the context of glaucoma can be a challenging ordeal for physicians with traditional glaucoma treatments having less-than-ideal results for the ocular surface. MIGS may present an alternate solution as it offers surgical intervention with minimal disruption to the ocular structures and decreases the topical glaucoma medication burden that can often lead to progression of OSD. Further studies directly examining the effect of MIGS on OSD may consolidate its role as an adjunctive ocular surface sparing procedure.

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1. Eykappo (chloramphenicol) Summary of Product Characteristics 2. Kaur IP et al. Ocular preservatives: associated risks and newer options. Cutan Ocul Toxicol. 2009;28(3):93-103 3. Novelia® PureFlow Technology. http://www.nemera.net/wp-content/uploads/2014/06/WP-Novelia-alternativetofilters-June2015.pdf (accessed March 2018) 4. Novelia® PureFlow http://www.nemera.net/wp-content/uploads/2014/06/Novelia-WP_Sept2014.pdf (accessed March 2018) 5. UK Drug Tariff March 2018

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Cataract & Dry Eye Disease Q & A's

Mr. Allon Barsam & Mr. Bruce Allan.
Edited by Åsa Baudin

Dry eye disease and cataract surgery is a hot topic at the moment. What is the best practice to optimise a compromised ocular surface pre and post surgery and achieve the best visual outcome, we are hoping to find out... This is the first round of opinions from Allon Barsam and Bruce Allan, more to come in the next issue.

1. Do you perform any specific tests or diagnostics to rule out Dry eye disease (DED)?

Allon Barsam: Yes we use Fluorescein testing , lissamine green testing and we always record tear break up time. We observe the TBUT both before, and after Meibomian gland expression. We look at the tear meniscus height, the conjunctival architecture and any problem with the corneal epithelium. We don't routinely use Schirmer testing and we don't routinely do point of care diagnostic testing such as tear film osmolarity.

Bruce Allan: No - ocular surface problems are obvious from the history and examination. Additional investigation is not routinely required.

2. How do you manage patients with DED in preparation for cataract surgery?

Allon Barsam: We always treat DED prior to surgery, we also counsel them carefully about their expectations post operatively. If we are considering any kind of premium lens technology then we would always treat the dry eye disease before surgery. We would then bring them back in order to re-evaluate them and repeat the scans and diagnostic , to help us select the lens most accurately prior to proceeding with surgery.

Bruce Allan: It very much depends on the category. Most commonly it would simply be treatment for MGD - warm compresses, lid massage, lubricants + pre-treatment with Doxycycline 100mg and topical unpreserved Dexamethasone once daily starting 2 weeks prior to surgery.

3. Who would this be managed by? (Consultant, nurse or other?)

Allon Barsam: We have a team in the clinic, which includes technicians, optometrists and myself. The patients will see all three of us at every visit.

Bruce Allan: Ocular surface assessment, treatment, and surgical planning would be by the medical team (consultant or trainee) at the pre-operative consultation.

4. If a patient is found to have blepharitis at pre-op how would you deal with it?

Allon Barsam: It depends on the severity, the nature of the symptoms and what effect it is having on the tear film and the ocular surface. It also depends on what kind of lens we might be planning for surgery so the more severe symptoms, the more profound the effect on the ocular surface. If we are considering premium lens technology, the more likely we are to treat the symptoms prior to surgery and see the patient again prior to proceeding with the procedure. Often we advise patients on conservative measures in the build up to cataract surgery if the symptoms are mild, the effect on the ocular surface is minimal and we are not using a premium lens. We have noticed with some of our patients if they are over zealous with hot compresses in the early post operative period, we believe the instance of post operative inflammation including cystoid macular edema is greater. As far as I am aware this conclusion has never been scientifically evaluated and it is unpublished. However, in my opinion there is a lot of plausibility in how applying heat to the anterior part of the eye might break down the blood aqueous barrier and promote the potential for inflammation. We advise all our patients to cease hot compresses 3 days prior to treatment and not to resume their routine until 2 weeks at the earliest post operatively. In most cases we make patients wait until 6 weeks post operatively, and then we only allow them to use hot compresses once or twice a week and no more. Once they have cleared the period of time for which the greatest risk exists for rebound uveitis or cystoid macular edema, which is beyond 6 weeks, then they can go back to their pre operative regime. As far as I am aware this approach is unique to our practice but something that I think will need further evaluation.

Bruce Allan: Most commonly this is primarily MGD, but if there are specific additional features (Demodex, staphylococcal) then we would target these specifically.

5. Do you prefer to repeat biometry after you have managed DED? Do you believe that refractive surprises could arise from biometry errors when patients are having moderate to severe DED?

Allon Barsam: Yes, if they have moderate and severe dry eye disease, I do believe it will impact on the accuracy of the biometry and the disease should be treated first and then the diagnostic tests should be repeated.

Bruce Allan: Certainly, if the pre-corneal tear film is unstable and TBUT is too low to allow accurate optical biometry, we would work on the optical surface before planning surgery. But the majority of DED problems are mild and do not impact on biometry significantly.

6. Do you take any extra precautions when performing cataract surgery on a patient with DED?

Allon Barsam: Yes, I will not perform limbal relaxing

incisions as that can make the dry eye disease worse. I will counsel the patients about the way we might be able to manage refractive error. If the patients do not have dry eye disease we will most likely carry out laser refractive surgery enhancement if neccesary. In the unlikely event that a patient with moderate to severe dry eyes has a refractive surprise, the only option would be a piggyback sulcoflex intraocular lens insertion. This is something that we explain to them preoperatively. As far as surgery goes, we take great care to protect the ocular surface. With normal patients we will use a topical non steroidal anti-inflammatory, we use Yellox eye drops 3 days prior to surgery and for 1 week post operatively, in order to minimise the risk of cystoid macular edema. However, in Patients with moderate to severe DED we often abstain from using these drops as they can make the cornea neurotrophic and worse.

Bruce Allan: We optimise the ocular surface prior to surgery. Beyond this, we may use unpreserved treatment postoperatively and would continue Doxycycline throughout the preoperative period. We map out any thin areas in the cornea for entry site planning at the preoperative consult.

7. Do you use any viscoelastic fluids to coat the cornea during the surgery?

Allon Barsam: Yes, I use dispersive viscoelastic, normally HPMC

Bruce Allan: Yes - dispersive viscoelastic in every case both to protect the surface and to promote good visualisation.

8. Do you advise your DED patients of any additional treatment after cataract surgery? for example: Would you prescribe any artificial tears to patients pre or post cataract, what is your criteria? Would you consider Preservative free eye drops?

Allon Barsam: We advise all of our post operative intraocular lens patients to use preservative free artificial tears, as and when required. Patients with moderate to severe DED we advise very frequent use of artificial tears, especially in the early post operative period when we expect the ocular surface disease symptoms to temporarily become worse.

Bruce Allan: For severe aqueous DED (eg Sjogrens), we would run though our usual treatment algorithm prior to surgery: steroid treatment and intensive unpreserved lubrication, temp. plugs in lower, then upper, puncta once the ocular surface is quiet, followed by punctal cautery if no epiphora.

9. In your opinion does cataract surgery induce dry eye syndrome? If yes, at what time-point after surgery?

Allon Barsam: Catract surgery can make DED symptoms worse which can manifest itself as early as the first day after surgery. Nevertheless, cataract surgery doesn't cause the DED and I think this is an important point to make to patients. What the surgery can do is potentiate symptoms when patients are predisposed to DED but those symptoms should be resolved in a few weeks. In some cases the patient fails to properly control their symptoms with the appropriate treatment. It is in these cases with poor compliance that patients may have prolonged symptoms, beyond the first few weeks following surgery. We also try to educate patients about DED as much as possible, in order to prevent it from happening.

Bruce Allan: All eye surgery temporarily destabilises the tear film to some degree, and an exacerbation of obstructive MGD in the later post-op period is not uncommon (perhaps because patients are reluctant to rub their eyes or cautious with lid hygiene after surgery). Asymmetric foreign body discomfort is common after cataract surgery - possibly in association with nerve injury at entry sites. It normally resolves without any intervention.

10. Do you see a role for Ciclosporin (CsA) eye drops in pre or post operative management?

Allon Barsam: Yes, for patients with severe DED I will prescribe this pre-operatively and they will continue postoperatively

Bruce Allan: Not really. It is rarely required and too expensive for routine NHS use.

11. When consenting patients for Cataract surgery, do you mention DED as a complication?

Allon Barsam: Yes, we always counsel the patients very carefully to manage their expectations post surgery, that this is a common condition.

Bruce Allan: Not routinely - patients are interested in the headlines: rates of severe visual loss, secondary intervention and laser intervention. Tear film destabilisation after surgery is temporary. If patients have a pre-existing problem with DED prior to surgery, we would certainly discuss treatment prior to surgery though.

12. How often are you faced with unsatisfied patients after cataract surgery due to dry eye, whether due to symptoms or variation in the vision?

Allon Barsam: All the time. I would estimate at least on a monthly basis but sometimes even more frequently. I have a high volume practice and operate on hundreds of patients every year but this is a very frequent problem no matter how much counselling we do. Despite all the preparation and pre-treatment it is inevitable that some patients will have symptoms because they have a pre-existing condition. Anything can send this patient group over the edge in terms of symptom manifestation, like long hot summers with constant exposure to air-conditioning. Half of the population will have dry eye symptoms at some point in their life. It is so unbelievably common. Anyone who says dry eye is not a huge problem are either in denial or not listening to their patients.

Bruce Allan: Not too often. The key is to optimise tear film stability preoperatively and maintain treatment (Dox 100mg od) in the perioperative period.

The Use of Blood-Derived Eye Drops in the Treatment of Dry Eye Syndrome

by Dr. Alexander Whiteman & Mr. Mohamed Shafik Elalfy

For a significant proportion of patients conventional treatment for dry eye syndrome (DES) is simply not sufficient in ameliorating symptoms. There is growing interest in various blood-derived products that may better replicate the complex composition of our natural tears, theoretically promoting recovery from DES through the presence of various growth factors and cytokines whilst also providing good lubrication. This article aims to give an overview of the preparations currently being investigated and to evaluate the evidence for their efficacy in the treatment of DES

Serum Eye Drops

Serum eye drops (SED), prepared by retaining the liquid component of donor blood that has been encouraged to clot, are the most widely used eye drop preparation worldwide. Like natural tears, serum contains a rich mix of biochemical factors including amino acids, carbohydrates, electrolytes, vitamins, enzymes, cytokines, immunoglobulins and growth factors vital for supporting growth and proliferation of epithelial cells.[1] They also compare in osmolality and pH.[2] The scientific rationale behind the therapeutic effect of SED is thought to be due to a mimicry of the biochemical, lubricant, antimicrobial and epitheliotrophic properties of human tears. However, not all factors may be beneficial. TGF-β, responsible for reducing epithelial cell proliferation, is found in concentrations five times higher in serum than in tears. Many preparations are diluted to either 20% or 50% so as to replicate the concentration of TGF-β in tears and avoid complications. SED can be sourced from autologous or allogenic donors, each with their benefits and drawbacks.

To standardise practice, outcome monitoring and access to SED, the Royal College of Ophthalmology issued guidance on their use in September 2017.[8] As an unlicensed medication, SED must be reserved for patients with a special need (see eligibility criteria), including severe dry eye, for whom other treatments have failed. Patients should have a follow-up at 6 months and annual review. They advise prescribing a preparation of 50% dilution with 0.9% sodium chloride, with a frequency and duration that is dependent on each patient's response to treatment.

Eligibility criteria for severe disease:

- Severe, persistent ocular surface symptoms for > 1 year
- Patient severity score
- Visual Analogue Score (VAS, 0-10): >8
- Ocular surface disease index (OSDI, Max 100): >33
- Tear film Break Up Time: <3s
- Staining domains
- Van Bjiserveld score (Max 9) = 8 to 9
- Ocular Surface Staining Score (Max 12) = 9 to 12
- Oxford Staining Score (Max 15) = 11 to 15
- Persistent epithelial defect unresponsive to standard treatment

Courtesy of the Royal College of Ophthalmology8

Platelet-Derived Plasma Preparations

The variable success rate of studies into SEDs has led researchers to investigate platelet-derived preparations. They contain a relatively higher concentration of platelet growth factors and cytokines compared to SED, theoretically improving the efficacy. These preparations have been widely used in maxilla-facial surgery and orthopaedics to accelerate and improve wound healing.

Platelet-Rich Plasma (PRP)

PRP is prepared by extracting blood with anticoagulant and using a centrifuge to separate the blood into three layers, the middle of which (containing a high concentration of platelets) is aspired and prepared into eye drop applicators. Tivron et al. recently found that a further freezing stage can increase platelet-derived growth factors, possibly providing additional efficacy to this preparation.[9] A large prospective case-series by Alio et al. treated 368 patients with DES to 6 weeks PRP monotherapy. Symptoms improved in 87.5% of patients, a decrease in corneal fluorescein staining seen in 76.1% and 28.8% of patients improved 1 line of BCVA.[10] Proponents of PRP report efficacy, cost and ease of production as the main benefits of this preparation, however there is a paucity of study data available at this time.

Plasma Rich in Growth Factors (PRGF)

PRGF is manufactured using the Endoret system (BTI Biotechnology Institute, S.L., Miñano, Álava, Spain). Production is a closed system technique that reportedly makes the manufacturing process safer and more reproducible. The addition of calcium chloride as a platelet activator enhances the release of growth factors, creating an 'activated' PRP. Using a heating process (56°C for 1 hour), the concentration of pro-inflammatory mediators immunoglobulin E and complement are reduced.[11] In addition, the PRGF eye drops are not diluted, as usually happens with AS. PRGF remains stable for up to 3 months when frozen. Concerns have been raised regarding the increased concentration of certain growth factors which may impair healing or cause neovascularisation.[12]

Investigations have shown PRGF effective in treating a number of ocular surface disorders including DES. Lopez-

Plandolit et al. studied 16 patients with moderate to severe DES who received PRGF treatment for at least 3 months.[13] Response to a Dry Eye Questionnaire showed significant symptomatic improvement, but objective tests, including lissamine green dye staining and conjunctival impression staining, were not improved by treatment. Merayo-Lloves J et al. studied 41 patients with refractory DES and reported statistically significant reductions on the OSDI scale (39.27%), VAS frequency (38.9%) and severity (40.3%), and a significant improvement in BCVA (54.86%). 63.8% of patient required only one or two cycles (1 cycle = 6 weeks), 36.3% received 3 to 4 cycles of PGRF.[14]

Fingerprick Autologous Blood (FAB)

FAB has been proposed as a simpler, cheaper and effective alternative to other blood-derived products. The aforementioned preparations require the frequent drawing of blood which excludes certain patients, such as those whom are anaemic or have heart failure. Production methods also bring about delay and are expensive. Than et al. investigated 29 eyes (16 patients) in a prospective non-comparative study, with patients using a blood lancet to prick their finger and administer a drop of blood to the fornix of the affected eye four times a day for 8 weeks.[15] At 8 weeks, there was improvement in mean Oxford Grading Scale (3.31 to 2.07 ($P<0.0001$)), TBUT (5.00 to 7.80 s ($P<0.05$)), visual acuity (0.08 to 0.01 LogMAR equivalent ($P<0.05$)), and Ocular Comfort Index (OCI) score (56.03 to 39.72 ($P<0.0001$)). There was no statistically significant change in Schirmer's test results. At four weeks post-cessation versus immediately after conclusion of FAB therapy, mean staining grade deteriorated from 2.07 to 2.86 ($P<0.0001$). OCI score worsened from 39.72 to 44.67 ($P<0.05$). Long term compliance (448 pricks in 8 weeks in this study) may be a barrier to some patients, although the study authors report this was generally not an issue due to significant symptom relief.[12] This is the only published study to date but a number of further trials using FAB have been registered.[16-18]

Conclusion

DES is a very common eye condition that presents with a variety of causes and severity. The effect on the quality of life of patients and the socioeconomic burden are well known to ophthalmologists. Blood-derived eye products may provide a novel approach to treating DES. As we have seen, more studies are required to determine correct production methods, treatment protocols, efficacy and the short and long-term safety of these preparations. The inconvenient production methods and overall cost remain barriers to treatment of DES with blood-derived products. Nevertheless, regenerative therapies in the form of blood-derived eye preparations may provide a new perspective in the management of this complex disease.

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Neuropathic corneal disease

by Dr. Yumna Busool

Corneal neuropathy is currently an ill-defined disease. Neuropathic pain is defined as pain caused by a lesion or disease of the somatosensory nervous system[1]. Patients experience unpleasant and often severe sensation of pain, light sensitivity, irritation results in impaired functioning and interferes with the ability to perform daily life activities; including reading, driving and working.

The impact on physical and social functioning can be debilitating. This condition can mimic dry eye symptoms. However, the severity of symptoms are disproportionate to clinical examination, therefore, patients are often diagnosed with this morbidity through dry eye investigations. Although the underlying mechanisms are poorly understood, this disease is associated with conditions that result in damaged corneal nerves, namely, refractive surgeries, ocular surface diseases such as chronic dry eye disease, recurrent corneal erosions, corneal neuropathic infections such as herpetic simplex and zoster, and systemic neuropathic conditions such as diabetes, exposure to topical and systemic drugs, radiation keratopathy and chemotherapy[2 3] . Nevertheless, in many instances evidence for an underlying pathophysiology is lacking.

Anatomy and Physiology of Normal and Iinjured Corneal Nerves

The cornea is the most densely innervated structure in the human body. The sensory nerve supply is derived from the ophthalmic division of the Trigeminal nerve, which gives branches to ciliary nerves that enter the preichoroidal space 1mm behind the limbus. About 60-80 myelinated branches enter the cornea. The density of nociceptors in corneal nerve endings is about 300-600 times that of skin and 20-40 times that of tooth pulp. Corneal nerves are responsible for sensations of touch, pain, and temperature and play an important role in blink reflex, wound healing[4] and tear production and secretion[56]. After penetration, majority of the nerves turn 90 degrees and run parallel to the epithelial surface in the sub-basal layer forming the corneal subbasal corneal nerve plexus that runs towards the corneal centre in a clockwise centripetal pattern. Some of the nerves terminate as free nerve endings[7]. Corneal nerves are functionally heterogeneous: about 20% respond exclusively to noxious mechanical forces (mechano-nociceptors); 70% are additionally excited by extreme temperatures, exogenous irritant chemicals and endogenous inflammatory mediators (polymodal nociceptors), and 10% are cold-sensitive and increase their discharge with moderate cooling of the cornea (cold receptors). When the cornea is severely wounded (often surgical such as keratorefractive surgery), corneal nerves are excited and eventually severed in a variable degree and local inflammation is produced. Pro-inflammatory mediators such as prostaglandins, cytokines and neuropeptides are released. These neuropeptides induce nerve regeneration. Unregulated and ineffective nerve sprouting at the ends of the injured nerve stumps leads to formation of traumatic neuromas that further cause sustained inflammation leading to a vicious cycle. Moreover, nerves that are sensitised by pro-inflammatory mediators exhibit spontaneous activity, lowered threshold and enhanced responses to new stimuli. This leads to spontaneous pain and hyperalgesia[8]. Central sensitisation occurs as a result of repeated nerve stimulation that act post synaptically in the spinal cord causing direct depolarisation along the central pain pathway[9 10 11]. This causes more rapid response to similar stimulus in the future known as neuronal plasticity[12]. This amplification of the neuronal hypersensitivity persists despite removal of the initial stimulus, resulting in neuropathic pain.

"The cornea is the most densely innervated structure in the human body..."

Management of Neuropathic Corneal Pain

Management of neuropathic pain should be individualised based on the aetiology and severity of

symptoms. An essential starting point is preventing further insults to the corneal nerves, decreasing ocular surface inflammation and restoring the ocular surface. It is of high importance to detect central sensitisation components, as local surface treatment is insufficient in those patients[13].

Dry Eye Treatment

Artificial tears, lubricating ointments and gels provide symptomatic relief. Decreasing the hyperosmolarity of tears may halt the over-stimulation of nociceptors. Managing blepharitis with lid hygiene treatments, warm compresses, glands expression, Intensive pulsed light therapy, and proper topical and systemic antibiotics, improve evaporative components of the dry surface.

Treatment of surface inflammation

Steroids are the mainstay of treatment for the majority of ocular surface inflammatory diseases, however, their usage has been limited to short durations due to the possible side effects, mainly high intraocular pressure and cataract development. Non-steroidal anti-inflammatory therapies include, Topical cyclosporine A 0.5%, an immunomodulator that inhibits T lymphocyte proliferation, has been shown to decrease the surface inflammation14. A new drug, Lifitegrast, blocks the interaction of inflammatory modulators, ICAM-1 and LFA-1, has been shown to improve inflammation associated with dry eye disease[15].

Neuro-regenerative therapy

Autologous serum tears contain high concentration of nerve growth factor (NGF). NGF plays an important role in nerve regeneration and restoration of function of nerves[16 17]. However, NGF may also result in ocular and periocular pain[18 19 20] , it is still not clear if NGF agonists will be good options for patients with neurotrophic pain.

Also, various neurotrophic growth factors and epithelial growth factors present in high concentration in serum tears, which help in proliferation, differentiation and maintenance ocular surface health.

Contact lenses

Scleral contact lenses are increasingly used in neurotrophic cornea patients as they improve the evaporative hyperalgesia component.

Oral medications

Calcium channel alpha 2 delta ligands:

Gabapentin and pregabalin influence central nerve function through interactions with Ca+2 channels and inhibition of voltage gated calcium currents that mediate excitatory neurotransmitter release. They have been used off-label in treating corneal neurotrophic pain with some success[21].

"Corneal nerves are responsible for sensations of touch, pain, and temperature and play an important role in blink reflex, wound healing[4] and tear production and secretion[56]..."

Anti-depressants

Used in the treatment of neurotrophic pain; however, no data is available regarding their use in corneal neuralgia.

Omega-3 fatty acids

lipid mediators derived from omega-3, such as resolvins and protectins have anti- inflammatory effects. Omega-3 was shown to reduce ocular surface inflammation[22]. The efficacy of Omega-3 in ocular neuralgia has yet to be studied.

Novel Therapies

Vascular Endothelial Growth Factor (VEGF)

Recent investigations outline that the angiogenic growth factor, VEGF-A, is integral for the modulation of nociception and onset of chronic pain[23]. The results of a study published by Lin et al[24] show that VEGF is involved in the pathogenesis of neuropathic pain and VEGF primarily potentiates pain responses mediated by P2X2/3 receptor on dorsal root ganglia neurons. Anti-VEGF treatment in rats may alleviate chronic neuropathic pain. Human studies are needed to verify these results, and potentially utilising anti VEGF as a therapy for corneal neuralgia.

Electrical Stimulation of the Trigeminal Ganglion and Intrathecal Drug Delivery Systems

A case report published by Sayegh et al[25] reports a novel treatment in two recalcitrant cases of corneal neuropathic pain. The procedure involves implantation of an electrode for the electrical stimulation of the trigeminal ganglion followed by implantation of an intrathecal infusion system for fentanyl and bupivacaine delivery at the C1-C2 level. The procedure was successful in managing corneal neuralgia for a year.

Amniotic membrane

In a recent study by[26] Morkin et al, self-retained cryopreserved amniotic membrane (ProKera®) was shown to improve neuropathic pain.

Nerve growth factor (NGF)

Cenegermin is a recombinant form of human nerve growth factor. The indication is treatment of moderate-severe neurotrophic keratitis. Future studies are warranted to assess its effectiveness in neuropathic corneal pain.

Regenerative therapy

Cacicol is a regenerating agent, a dextran derivative polymer and heparan sulfate analog, used for matrix therapy in neurotrophic cornea. Several studies have addressed its efficacy in healing chronic corneal ulcers resistant to conventional therapies[27 28 29]. Also, Cacicol was shown to enhance corneal healing and reduces corneal neuralgia associated with epi-off crosslinking[30].

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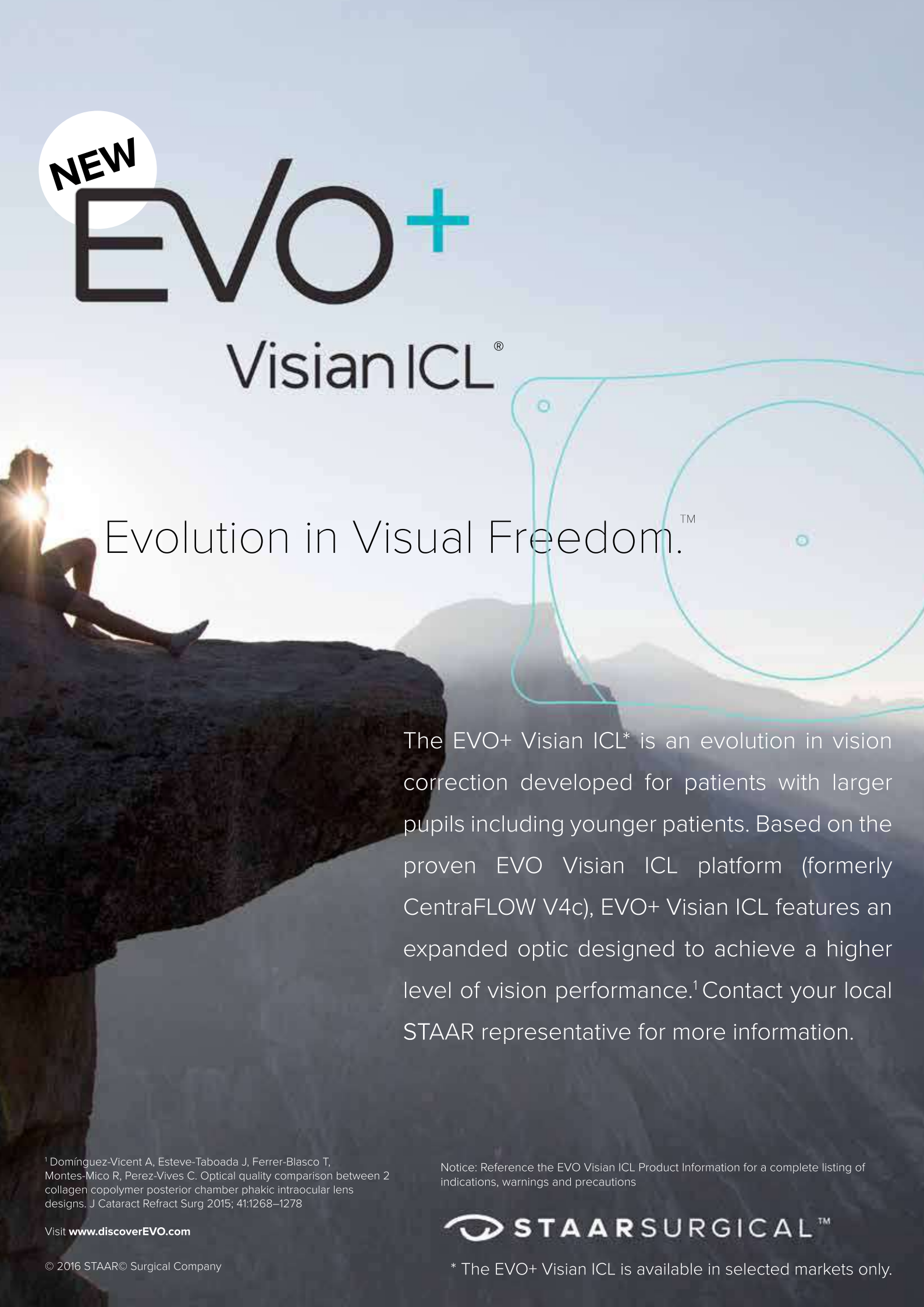

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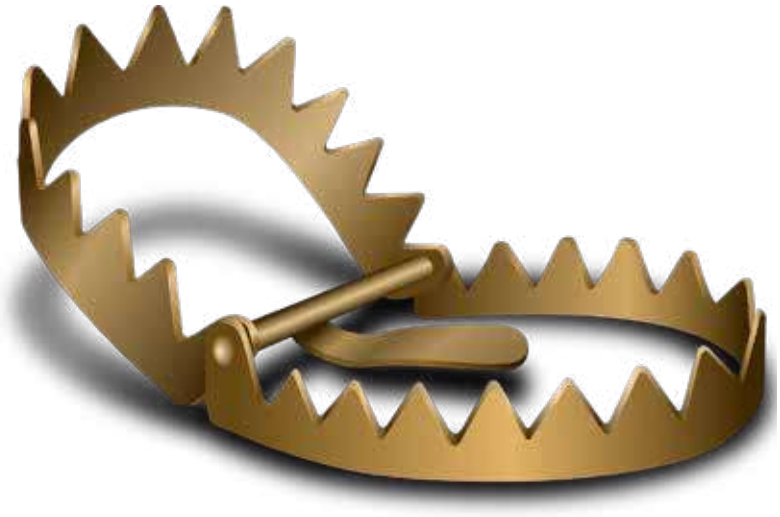
Booby Traps on the Road to Refractive Surgery



By Mr. Erik L. Mertens, MD, FEBOphth

Recognizing tear film insufficiency and treating it adequately prior to scheduling surgery will lead to better postoperative outcomes and, ultimately, happier patients.

Dry eye disease (DED) is everywhere, and in fact it is the most frequently encountered disease state by eye care professionals. According to a 2013 Market Scope analysis,[1] more than 25 million people living in Europe suffer from DED. What is an even more staggering statistic is that these people spend about €3.2 billion annually in the European Union on medications and prescriptions that provide DED symptom relief.

Given these statistics, it is no wonder that we see so many patients with DED. The presence of DED is not a contraindication to refractive surgery, however, as long as it is recognized and treated adequately prior to scheduling surgery. In this article, I will review the two most primary forms of DED and overview some of the best methods to treat the condition.

Categorise The DED

Before you can recognize the presence of DED, you must understand the difference between the two primary forms, evaporative and aqueous deficient.

Evaporative DED. This form of DED, which is a lipid deficiency caused by Meibomian gland dysfunction, accounts for roughly 86% of the DED patients you will see.[2] Evaporative DED occurs when the aqueous in tears evaporates at a faster than normal rate. The severity of the disease can range from mild to severe.

Aqueous deficient DED. This form of DED is more rare, as it only constitutes about 14% of the DED patients you will see.[2] In patients with aqueous deficient DED, aqueous generation from the lacrimal gland is insufficient to keep the eyes moist. The severity of the deficiency can range from a tear meniscus dimension of 0.2 mm to 0.0 mm.

Diagnose The DED

Diagnosing both evaporative and aqueous deficient DEDs requires both subjective and objective testing. Luckily for us, the Tear Film and Ocular Surface Society recently released its Dry Eye Workshop II (DEWS II) study, which generated a global consensus on multiple aspects of DED, including an updated definition and classification system, a regimen for diagnosis of DED, and recommendations for pharmaceutical interventions for DED treatment (Figure 1).

The first and foremost step is to talk to each patient who walks through your door. A DED questionnaire such as the Standardized Patient Evaluation of Eye Dryness (SPEED) or Ocular Surface Disease Index (OSDI) questionnaires are both appropriate and helpful tools to help identify patients with DED. Further, patients should be asked about what kind of medications they are on and have been on in the past, including antihistamines, decongestants, antidepressants, and glaucoma eye drops. Patients should also be assessed for any anatomical lid defects.

Another important step in the analysis of patients for DED is to perform a systemic history, including Sjogren syndrome, rheumatoid arthritis, rosacea, thyroid dysfunction, lupus, and hormonal changes.

In my office, I perform the following diagnostic testing in addition to the SPEED/OSDI patient questionnaires:

- Corneal and conjunctival staining with fluorescein, lissamine green, or rose Bengal;
- Tear film breakup time TBUT);
- Schirmer test;
- Meibography;
- Tear osmolarity;
- Matrix metallopeptidase 9 (MMP-9) and interleukin-1 receptor antagonist; and
- Epithelial thickness mapping.

"...people spend about €3.2 billion annually in the European Union on medications and prescriptions that provide DED symptom relief..."

A Deeper Dive

Some of the diagnostic testing we have available today is more advanced than the staining, TBUT, and Schirmer tests that most of us are comfortable performing. These tests are

still extremely relevant and important to perform, but other tests can help us to pinpoint the exact cause and severity of the DED.

Tear osmolarity. This is a relatively new innovation that can be useful to detect abnormal osmolarity or instability in the tear film. Normal tear osmolarity is 290 mOsms/L, but patients with DED will often present with an elevated reading (>308 mOsms/L), indicating loss of homeostasis. Likewise, the typical inter-eye difference in tear osmloarity is 2 mOsm/L; however, patients with DED who present with a difference >8 mOsms/L have instability of the tear film. If the patient is symptomatic but presents with normal tear osmolarity, additional considerations include conjunctival chalasis, mild allergic conjunctivitis, and epithelial basement membrane dystrophy.

It should also be noted that patients who do not present with DED symptoms can still have hyperosmolarity, and performing a tear osmolarity test will help to identify such patients. According to a study of 9,216 patients performed by Sullivan et al,[4] 51% of patients had a normal osmolarity,

"... Specifically, leaving a patient hyperosmolaric prior to IOL implantation could result in a significant difference in IOL power,..."

meaning that the other 49% had some form of DED. Of the patients who did not report any symptoms of DED (n = 5,191), 47% had hyperosmolarity.

Tear film assessment. TBUT can be assessed thoroughly with the HD Analyzer (Visiometrics). This tool can not only differentiate between eyes with healthy and unhealthy tear films, but it can also differentiate between a healthy eye with a normal TBUT cycle and a healthy eye with an accelerated TBUT cycle (Figure 2). The HD Analyzer can also create an ocular scattering index, which can correlate with visual function.

Inflammation. As another indicator of DED, it is important that we test the ocular surface for inflammation. Identifying elevated MMP-9 levels guides our therapeutic decision making because it can help to predict what patients will respond to anti-inflammatory therapy, and it can therefore help us to customize a treatment plan.[5] Traditional testing methods (TBUT, Schirmer, and even osmolarity) cannot predict what patients have inflammation, and therefore I use the RPS Inflammadry test (RPS).

In the presence of inflammation, many complications can occur if cataract or refractive surgery is attempted. These include less accurate presurgical measurements, leading to potentially worse visual acuity outcomes[7] and exacerbation of DED severity and symptoms.[8]

Putting It All Together

So why does diagnosing and treating DED preoperatively matter? For starters, it will help you to ensure that your patients have the best shot at excellent postoperative outcomes. Specifically, leaving a patient hyperosmolaric prior to IOL implantation could result in a significant difference in IOL power, as indicated by Epitropoulos et al.[6]

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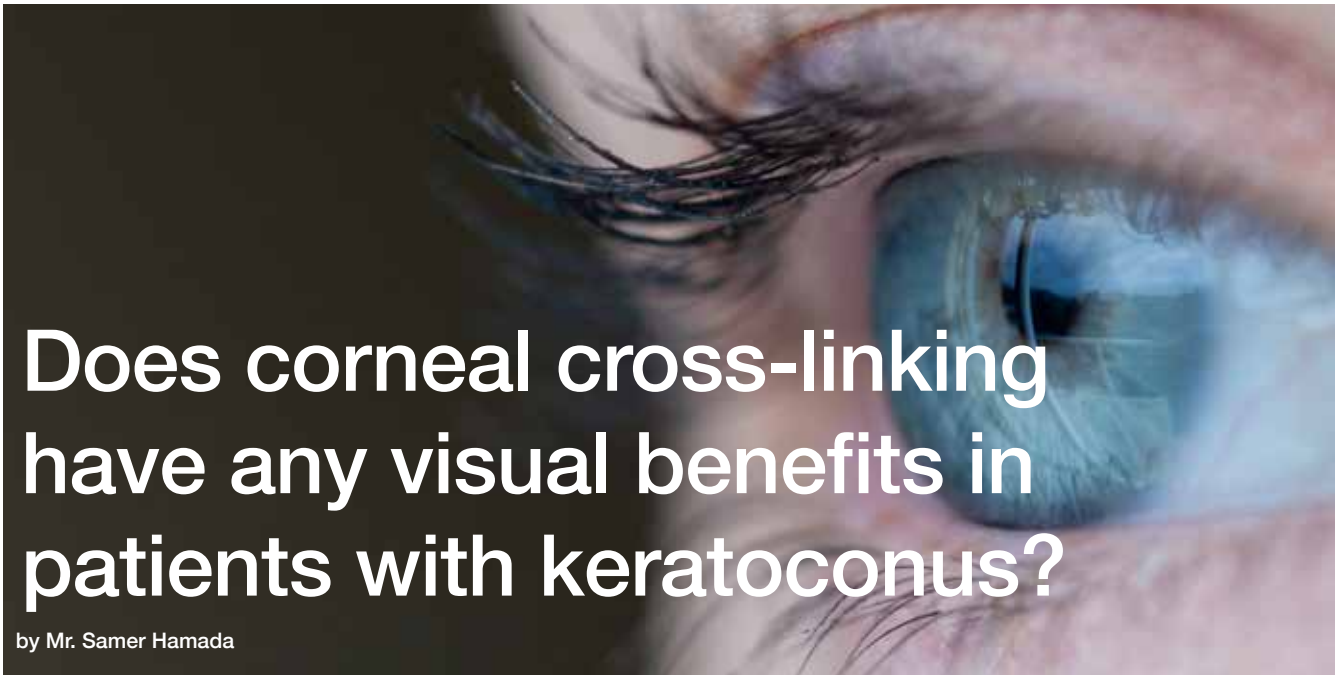

Does corneal cross-linking have any visual benefits in patients with keratoconus?

by Mr. Samer Hamada

Corneal cross-linking has become the gold standard in the management of progressive keratoconus or Ectatic corneal disease (ECD). With keratoconus the question that we are frequently asked is whether corneal cross-linking improves visual functions, and if so what are the factors that influence the magnitude of improvement in visual acuity. Furthermore can we really predict the degree of visual improvement or visual function rehabilitation, following corneal cross-linking in keratoconus patients.

Most of us who perform corneal cross-linking treatment in our routine practice know that visual acuity reduces both the uncorrected and best corrected vision, in the first month following corneal cross-linking. There is generally a myopic shift, and possible increase in magnitude of astigmatism. However, by 3 months following corneal cross-linking treatment visual function and the uncorrected visual acuity start to gradually improve in the treated eye. Following this and by 12 months the visual functions both uncorrected and best corrected, start to stabilise and potentially improve with time. We expect by that time keratrometric measurements both the maximum keratomtry reading and mean keratometry at various optical zones to remain stable, indicating that the treatment has been successful.

In a prospective randomised controlled trial with 1 year outcomes that was first published in the journal of Cataract and Refractive Surgery in 2011, Hersh et al found that the uncorrected distance visual acuity, maximum keratometric value, and the average keratometry were all improved following the treatment. The same group of authors later published another paper but with a larger group of patients (205 patients) with a mean follow up of 12 months. Again, they found that the uncorrected and best corrected visual acuities were both improved in these patients.

There are other randomised controlled trials, that describe improvement in the uncorrected and best corrected acuity. In Australia, Wittig-Silva et al reported a longer follow up averaging 36 months. David O'Brart from the United Kingdom has also found similar results with a mean follow up of 18 months.

"can we really predict the degree of visual improvement or visual function rehabilitation"

There is a large number of non-randomised controlled trials mostly prospective studies , which looked at the improvement in visual acuity. Out of all 10 papers reviewed 2008 – 2015 only two papers showed that the vision has not improved. The paper from Iran published by Hashemi et al in 2013 followed the patient for five years and found no change in the visual acuity with both the unaided and best corrected distance visual acuities. The second paper showed that the vision had decreased following treatment, however this study followed the patients for 9 month only. One can summarise so far that there is an overwhelming evidence to suggest visual acuity does improve following corneal cross-linking, but the improvement is delayed by at least 12 months.

The second question would be: what are the factors that could predict visual improvement following corneal cross-linking. This is an even more challenging question to answer but we will try to investigate four possible risk factors. They are: 1. Age 2. Cone centration 3. Pre operative visual acuity 4. Thickness of the thinnest point of the cornea

As for the effect of age of the patient, a retrospective study on a paediatric group of patients (less than 18 years old) by Soeters et al, found that the improvement in the vision in best corrected visual acuity after corneal cross-linking was the highest in paediatric eyes.

When studying the effect of pre-operative best corrected visual acuity on the visual outcomes of corneal cross-linking, we found a study by Godefrooij et al where they described the outcomes of prospective study looking at predictors for treatment outcomes after corneal cross-linking for keracotonus published in 2017. They found that the lower pre-treatment best corrected visual acuity was the only independent factor

predicting an improvement in the best corrected visual acuity at 1 year post treatment. Another interesting finding from the study was that the cone location affected the results, and the more central cones benefited more in terms of cone flattening. A study by Wisse et al also found similar results where the pre-treatment best corrected visual acuity was a positive predictive factor for post treatment visual acuity, in that the lower the best corrected visual acuity the better the improvement. Another intriguing paper reviewed predictive factors for visual outcomes after corneal cross-linking in progressive keratoconus at 1 year, by De Angelis et al. What they found was the predictive factor for best corrected visual improvement were the low pre-operative best corrected visual acuity, higher refractive astigmatism and advanced keratoconus. Whereas the predictive stability of post operative K max values were early keratoconus and central cones. Finally, a paper by Legare et al looked at the outcomes of treating mild to moderate keratoconus, with 2 year follow up. The paper was published in the Canadian Journal of Ophthalmology in 2013 and found that the baseline best corrected visual acuity worse than 0.1 LogMAR was associated with greater improvement in post operative best corrected visual acuity.

The third predictive factor which relates to the cone location was studied in the American Journal of Ophthalmology in 2014 by Wisse et al. The authors found that the cone excentricity was a major factor for predicting the maximum keratometry outcomes. De Angelis et al found that the early Keratoconus and the more central the cone, the better stability of post operatively maximum kerotometry.

We finally looked at corneal thinning and found a paper describing the predictive factor of standard cross-linking in adult keratoconus at 1 year by Bedawi et al and appeared in the Journal of Ophthalmology 2017,

"This effect is clearly a concern to both patients and clinicians with no clear explanation"

they found that the eyes with higher Kmax and relatively thinner cornea were relatively good predictors of improvement following corneal cross- linking.

One of the most discussed topics at present is the prolonged flattening effect of corneal cross-linking on the cornea which could last for years. On average this can result in 2 dioptres of flattening of the central cornea. In fact in some cases the cornea could continue to flatten to 10 dioptres, this has been the experience of some colleagues. This effect is clearly a concern to both patients and clinicians with no clear explanation. There is no study to show who is more likely to have this extensive effect on the cornea.

In conclusion, our review found the main predictive factors of the positive visual improvement following corneal cross-linking were lower pre operatively best corrected visual acuity and higher keratometry values. Younger patients seem to show the more flattering affect on the cornea following cornea cross-linking. Some evidence suggest that central cones and thinner corneas , were good predictors for vision improvement following corneal cross linking. There is no quantifiable predictive models proposed based on the parameters looked at who would benefit by how much based on pre-treatment best corrected visual acuity ,refraction, keratometry reading, topography and other parameters. This is an area that need more investigation and it is hoped that with the adoption of newer screening tools such as ABCD Keratoconus grading system designed by Michael Belin in 2016 Ophthalmologists will be able to determine predictive factors of positive outcomes of corneal cross-linking in cases of mild to moderate keracotonus.

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Why does the topic of Dry Eye seem to surface so often?

by Ms. Louise Veenhuis

Dry Eye is often seen as the 'naughty child' of the family: Everybody has one, but that doesn't assume clinicians necessarily enjoy rising to the challenge!

The definition of 'dry eye' continues to evolve. In 2007 Dry Eye was defined as being a disturbance of the Lacrimal Functional Unit (LFU). The 2017 DEWS Report elaborates and redefines dry eye as a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles.[1]

Therefore it is essential to continue educating ourselves as clinicians, in order to keep our knowledge current, as the older definition stated no aetiology and only listed the signs and symptoms of the condition.

Regardless of the evolution of the definition of Dry Eye, it is well understood to be a multifactorial disease state, afflicting at least 344 million people worldwide, and is one of the most frequent causes of patient visits to eye care practitioners.[1] Bearing in mind that it is believed that meibomian gland dysfunction (MGD) is the most common cause of evaporative dry eye,[2] we need to be aware of the fact that most patients are not aware that Meibomian Glands even exists! Therefore continued patient education is also a key element of spreading awareness of the condition, new therapies becoming available and the role that patients play to support management at home.

As Dry Eye (and MGD) appears to affect so many people, surely there must be a knock on economic effect?

Absolutely, and this can be also be seen on multiple levels.

Cost to industry: A study conducted at the Pharmacotherapy Outcomes Research Center at the University of Utah, found that the average annual indirect costs due to productivity loss averaged $11,302.00 due to absenteeism.

Cost to the consumer: The same study, after surveying 2171 respondents with DED OSDI score of higher than 12 (out of 100), found that the average annual cost of managing DED with over the counter therapies equated to $452.00. This value increased once punctual plugs and specialist treatment was added and eventually averaged on a cost of $2,698.00 for severe DED managed with cyclosporine. Ironically, after paying all that money for care, the compliance rate stated was a mere 33.9%.[3]

"...Word of mouth referral from a happy patient is often the best form of marketing..."

Cost to the NHS: In England in 2014, over 6.4 million prescription items for artificial tears, ocular lubricants, and astringents were dispensed in the community at a cost to the NHS of over £27 million.[4]

Cost to Clinicians: Let's start with contact lens patients. It has been estimated that there are currently more than 140 million contact lens (CL) wearers worldwide.[5] CL wearers are 12 times more likely than emmetropes and five times more likely than spectacle-wearers to report dry eye symptoms.[6] Considering the fact that approximately 50% of CL users report experiencing dry eye symptoms at least occasionally, the chair time taken up by attempts at resolving these symptoms is considerable.[7] We know that the primary reasons for CL intolerance are discomfort and dryness[8,9] (and as previously mentioned, the majority of dry eye disease stems from MGD). Lens wearers address the problem of CL-related discomfort by decreasing wearing time per day, then less days of wear and ultimately may become former lens wearers with permanent discontinuation of lens wear.[5,10] There is a negative financial effect on the clinical practice, as time investment to fit and execute contact lens instruction is not rewarded with the financial longevity of an extended period of contact lens sales due to drop out.

Secondly, laser in situ keratomileusis (LASIK) is the most common refractive surgical procedure. Although the procedure is well documented to be safe and efficient, dry eye syndrome is the most frequent post-LASIK complication in need of a clinician's time and attention.[11,12] Although 95% of patients may experience dry-eye symptoms immediately after LASIK, approximately 20% develop chronic dry-eye symptoms that persist beyond 6 months.[13] The major cause of LASIK-associated dry eye is corneal nerve damage,[14] where the loss of corneal sensation has been associated with a reduced blinking rate. This in turn leads to evaporative stress and lipid-deficiency dry eye, due to an altered meibomian gland function (MGD).[15-17] In short, it is possible that meibomian gland function may be altered following surgery.[18] The cost of chair and non-income generating follow-up appointments to resolve the ensuing MGD and dry eye symptoms, should not be discounted.

The cost of potential future referrals may also be affected by dry eye symptoms. Word of mouth referral from a happy patient is often the best form of marketing. However patients suffering the symptoms of dry eye disease often complain about poor vision. Several studies support the concept that an unstable tear film affects visual acuity. The tear film forms the first refracting surface of

the eye, making it critical for visual performance. Patients experiencing dry eye often complain of blurred vision even though their BCVA is normal (eg, 20/20 or 6/6) with the Snellen chart. The decreased in visual performance that these patients are experiencing may be the result of an irregular tear film surface,[19] leading to an increase of higher order aberrations.[20] Contrast sensitivity is reduced after the tear film breaks up, with the greatest decrease occurring at the higher spatial frequencies. The perceived result is that of blurry or unclear vision.[21] Considering the time and effort clinicians spend on customizing an optimum treatment profile for individual patients prior to LASIK, a suboptimal result due to the effects of dry eye can, at times, be frustrating. For the patient, the reduced contrast may detract from the expected visual results following the refractive procedure and has the potential of leaving patients feeling disappointed.

What are your thoughts on the perceived impact that Dry Eye Disease/ MGD has on patient quality of life?

Dry eye symptoms manifest in many different ways. Patient reports may range between dryness, grittiness or scratchiness, soreness or irritation, burning, watering or even eye fatigue. A study showing patient utility scores for the more severe forms of dry eye, are within the range of conditions like class III/IV angina (0.71). Conditions, such as angina, are widely recognized as lowering health related quality of life. These results illustrate how the condition of dry eye can have a significant psychological and physical impact a patient's general lifestyle.[22]

We are pleased to announce that in the next issue of Ocular Surface Insight we will feature a practical guide of MGD management. We will create a forum with practical pearls in the day to day management of MGD and tips how to overcome common pitfalls with patient compliance.

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Boston Keratoprosthesis

by Mr. Damian Lake

Following approval by NICE and agreement by NHS England to fund implantation of the Boston keratoprosthesis, it is expected that the rate of usage will increase in the UK over the next few years.This article reviews the Boston Keratoprosthesis Type 1 alone and is intended not as a comprehensive review of the literature but as a means to encourage readers to utilise the Boston Kpro whilst understanding its limitations and cautions that we have encountered in our 10 years of experience

Overview

The Boston Keratoprosthesis was developed by Professor Claes Dohlmann in the USA. It is a prosthetic Polymethylmethacrylate PMMA Optic lens held within a cornea donor carrier in patients with corneal blindness and otherwise healthy optics.Corneal opacity may have many differing aetiologies leading to corneal blindness. The traditional treatment of which has been either full thickness penetrating keratoplasty or selective lamellar keratoplasty. However some conditions are doomed to failure with these methods at which point the Boston Keratoprosthesis may be an option.

Workup - Ocular

The Boston Kpro is most likely to survive in the environment of a wet,blinking, uninflamed eye. Those conditions in which the eye is severely dry (Ocular Cicatricial Pemphigoid, Stevens Johnson Syndrome etc) have a particularly poor prognosis and should be excluded. Repeat graft failure and Aniridia are prognostically better, with viral, and chemical trauma intermediate. Lid function and fornix anatomy is often not paid enough attention to in the work up but can be critical post operatively. Patients with a Boston Kpro will wear a longterm contact lens over the Boston Kpro to provide wetting to the edge of the device and carrier donor material. Without this extrusions are common. Pre-operative assessment should consider how the lens will fit and whether there are any impediments to this such as fornix cicatrix, lids that are too tight to the ocular surface or too lax. Correction of any lid malposition, fornix reconstruction or occasionally orbital decompression (to decrease exposure and create space for contact lens fitting) should occur prior to Kpro implantation.

The patient by the nature of the problem will have corneal opacity, excluding the ability to examine in detail the intraocular structures.It is important to exclude those cases in which despite adequate placement of the device, vision will not improve. This may necessitate visual acuity measurement, visual field assessment, B scan ultrasound,UBM and Electrodiagnostics.

Patients require at least perception of light vision pre operatively to be candidates. We do not offer the Boston Keratoprosthesis for children, and we are very cautious on recommending the Boston keratoprosthesis to young people who may have a life expectancy of eight decades, whilst the device has reported outcomes rarely beyond five years. Vision should be preserved in all four quadrants of the visual field to be most effective, but particularly the inferior and nasal fields are important.

Retinal structure should be assessed with a B scan ultrasound to exclude a retinal detachment pre operatively. The ultrasound should be performed by an experienced ocular ultrasonographer in at least two planes that transect the optic nerve. Visualisation of the optic nerve head can also helpfully exclude severe optic nerve cupping indicating previous or current uncontrolled glaucoma and a likely poor outcome. Whilst ultrasound can provide confirmation of the structure of the retina, it will not provide a functional measurement. In conditions particularly chemical injuries severe enough to have caused corneal opacity, chemical may have leached within the ocular content and functionally damaged the retina. To assess this Electrodiagnostics may be helpful.

An idea of the anatomy of the anterior segment provides useful information on what is likely to be encountered during surgery and minimises surprises. Synechie will need to be divided and the iris resected. The lens status of the patient is useful to know. The device is provided in either a pseudophakic or an aphakic version. If the patient is pseudophakic, UBM will provide information on the stability of the intraocular lens and whether

it can be retained during surgery. If not, or if the patient is phakic the lens will be sacrificed during surgery. Removal of an artificial lens can be simple, but may not be if there are adhesions,pre operative UBM images can be helpful in planning a surgical strategy. Likewise if the patient is phakic, a measure of the lens density will allow planning for either an open sky intracapsular or extra capsular extraction. In the event of aphakia, the manufacturer will require an axial length measurement during the ordering process and an A scan ultrasound will need to have been performed.

Glaucoma

It is now our protocol to perform a glaucoma drainage device on all patients at risk of increased intraocular pressure who require a Boston keratoprosthesis. Often we perform this prior to Kpro surgery, although occasionally it is implanted at the same surgery. In the assessment it is important to note the health of the conjunctiva, and whether there is adequate space for the glaucoma drainage device. Thin, inflamed, scarred or adherent fibrotic conjunctiva may preclude placement of the glaucoma drainage device. In these cases ECP or CycloDiode may be an option.

Surgery

The device is prepared prior to the patient. The package provided by Massachusetts Eye and Ear Infirmary, Boston, MA contains a central optic with an anterior collar, a posterior titanium fenestrated back plate and a titanium locking ring. There is a 3mm trephine and sticky tab with which to hold the optic whilst the device is assembled, and a short plastic rod to compress the titanium ring flush against the back plate. A fresh or frozen corneal donor tissue is required from your local provider and an 8.5mm trephine.

The donor tissue is primarily trephined to 8.5 mm, with a secondary 3mm central trephination (with the trephine provided in the kit). The optic is placed anterior side downwards onto the sticky circular tab provided and the previously trephined donor carrier is placed snugly over the optic (anterior side down also) until flush with the anterior collar. Next the fenestrated titanium backplate slides over the threadless posterior optic and sandwiches the donor carrier between it and the anterior optic collar. Lastly

the titanium locking ring fits over the posterior optic and is compressed against the posterior back plate with the tool provided. Check that the device is not loose within the donor carrier, is located centrally and sits flush with the donor carrier surface. If so the device is ready to be implanted.

The surgery can be performed under either local (peribulbar or subtenons) or general anaesthesia with the patient supine in reverse Trendelenberg position. Intravenous ocular hypotensives such as acetazolamide (unless contraindicated) are injected pre operatively to minimise expulsion risk. The lids are prepared with iodine or chlorhexidine soak, and draped with lid retractor applied.

An 8.5 mm Trephination of the cornea is performed centrally. Total iridectomy is completed, and then either retain an artificial intraocular lens and implant the pseudophakic version of the Boston Kpro or perform lens extraction or intracapsular extraction and implant the Aphakic version of the Boston Kpro. If the aphakic version is utilised, we perform a core vitrectomy with triamcinolone guidance. The device is attached using 10/0 nylon interrupted sutures between the donor carrier and the host rim. We do not use running sutures in this high risk environment. The knots are rotated into the donor carrier. At the conclusion of surgery, 40mgs triamcinolone and cefuroxime are injected into the orbital floor, intraocular cefuroxime 2mgs, and a contact lens applied to the ocular surface.

Post operative care

It is recommended that patients with the Boston Kpro apply prophylactic antibiotics. The optimum regime is of some debate.Currently we use Vancomycin 1.4% and levofloxacin four times daily. It is also our practice to wash the fornices with povidone 5% at each clinic visit.

The contact lens should be removed regularly, and the ocular surface checked for epithelial defects and erosion of the prosthetic. Any epithelial defect should be treated aggressively, and infection ruled out and treated prospectively whilst awaiting microbiology results to prevent progression to endophthalmitis. If infection is excluded, poor ocular surface wetting should be addressed concentrating on lid position, a tarsorrhaphy maybe required, and contact lens refitting with a steeper back curve.

Glaucoma progression will need to be monitored with either central visual field testing (Goldmann central 90 degrees) or OCT of optic nerve head.Intraocular pressure cannot be monitored conventionally with a Goldmann tonometer, therefore either a digital estimate,scleral pneumatonometry, or Schiotz tonometry maybe preferred.

Lifelong topical steroids are applied to prevent intraocular inflammation and secondary retroprosthetic membrane formation.

Endophthalmitis

The Boston keratoprosthetic is synthetic and therefore does not integrate into the corneal tissue. There is therefore a potential conduit into the globe for microbes. Regular, lifelong follow up is required, with vigilance both from the patient and medical staff for early signs of infection is necessary. Any signs of intraocular inflammation should be assumed endophthalmitis and treated accordingly. A vitreous tap should be performed, with intraocular vancomycin,amikacin and an anti fungal agent injected. Less commonly a sterile uveitis is diagnosed and can be treated with steroids, but this is a diagnosis of exclusion.

Microbial keratitis

Microbial keratitis is not uncommon. The occurrence of fungal keratitis due to the long term use of topical antibiotics is high, particularly as patients have extended wear contact lens usage and long term steroid eye drops. Any suspicious corneal opacity should be investigated with corneal scrapes to exclude infectious keratitis. Aggressive treatment with fortified antibiotics and anti fungals should be commenced in the absence of a culture result, and consideration for either intravitreal antibiotic and anti fungal injection, and or removal of the keratoprosthesis device.

Retroprosthetic membrane

A chronic intraocular inflammatory reaction promotes the formation of a retroprosthetic membrane. This membrane can be treated with YAG laser membranectomy, but caution should be used to avoid cracking and pitting of the implant. The power used should be as low as possible and posterior offset focus used. A post laser orbital floor triamcinolone depot may help prevent reformation.

Device extrusion

Most commonly this is secondary to either infection, ischemia,dense retroprosthetic membrane or poor wetting at the implant edge and will require implant removal. Retention rates vary dependent on aetiology, with Stevens Johnson Syndrome least favourable.

Outcomes

Outcomes data should be interpreted based upon the model used and the device modifications (the Boston Keratoprosthesis has had many modifications over time, therefore data pertaining to the Boston Keratoprosthesis 10 years ago does not necessarily reflect the current model). In a 2015 review by the American Academy of Ophthalmology, BSCVA of 20/200 or better occurred in 45- 89% of eyes, 20/50 or better in 43-69% of eyes and 20/40 or better in 11-39% of eyes. Retention varies from 65-100%, retention is particularly poor in Stevens Johnson syndrome cases.

The most common causes for visual loss are endophthalmitis in which rates of up to 12.5% have been reported and raised intraocular pressure with rates up to 65%.

Longer term outcomes of 7 years have been reported with a cumulative incidence of complications 49.7% for retroprosthetic membrane formation, 21.6% for glaucoma surgery, 18.6% for retinal detachment, and 15.5% for endophthalmitis.

Summary

The Boston Keratoprosthesis is a useful device in a select group of patients who may have poor outcomes from repeat penetrating keratoplasty, or primary cases with a poor prognosis. When developing a new service offering the Boston Keratoprosthesis, time spent at a training course and watching an established service will be time well spent. A multi disciplinary team involving Corneal, Vitreoretinal and Oculoplastic surgeons are required, with 24 hour a day, 365 days a year cover for complication management. The surgical procedure is uncomplicated for an established keratoplasty surgeon, the skill is often in selection of the most appropriate cases and constant vigilance for post operative issues dealt with early and aggressively.

Further Reading

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Enhanced assessment of the Ocular Surface using an objective digital grading system

by Dr. Sandip Doshi, PHD BSC MCOPTOM

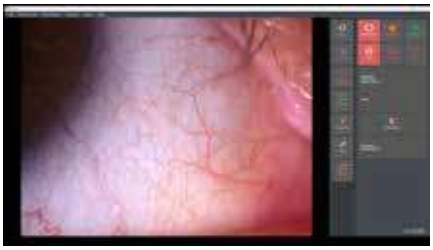
There is an increasing incidence of patients who present with symptoms of dry eye. The cause of this is thought to be multifactorial including: increased screen and digital device use, environmental features (such as heating, air conditioning and pollution), an ageing population and medications. The practitioner often faces an uphill challenge in managing these problems as it is often difficult to get them to fully understand the cause of their symptoms and hence be compliant with any suggested treatment regimen, particularly in the absence of any overt clinical signs. How often is one faced with a patient who says their eyes are red and sore and not getting better with treatment but fail to comply with the suggested treatment plan.

Examination of these patients can sometimes be very cursory, in some instances it may be no more than an examination on a slit lamp. Quite often there is no measurement of baseline information other than the patient symptoms. Treatment is often based on the patient's symptoms alone and any follow-up is often reliant on the patient reporting an improvement on these symptoms but with no objective follow up. This is of course fraught with error as the patient may only report their symptoms at the time of asking or may be inaccurate with their reply (particularly as they may be keen on not wanting to upset the clinician).

Currently the objective resources available to the practitioner can be limited. The two most widely used are the CCLRU and Efron Grading scales. These laminated sheets grade pathology from 0-4. The former is based around photographs of six conditions, two of which are presented in multiple manifestations while the latter consists of a series of artist illustrated depictions of 16 different conditions. The CCLRU photographic scales (now been rebranded as the Brien Holden Vision Institute or BHVI system) have been criticized for the lack of perfect homogeneity between images representing the same condition, either in terms of different illumination conditions or variable size of the area under display. While Efron overcomes these difficulties by encouraging artistic clarity and license to emphasize and isolate the condition that is being evaluated, it is considered by some a departure from the real-life situation in as much as different conditions feed and depend on each other and therefore, occur simultaneously and should appear as such in a single image.

"Arguably the main concern with the current objective grading scales are the large inter-user variability..."

Arguably the main concern with the current objective grading scales are the large inter-user variability, recent studies have shown that the reliability between clinicians can be as low as 47%, when using just an analogue slit lamp and grading card, this increases to +60% when a digital slit lamp and grading card is used. The lack of digital slit lamps in the market place means that the reliability and variability still remains low.



With the advent of digitally enhanced applications, higher specifications of cameras and smartphone technology, I have been using an objective grading software that is capable of bridging the gap between analogue and digital slit lamps, with the use of a smartphone, and more importantly reducing the patient variability and reliability by offering an objective result which is between 98.2% - 99.8% accurate and repeatable across CCLRU and Efron.

AOS Anterior is a device agnostic software designed to automate ocular surface analysis of any digital image of the eye and automate the grading of:

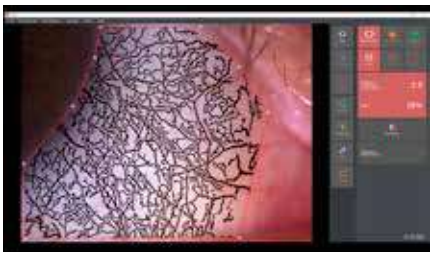
(1) Bulbar Redness

(2) Lid Redness

(3) Meibomian Glands

(4) Fluorescein

AOS Anterior removes subjectivity during the diagnoses and/or monitoring of my patients. Each feature allows me to evaluate a variety of conditions effortlessly and record their results, which I use during follow-ups again to build up a picture overtime.



AOS Anterior is a powerful diagnostic tool developed to work in any practice and is intuitively designed to fit within the workflow of an every-day practice. It has multiple features that I use to improve my patient's evaluations, covering:

1. Contact lenses
2. Dry eye
3. Red eye
4. Blepharitis

In general, any condition/pathology which affects the bulbar redness, ocular surface, staining, and lid roughness (e.g. allergy).

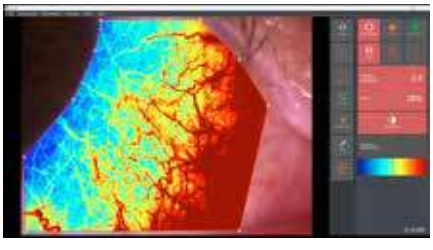
By eliminating subjectivity, the software provides me with consistent, objective grading. With current grading systems being affected by a practitioner's subjectivity and experience, the assessment of a patient could be very different between practitioners (for example, clinician (A) may grade a patient Level 2; while clinician (B) could grade the same patient Level 3 - The difference may result in a pathology being misdiagnosed or being under or over-treated.

AOS Anterior provides me and my patient with an objective test, which demonstrates to my patient the effectivity of any treatment being applied and helps determine which patients we should observe vs manage vs treat.

Patient education and "ownership problems" are another challenge that I have found AOS Anterior aids in, improving compliance with treatment. It simplifies explaining why the treatment options have been recommended, visually and objectively, giving a "score" which the patient can relate to easily (the 0-4 grading scale).

AOS anterior platform is having a positive impact on clinical research, and is being used at several of the most recognized institutes both here and in the USA. By introducing an accurate, consistent and repeatable system that eliminates variability between practitioners particularly in multi-center trials and single center studies with multiple investigators.

I have been using the software in my practice for almost 3years. It is easily integrated into daily clinical practice as it has been designed to present the clinical information within 3-clicks. AOS Anterior has enhanced, rather than restricted patient flow as the information is presented in an easy to understand and explain format. I have found it an essential tool in improving patient compliance with treatment regimens as they are enthusiastic to



improve their 'score'. In the case of red-eyed patients, the redness maps have been an excellent visual tool for the patient to fully understand their problem. Moreover, in my practice it has allowed myself and colleagues to give consistent advice to our patients.

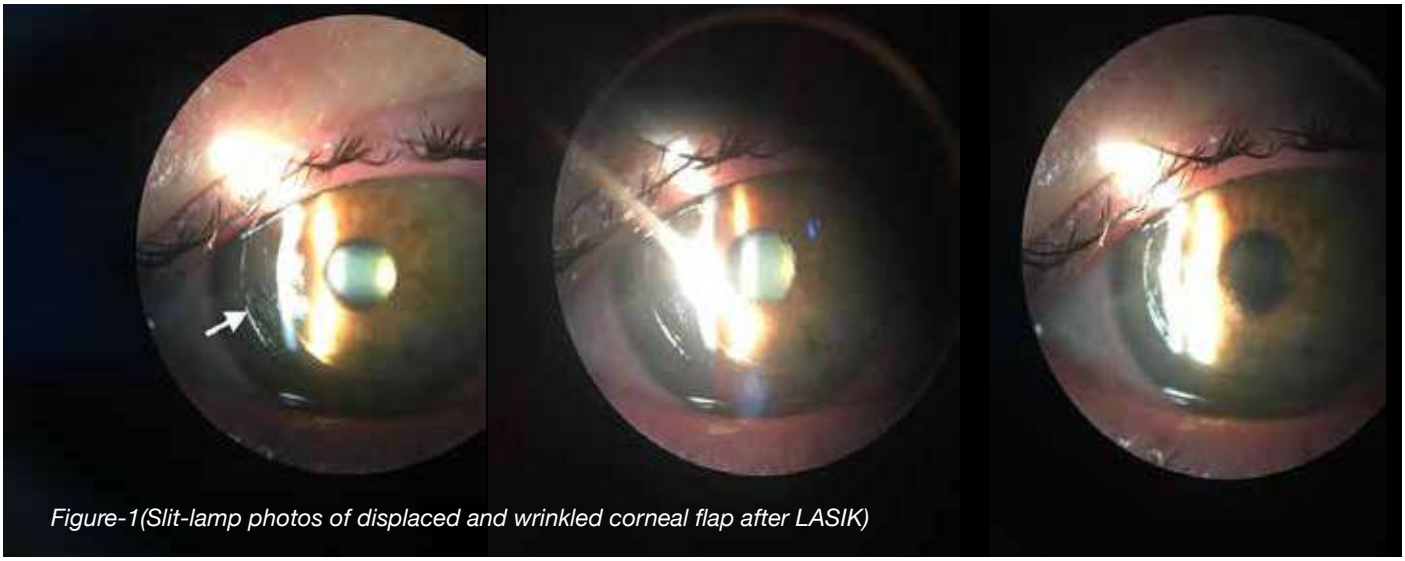


Figure-1(Slit-lamp photos of displaced and wrinkled corneal flap after LASIK)

The use of VitA-POS eye ointment after LASIK Refractive Surgery

by Mr. Azher Q. Eldouri & Professor Michael O'Keeffe

In order to minimise any flap complication post LASIK refractive surgery we introduced a new protocol using eye ointment and bandage contact lenses post surgery. We identified VitA-POS as our preferred ointment agent due to its viscosity being ideal for the very delicate nature of the flap post femtosecond laser treatment.

What is VitA-POS eye ointment?

VitA-POS is a preservative-free, phosphate free, sterile, vitamin A eye ointment that consists of retinol palmitate 250 iu/g, liquid paraffin, light liquid paraffin, white soft paraffin and wool fat.

Due to its gel-like texture, It moisturises the eye in a uniform smooth way and at the same time the eyelids are kept very well lubricated.

It remains in the eye for up to 6 hours after insertion, enabling excellent moisturization particularly during the night. It remains sterile and can be used for up to 6 months after first opening.

Who can use VitA-POS eye ointment?

It is suitable for adults and children of all ages with moderate to severe dry eye conditions and can also be safely used during pregnancy and breast feeding. It is designed to be administered at night time.

Key features of VitA-POS:

- It is mainly used to treat moderate to severe dry eye diseases.
- It has the advantage over other eye lubricating ointments that it is less viscous and more easily tolerated.
- It provides lubrication to the eye surface with excellent duration of action offering a minimum of 6 hours of comfort.
- It is very cost effective with 300 applications in a single 5g tube

We have found that VitA-POS is a particularly useful agent after LASIK Refractive Surgery.

In LASIK Refractive Surgery, we cut a thin corneal flap of average of 100 micron thickness using Femtosecond Laser Ziemer-6 (Femto LDV Z6) technology.

Post surgery, these thin corneal flaps can get very dry, wrinkled and can easily be displaced overnight.

To date, methods try to prevent these flap-related complications include the use of bandage contact lenses and lubrication have been partially successful.

A significant number of these LASIK flaps end up with folds and displacements which need repositioning the following day. (fig.1)

In order to try and overcome this, we have used VitA-POS eye ointment immediately after LASIK and also the first postoperative night in the last 60 LASIK cases performed at our Refractive Surgery Centre.

This has resulted in no further flap related issues, ie. pain, displacement, wrinkles or microscopic folds and the patients are asymptomatic with very good visual outcome at day 1 postoperatively.

It is possible that other eye lubricating ointments may have the same effects but the drawback that some of these ointments are too viscous.

Conclusion

In conclusion, we believe that in addition to the use of VitA-POS eye ointment in dry eyes it has added a major significant advantage and further usage after LASIK surgery.

NB. As authors, we have no proprietary interest.

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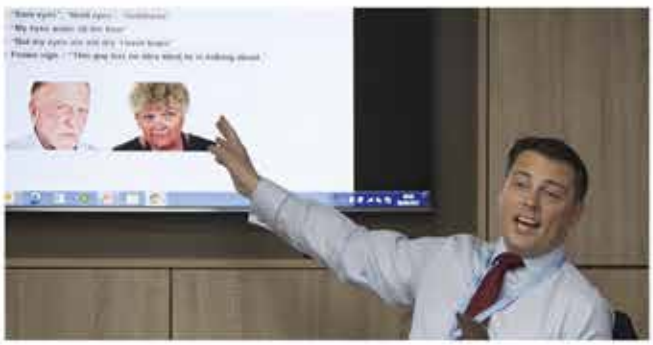

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