APACRS EyeWorld
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New Advancements in Refractive Surgery:

Supplement to EyeWorld Asia-Pacific December 2020

The ZEISS Live Webinar on June 7, 2020 provided a breadth of knowledge on refractive surgery and its newer advancements including a clinical and scientific perspective on Lenticule Extraction with SMILE® (Carl Zeiss Meditec AG, Jena, Germany).

3D Nerve Imaging following Small Incision Lenticule Extraction

Professor Jod Mehta from the Singapore National Eye Centre first presented "3D Nerve Imaging following Small Incision Lenticule Extraction (SMILE on VisuMax Femtosecond Laser, Carl Zeiss Meditec AG, Jena, Germany)." With SMILE, a small keyhole incision is made through which the lenticule is extracted. Because SMILE creates a much smaller surface wound, there are benefits to patients including a smaller wound on the surface of the cornea, less postoperative discomfort and tearing, and potential for less dry eye problems. A few years back, Professor Mehta had investigated the difference between Lenticule Extraction with SMILE and LASIK with respect to nerve innervation. At two weeks after surgery, the nerves in both a Lenticule Extraction and LASIK patient were intact in the inferior area with the small superior incision. However, at 8 weeks, there was a difference in the innervation in that Lenticule Extraction with SMILE provided greater innervation from the inferior side as well as the superior side, whereas LASIK showed very little innervation on the inferior side. So, there was a faster nerve recovery seen in Lenticule Extraction with patients compared to LASIK patients. In another comparison, it was shown that the LASIK group showed greater sprouting of sub basal nerves, indicating nerve regeneration, while the SMILE group had a greater number of longer sub basal nerves which is indicative of normal cellular physiology and better nerve regeneration. Finally, patients who under went surgery with SMILE showed better tear break-up time and ocular surface index at one month, three months, and six months post-surgery than LASIK patients.

Professor Mehta also conducted a lenticular nerve study in which a 2D image was created from all Z-stacks after spinning-disk confocal laser microscopy. One can see the nerves traversing in both the X, Y, and Z axis as well as the interconnecting fibres between the nerves and shortened neurite crunching. From analyzing the data, comparing lenticular nerve density to power of correction gives a quadratic prediction plot which shows a minimal difference in nerve loss between -5 to -10 D (10mm/mm^3), but a greater loss between -2 and -4 D (30mm/mm^3). This means that if you are doing a larger correction, the innervation amount will be the same whether at -5 or -10 (See Figure 1).

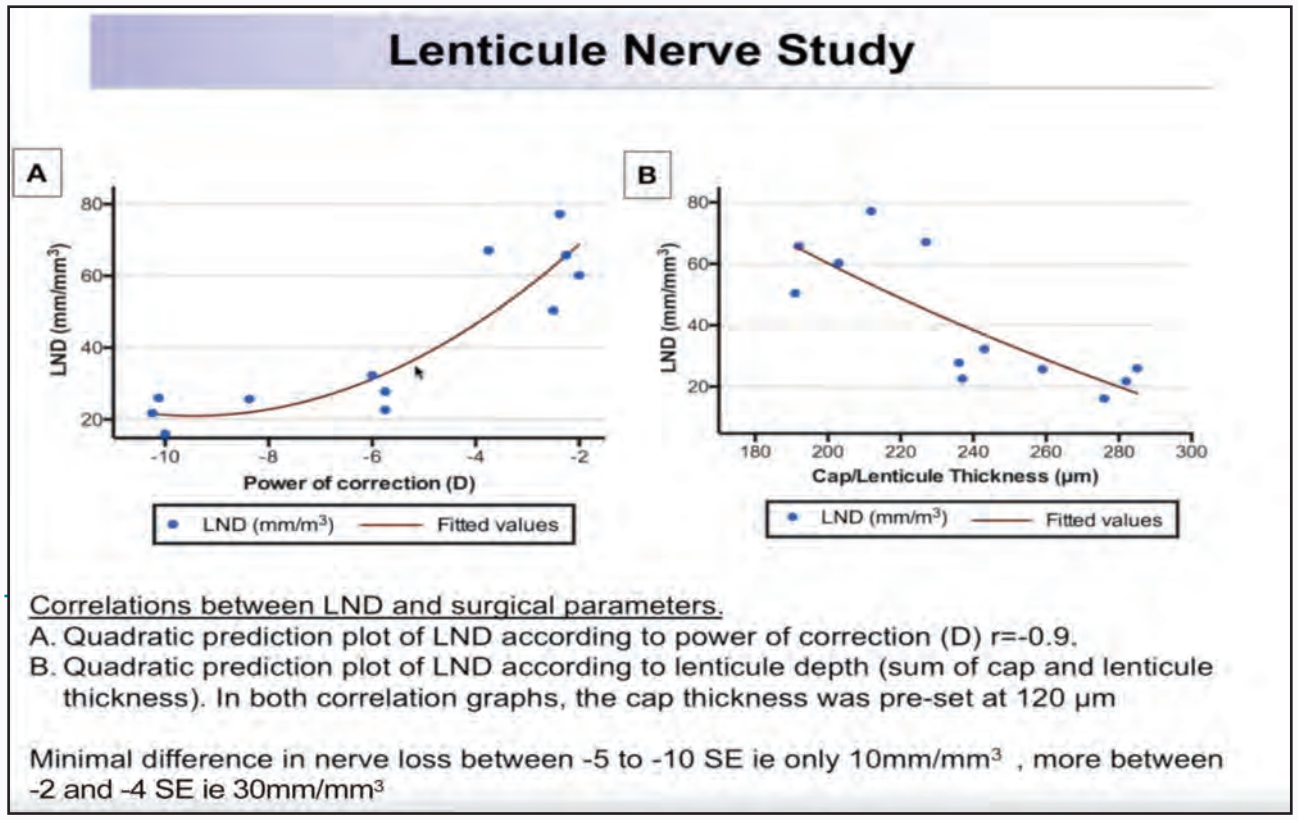

Figure 1. Lenticule nerve study showing less of a difference in nerve loss at a larger correction than at a lower correction.

Source: Bandeira F et al. Invest Ophthalmol Vis Sci 2019

Additionally, nerves may be viable after freezing: after 48 hours at 4 degrees Celsius, one can still see nerve stimulation (35.6% of nerve images still had calcium signal). At one month, however, 7% of the nerves still showed some active function. This data is important with respect to when it is necessary to put nerves back for lenticular implantation, hyperopia, or presbyopia.

Nerves: Ectasia Model

Dr. Natasha Pahuja continued the webinar series with a presentation on Nerves: Ectasia Model. Ectasia, a cellular or a microscopic phenomena, at times may show up in patients who present with normal topography preoperatively. To study the ectasia model, Dr. Pahuja looked closely at the corneal nerves since they have a role in maintaining the ocular surface microenvironment. Corneal nerves connect the ocular surface to the rest of the body and brain in order to maintain ocular surface homeostasis. How, then, can we image and quantify corneal nerves? Using the Heidelberg Retinal Tomography (HRT) scan, "we can measure the different layers starting with the epithelium to the endothelium." Dr. Pahuja further noted that to measure the sub-basal nerve plexus, one can map the corneal nerves using normal confocal microscopy which provides various metrics including the fiber density and branched density to analyze different corneal diseases.

In Dr. Pahuja's research, she studied the naturally occurring ectasia - keratoconus. Corneal nerves are affected in keratoconus in terms of decreased and significantly altered nerves. Looking at morphology and quantifiable data, Dr. Pahuja found that the corneal nerve fiber density and fiber length are predictors of subclinical disease. When looking at refractive surgery techniques, it was shown that LASIK results in significant nerve loss as well as increased tortuosity that is noticed at the end of five months and nerve beading after 8 months. These abnormal nerve findings are what causes dry eye symptoms. With SMILE (since SMILE is the software for Lenticule Extraction), on the other hand, there is regeneration of these nerves and activated keratocytes, which improve normal healing, at the end of 6 months. In other studies, it has been shown that 90% of the nerve bundles are severed after LASIK.

In Dr. Pahuja's published study, she also found that patients with normal preoperative topography showed decreased nerve density but increased dendritic cells, which are inflammatory and present in dry

Imaging, Aerosol Generation, and Retreatment

eye disease, after LASIK. Dr. Pahuja concluded that corneal dendritic cell density is associated with sub-basal nerve plexus features and increased ocular surface disease index. Thus, it is crucial to choose a nerve-sparing procedure to maintain the homeostasis and cause less injury to the ocular surface and cornea.

Dry Eye after Laser Vision Correction (LVC)

Next, Prof. Walter Sekundo presented a variety of studies on dry eye after Laser Vision Correction (LVC). In a meta-analysis of 14 studies, there was a significant reduction found in tear break-up time in LASIK as well as a significant reduction of tear osmolarity in LASIK compared to photorefractive keratectomy (PRK).[1] Contrastingly, there was a non-significant reduction of break-up time with SMILE and PRK.[2] In a different large series study of 13,319 patients, it was found that PRK patients had more subjective symptoms than LASIK patients, specifically in women. Additionally and interestingly, patients with worse preoperative dry eye symptoms were more likely to improve.[3] One study reported that mitomycin C (MMC) did not affect dry eye syndrome in PRK procedures, and in Dr. Sekundno's experience in using MMC, he never saw significant traces of haze, even in the worst cases.

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>
> *Dr. Pooja Khamar*

For the treatment of dry eye after laser refractive surgery, there is no specific algorithm. However, in the literature, tear supplements (lubricants) have been found to work well. These supplements include 0.1% or 0.3% hyaluronic acid and even ointments. Anti-inflammatory preparations may also be used and these include cyclosporine A 0.05%, rebamipide, or liftegrast. Liftegrast works similarly to cyclosporine A, thus making it a good choice for patients who may not be able to tolerate cyclosporine A. For Meibomian Gland Dysfunction (MGD), Prof. Sekundo suggested metalloproteinase inhibitors (e.g. low dose tetracycline or azythromycin) given three days prior to surgery and continued for two days after surgery. "We know that the drug is enriched in the tissue and released over the period of almost one month, so it does help." Warm compresses and eyelid scrubs may also help with blepharitis symptoms.

In Prof. Sekundo's personal experience, he will pretreat patients with blepharitis symptoms typically with tetracycline for at least six weeks at 50mg per day. He stated that he never uses lipid flow or IPL as a pretreatment due to the cost. For patients complaining of more severe pain, Dr. Sekundo stated that this percentage of patients complaining of such pain is quite small and there has never been a case he hasn't been able to treat.

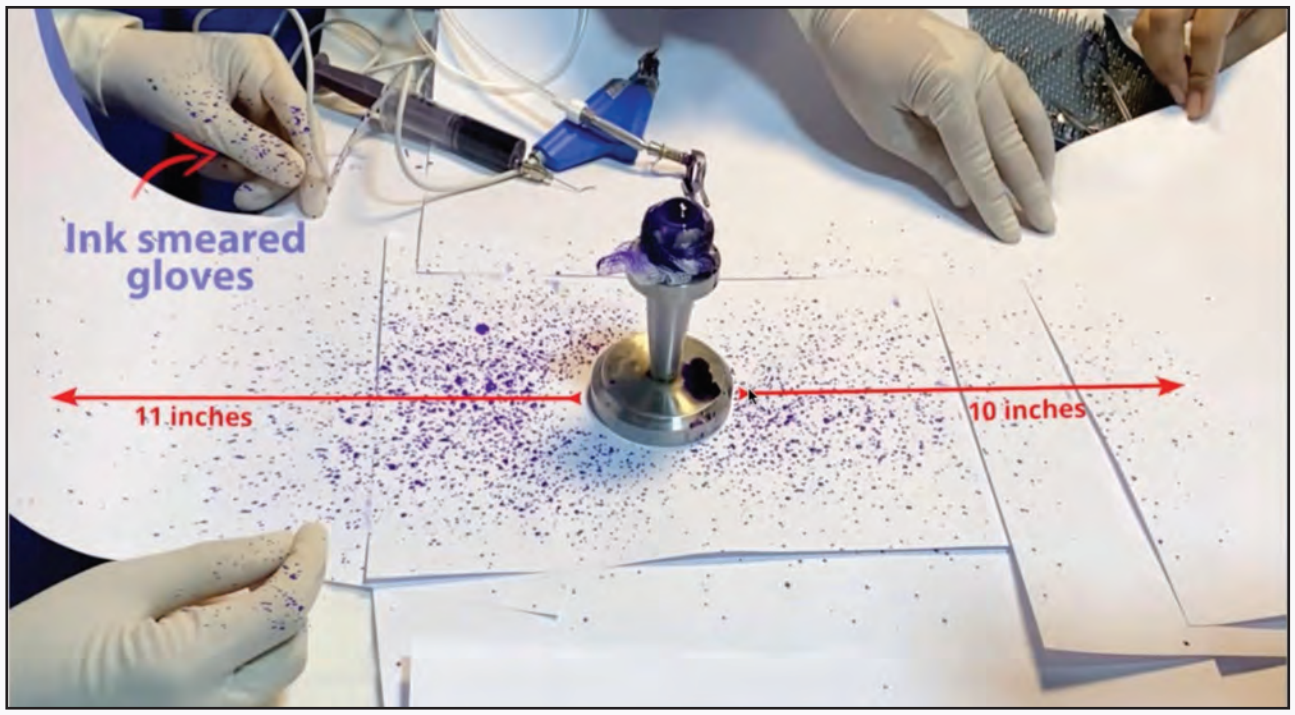

FIgure 2. During microkeratome LASIK, droplets are dispersed at a maximum distance of 10 to 11 inches on both the surgeon side and the opposite side.
Source: Khamar P et al. J Cataract Refract Surg 2020

Aerosol Experiments on Lenticule Extraction Vs. the Rest During COVID Times

The next presentation was given by Dr. Pooja Khamar on Aerosol Experiments on Lenticule Extraction with SMILE (Carl Zeiss Meditec AG, Jena, Germany). She first began with a touch on current events by discussing whether SARS-CoV-2 related markers are present in ocular tissue. What Dr. Khamar did to study this topic was to take donor human eyes, which are not suitable for transplantation, and dissect them layer by layer. The cornea was separated from the epithelium, stroma, endothelium, conjunctival cells, retina, etc. The primary results showed that the conjunctival epithelial cells and the corneal epithelial cells had the highest amount of the priming or entry related genes and interferon response genes present. Additionally, there were many markers present in the stroma and iris. Interestingly, the retinal pigment epithelium contained the least amount of the priming or entry related genes and interferon response genes. This experiment is important clinically. The Lenticule Extraction procedure with SMILE (Carl Zeiss Meditec AG, Jena, Germany) is performed mainly in the corneal stroma. The corneal stroma can also be used for cross-linking or implantation in the eyes, resulting in a high impact of safety for the patient.

Continuing with her presentation, Dr. Khamar designed a small study to investigate aerosols in refractive

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>
> *Dr. Ritika Sachdev, India*

surgery. First, she studied whether aerosols are generated while incising a microkeratome. In this study, Dr. Khamar stained the microkeratome and placed a sheet of paper at the bottom of the stand while creating the flap during incision. What resulted were droplets dispersing at a maximum distance of 10 to 11 inches towards the surgeon side and the opposite side (See Figure 2).

The next question Dr. Khamar studied was aerosol generation with a hansatome. Incising a hansatome utilizes a circular motion with a lower speed. The droplets traveled a much less distance with this technique than with the microkeratome. With femtosecond LASIK, there were no visible aerosols while incising a flap. In Small Incision Lenticule Extraction, there were also no visible aerosols.

Dr. Khamar then provided recommendations for refractive surgery for the COVID-19 pandemic according to the Preferred Practice Guidelines, published by the All India Ophthalmological Society. Before starting surgery, it is recommended to use 0.25% betadine solution, wait for ten minutes, and then wash before beginning surgery. At times, there may be pooling of fluid in the cul de sac while cleaning, which is a potential for generating aerosols. To resolve this, one can take a dry swab to dry the ocular surface. To work with social distancing guidelines, the foot pedal may be moved away from the patient headrest as much as possible. While performing the laser portion of the Small Incision Lenticule Extraction procedure, surgeons can use a screen to protect both themselves and the patient. Additionally, one can cover the patient completely as well as changing gloves after operating on each eye. Finally, disposal of patient interface after cleaning with proper disinfectant as a last step is important. After surgery, Dr. Khamar will take a shower so that she is safe on her end as well.

Retreatment Post SMILE

Dr. Ritika Sachdev presented next on Retreatment Post-SMILE. Since Lenticule Extraction with SMILE, (Carl Zeiss Meditec AG, Jena, Germany), was introduced nearly a decade ago, there was much debate and speculation of the procedure and post-procedure treatment. There are now many options to treat a patient post-SMILE. Recent literature shows that refractive enhancement rates range from 1% to 6% for LASIK and 2% to 4% for Lenticule Extraction with many factors influencing the enhancement rate including age, preoperative-refractive error, corneal thickness, and ocular condition.

If a patient does require enhancement after Lenticule Extraction, options exist which include surface ablation, creating a thin-flap or a cap-to-flap, or secondary small-incision lenticule extraction (SMILE

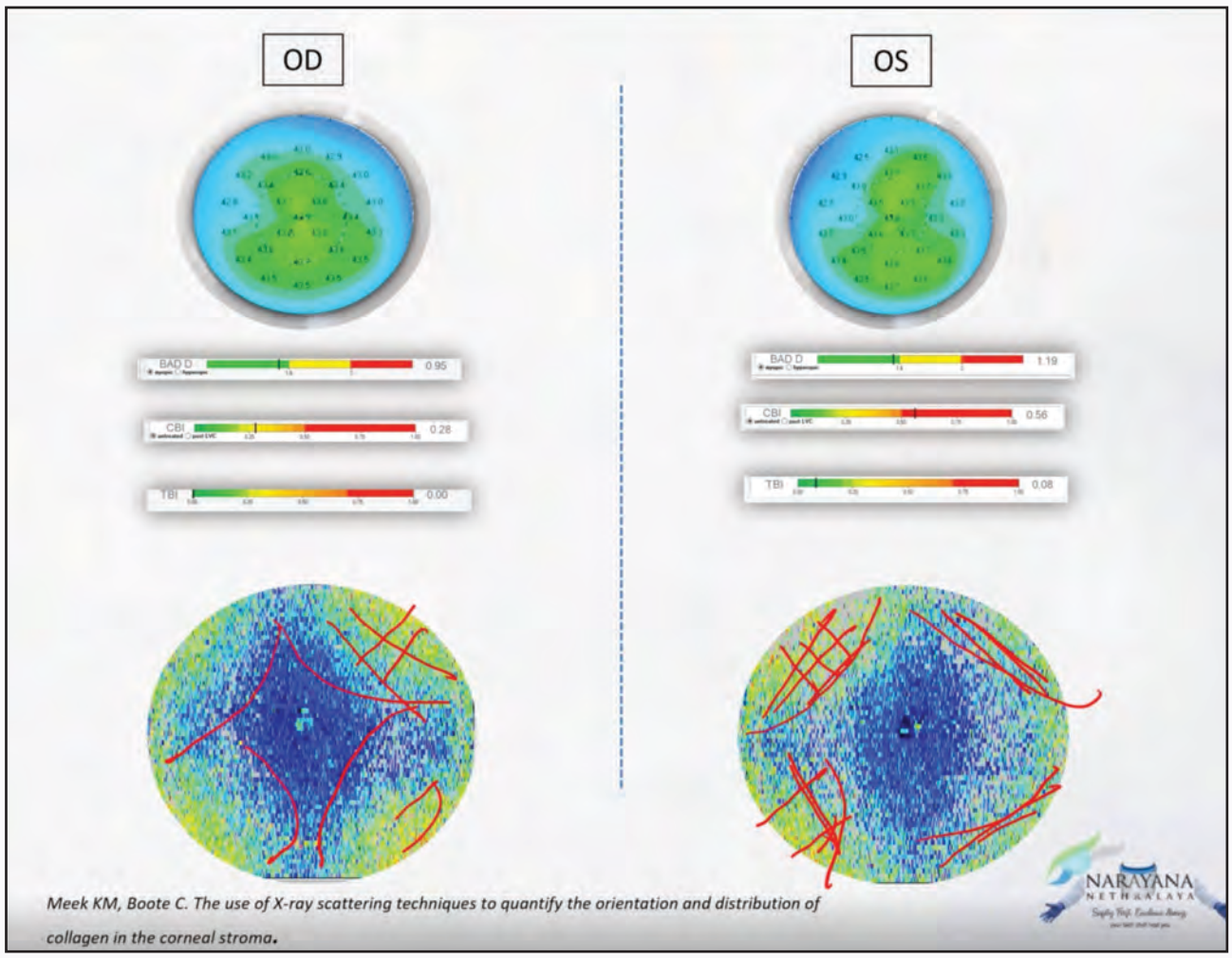

Figure 3. In two near normal eyes, the green color represents tightly bound fibers and the blue represents less tightly bound fibers. This fibrous orientation is strikingly similar to imaging from polarization sensitive OCT.

Source: Meek KM et al. Prog Retin Eye Res 2009

on SMILE). Looking at the different options, surface ablation after SMILE may be the simplest, safest, and most straight-forward retreatment procedure, especially in patients whose cornea needs to be biomechanically protected. The downside in surface ablation, apart from pain, is that there are more inflammatory responses after a surface ablation following the SMILE procedure than a primary surface ablation. Dr. Sachdev recommended a 0.02% mitomycin C for 20 to 30 seconds. Regarding the results of surface ablation after SMILE, Dr. Sachdev described it as "gratifying." Though individual recovery may be longer than the flap method, it is important to note that the tissue-saving method provided good results, whereas enhancement with the aspherically optimized profile resulted in overcorrection.

Thin flap LASIK post-SMILE is recommended for patients with a thick cap because of the clear zone between the epithelium and the cap. This is because if one has too many interfaces, gas bubbles may migrate to the interfaces, causing unwanted slivers of tissue. Thin flap LASIK post-SMILE does give good outcomes, though one has to be aware that inflammation rate may be higher. In cap-to-flap procedures, the cap of the primary surgery with SMILE is converted into a full flap. Patients who undergo this procedure often report no pain and a speedier recovery, although the procedure as a whole may be counterintuitive in enhancing a flapless procedure with a flap.

Table 2: Visual acuity and refraction along the postoperative follow-up period.

	1 month	3 months	6 months	12 months	24 months
SMILE Xtra: UDVA (logMAR)	0.068 ± 0.08	0.033 ± 0.07	0.031 ± 0.06	0.030 ± 0.06	0.031 ± 0.06
SMILE: UDVA (logMAR)	0.041 ± 0.07	0.031 ± 0.06	0.029 ± 0.06	0.028 ± 0.06	0.028 ± 0.05
P value	0.003*	0.124	0.122	0.130	0.144
SMILE Xtra: CDVA (logMAR)	0.021 ± 0.09	−0.028 ± 0.07	−0.042 ± 0.06	−0.051 ± 0.05	−0.055 ± 0.05
SMILE: CDVA (logMAR)	0.002 ± 0.07	−0.038 ± 0.06	−0.048 ± 0.06	−0.055 ± 0.06	−0.057 ± 0.05
P value	<0.001*	0.031*	0.171	0.190	0.272
SMILE Xtra: MRSE (D)	−0.12 ± 0.23	−0.16 ± 0.25	−0.19 ± 0.21	−0.20 ± 0.21	−0.18 ± 0.19
SMILE: MRSE (D)	−0.18 ± 0.19	−0.20 ± 0.22	−0.21 ± 0.21	−0.22 ± 0.20	−0.19 ± 0.18
P value	<0.001*	0.038*	0.267	0.278	0.361

The efficacy index
1.09- SMILE XTRA
1.12- SMILE

Mean safety index
1.29 -SMILE XTRA
1.28 -SMILE

*Post-op CRF was significantly higher in the SMILE Xtra group and remained stable over the 24 months of follow-up

Figure 4. SMILE Xtra at 24-month follow-up shows significantly higher postoperative corneal resistance factor (CRF) compared to traditional surgery with SMILE.

Source: Ganesh S et al. Indian J Ophthalmol 2018

Imaging the Collagen and its Impact on SMILE Surgery

The next presentation was given by Dr. Rohit Shetty on "Imaging the Collagen and its Impact on SMILE Surgery." Dr. Shetty began by discussing how the wavelength of light typically used in imaging is not very suitable for imaging collagen. Meek et al.[4] studied the use of x-ray scattering techniques to image collagen and it was found that in a normal eye, one can see the darker colors on imaging representing tighter bound fibers with the four zones in the corner of the eyes. When a suspect eye was imaged, the coloring of the tightly bound fibers is weakened along with poor corneal biomechanics (See Figure 3). In keratoconus, there is no healthy collagen reflected in imaging. When comparing preoperative imaging in surgeries with LASIK, SMILE, and PRK to postoperative (3 months), it can be seen that both SMILE and PRK maintain a lot of integrity of the cornea in terms of collagen structure.

In Dr. Shetty's own research, he studied the biomechanics of LASIK flap and SMILE cap and assessed collagen imaging after both surgery with LASIK and SMILE. The results showed that there was a huge drop in the biomechanics and collagen, but the imaging after both procedures were similar. Dr. Shetty also found that a gene analysis preoperatively matched the collagen mapping, thus showing that collagen imaging is quite accurate.

SMILE Xtra: My Take

Dr. Sheetal Brar next presented on SMILE Xtra and its techniques. Dr. Brar introduced suspect topographies including inferior steepening, I/S asymmetry (> 1.4 D), posterior elevation, thin pachymetry, and steep corneas that can potentially be managed with a new modality: corneal refractive surgery plus accelerated cross linking (Xtra procedures). In Dr. Brar's research, she reported a good safety and efficacy profile with SMILE Xtra procedures. However, surgeons may hesitate to utilize this procedure due to unclear eligibility criteria, an unstandardized cross-linking protocol, potential side effects of haze, hyperopic shift and corneal flattening over a long-term period, and increased overall cost (See Figure 4).

Speaking to eligibility criteria, Dr. Brar considered patients eligible for SMILE Xtra if they have high myopia or myopic astigmatism, borderline corneal thickness (480 microns or less), suspect topography, age less than 30 years old, atopy, and/or keratoconus in one eye. In a retrospective study by Dr. Brar, 4,630 eyes were studied with 3,932 normal topography eyes undergoing SMILE. Out of the 3,932 eyes, only 2 eyes (0.05%) experienced ectasia. In eyes with border topography undergoing SMILE Xtra (522 eyes), none experienced ectasia while 5 eyes out of 176 eyes (2.84%) undergoing SMILE experienced ectasia. Dr. Brar concluded that SMILE Xtra is safe and effective for prophylaxis of corneal ectasia in borderline corneas. Additionally, there is anecdotal evidence that the biomechanics with SMILE Xtra may be better compared to SMILE alone, though further data is necessary to validate these results.

References:

1. Sambhi RS et al. Can J Ophthalmol 2020
2. Lee JB et al. J Refract Surg 2000
3. Schallhorn JM et al. J Refract Surg 2019
4. Meek KM et al. Prog Retin Eye Res 2009