Point/Counterpoint: Epithelium On Versus Epithelium Off

Surgeons discuss whether to remove the outer corneal layer during CXL.

BY PARAG A. MAJMUDAR, MD; REBECCA MCQUAID, MSc; ARTHUR B. CUMMINGS, MB ChB, FCS(SA), MMed(Ophth), FRCS(Edin); AND MICHAEL MROCHEN, PhD

The Case for Epithelium-On CXL

Standardization will help overcome objections to transepithelial CXL.

By Parag A. Majmudar, MD

Corneal collagen crosslinking (CXL) has gained worldwide popularity over the past several years as an effective means of strengthening the cornea and thereby reducing, if not eliminating, the progression of ectatic disorders of the cornea such as keratoconus, pellucid marginal degeneration, and post-LASIK ectasia.

Vitamin B2 (riboflavin), in the presence of ultraviolet-A (UV-A) light, has been purported to create links between collagen fibers in the cornea. With the creation of these links, the cornea theoretically becomes more rigid and resists further ectatic progression. As an additional benefit, corneal remodeling may result in improved refractive and visual outcomes, although patients must be counseled that refractive correction with contact lenses will still be required. Patients frequently become more contact lens tolerant following CXL.

An essential requirement for CXL is obtaining an adequate concentration of riboflavin within the corneal stroma. This step serves two main purposes: (1) Riboflavin acts as a photosensitizer so that UV-A light can complete the CXL process, and (2) riboflavin absorbs excess UV-A so that damage to deeper structures within the eye (the endothelium, lens, and retina) is minimized.

In the late 1990s, the first clinical studies of CXL were performed by a group in Dresden led by Theo Seiler, MD, PhD.[1,2] The photosensitizer used at that time was 0.1% isotonic riboflavin solution in 20% dextran. This formulation had limited ability to penetrate the intact epithelium. The Dresden protocol therefore required epithelial removal in order to allow better penetration of the riboflavin preparation. Their successful results became the basis for the rapid adoption of this procedure.

EPI-OFF OBSTACLES

Unfortunately, there are several major obstacles, at least from the patient's perspective, when epithelial removal is performed during the traditional epithelium-off (epi-off) CXL procedure. Patients experience considerable pain for up to 7 days after this procedure. Removing the epithelium also eliminates a natural barrier to infection, and, therefore, the risk of infectious keratitis is increased. Wajnsztajn and colleagues[3] conducted a retrospective review of ocular complications in 206 eyes of 180 patients treated according to the Dresden protocol between 2007 and 2012. They observed 28 ocular complications in 23 eyes (11.2%) of 22 patients (12 males, 10 females). These included delay of epithelial healing for up to 30 days in four eyes, hypertrophic epithelial healing in four eyes, marked superficial punctate keratopathy for greater than 30 days in 11 eyes, corneal sterile infiltrates in four eyes, microbial keratitis in four eyes (culture-positive in two), and marked corneal edema with scarring in one eye.

During the period of delayed wound healing, most patients are unable to work or, in the case of children, attend school for a significant length of time. Moreover, contact lenses, which are so vital to a keratoconic patient's visual functioning, may not be worn for up to several weeks. Many of these concerns could be greatly reduced if CXL could be performed without removing the epithelium. Ocular discomfort would be minimal, and patients might be able to resume contact lens wear and normal work or school activities within several days in most cases.

EPITHELIUM-ON AS AN ALTERNATIVE

The concept of epithelium-on CXL is not new. The main concerns with so-called transepithelial CXL (TCXL) are that riboflavin cannot penetrate an intact epithelium and that the presence of the epithelium will block approximately 20% of the UV-A light from reaching the stroma. Both of these concerns are valid, but these assumptions may not be entirely correct.

The major objection to TCXL stems from studies that have found a lack of efficacy. Wollensak and colleagues found that corneal biomechanical stiffening was five times greater after epi-off CXL compared with TCXL in an animal model.[4] Other clinical and laboratory studies have reported weaker or no effect of CXL using the epi-on method.[5-10] Touboul et al[11] compared conventional, transepithelial, and accelerated CXL in 24 patients. Confocal microscopy showed corneal changes in conventional and accelerated crosslinking (ie, when the epithelium was removed), but in TCXL, there were no observable changes in the cornea. They concluded that TCXL had no benefit.

These studies suggest that TCXL has a significantly weaker biomechanical effect. Part of this may be due to insufficient transepithelial riboflavin diffusion into the corneal stroma. A limitation of most of these studies, however, is that standard riboflavin formulations were used. This formulation has been shown to have minimal penetration through an intact epithelium due to the large molecular sizes of riboflavin and dextran. For this reason, newer formulations of riboflavin such as Ricrolin TE (Ofta hi-tech Innovazione Tecnico Chirurgica) have been formulated using alternative vehicles, and these commercially available solutions are being used with greater frequency outside of the United States. Moreover, many earlier authors did not attempt to enhance the penetration of riboflavin using any of several methods, including alteration of the riboflavin formulation by using additives such as benzalkonium chloride or by changing tonicity.

Another area of concern with these studies involves the physical act of riboflavin loading. An eye with an intact epithelium requires a significantly longer time (60–80 minutes) than one in which the epithelium has been removed (typically 30 minutes). This is the case even with non–dextran-containing vehicles. Many studies that claim decreased effectiveness of TCXL used a fixed loading time of only 30 minutes, and typically the cornea was not checked to determine whether there was sufficient corneal riboflavin saturation before UV-A treatment. In cases in which the surgeon notes inadequate riboflavin loading, continued loading with topical riboflavin may eventually result in a sufficiently loaded cornea to proceed with the UV-A treatment stage, but if a rigidly timed loading protocol is used, that may be the reason that suboptimal crosslinking is demonstrated.

NEWER STUDIES

On the other hand, more recent studies have shown support for the efficacy of TCXL. Pinelli and colleagues[12] reported no significant difference in the analyzed parameters between TCXL and standard CXL. Filippello et al[6] performed bilateral TCXL in 20 patients with progressive keratoconus. In treated eyes, there were statistically significant improvements in BCVA and UCVA, keratometry, cone apex power, and higher-order aberrations, compared with untreated control eyes. Their conclusion was that TCXL treatment appeared to halt keratoconus progression and provide statistically significant improvements in visual and topographic parameters.

Stojanovic et al[13] evaluated the efficacy and safety of TCXL using a multifactorial approach to achieve proper stromal riboflavin saturation. The authors used a non–-dextran-containing, hypotonic solution and employed superficial disruption of the epithelial surface in order to enhance penetration of riboflavin. Riboflavin saturation was confirmed via slit lamp, rather than using an arbitrary time limit. Their results showed that distance UCVA and BCVA improved significantly. No eyes lost lines of acuity, while 27.4% of eyes gained 2 or more lines. Mean spherical equivalent decreased by 0.74 D, and mean cylinder reduction was 1.15 D. Scheimpflug-based topography showed a significant decrease in irregularity and asymmetry.

Rubinfeld et al[14] presented a retrospective evaluation of TCXL at 6 (147 eyes) and 12 (79 eyes) months. Reduction in maximum keratometry (Kmax) on Pentacam (Oculus Optikgeräte GmbH) was 0.997 D at 6 months and 1.17 D at 12 months.

The presence of a demarcation line after CXL has been thought to indicate the efficacy of corneal crosslinking.[15] In fact, the significance of the demarcation line is uncertain. The increased optical density seen on optical coherence tomography (OCT) or confocal microscopy may represent keratocyte apoptosis and subsequent repopulation.[16] While a demarcation line after epithelium-off CXL has been shown at 300 to 350 µm depth,[17] keratocyte apoptosis has been demonstrated after TCXL.[4] Filippello et

By Jesper Hjortdal, MD, PhD

Corneal collagen crosslinking (CXL) has become widely used in recent years to treat early stages of keratoconus and iatrogenic corneal ectasia.[1] Riboflavin (vitamin B2) has a molecular weight of 376.36 g/mol and is a hydrophilic molecule. Because there are tight junctions between individual cells in the corneal epithelium, riboflavin cannot penetrate an intact corneal epithelium. The standard CXL treatment therefore includes mechanical debridement of the corneal epithelium within a 9-mm-diameter zone and subsequent application of 0.1% riboflavin every 3 to 5 minutes for 30 minutes before initiating ultraviolet-A (UV-A) irradiation (370 nm, 3 mW/cm^2) for 30 minutes in combination with continual riboflavin application.[2]

During UV-A irradiation, stromal collagen and/or glycosaminoglycans are photochemically crosslinked via the natural lysyl oxidase pathway.[3] Riboflavin acts as a photosensitizer for production of oxygen free radicals, which are necessary for the CXL process, but it also absorbs the UV-A irradiation and prevents damage to deeper structures such as the corneal endothelium, lens, and retina. The efficacy and safety of a CXL treatment depends on proper imbibition of the corneal stroma with riboflavin.

Most publications reporting short- and long-term safety and efficacy of CXL have used the original protocol for CXL as described above.[2,4-6] CXL is generally considered to be safe, but the epithelial debridement associated with the standard CXL treatment is followed by a few days of discomfort and pain and slow visual recovery. In order to reduce these side effects, various attempts to perform the CXL procedure with the epithelium on have been suggested.

Riboflavin penetrates readily into the anterior portion of a debrided cornea. Basic animal studies by Spoerl et al,[7] however, indicate that a reasonably high riboflavin concentration is obtained only in the anterior 200 to 300 µm of the corneal stroma. Similar findings have been obtained with fluorescence microscopic measurements of intrastromal riboflavin concentrations.[8] Increasing the riboflavin concentration from 0.1% to 0.2% results in a higher intrastromal riboflavin concentration,[8] but biomechanical tests suggest that similar stiffening of the corneal tissue is obtained with riboflavin concentrations ranging from 0.015% to 0.15%.[7]

Instead of complete debridement of the corneal epithelium, researchers have investigated whether superficial scratching of the epithelial surface manually or by excimer laser ablation would be sufficient to ensure penetration of riboflavin to the corneal stroma. These investigations have shown that, even if the tight junctions between superficial epithelial cells are removed with an excimer laser, the basal epithelial cell layers act as a barrier to riboflavin penetration.[9] Similarly, superficial scraping with a thin needle, creating a grid pattern, was found to be insufficient to allow riboflavin penetration to the stroma.[10]

A number of chemical substances have a toxic effect on the corneal epithelium. Thus, benzalkonium chloride (BAK), tetracaine, pilocarpine, ethylenediaminetetraacetic acid (EDTA), gentamycin, oxybuprocaine, and tromethamine have been used to enhance riboflavin penetration through intact epithelium. Experimental studies in vitro have shown that 0.01% to 0.02% BAK in a hypoosmolar (0.44% NaCl) solution can increase the uptake of riboflavin to approximately one-third the concentration obtained in debrided corneas.[11,12]

Clinically, using 0.005% BAK and riboflavin 0.1% in 20% dextran T-500, Wollensak et al[13] found that CXL without epithelial debridement reduced the biomechanical effect to approximately one-fifth that of standard CXL. Clinical studies also suggest that 0.005% BAK is insufficient to promote riboflavin uptake through an intact epithelial layer.[14]

Tromethamine and EDTA can be used to enhance riboflavin uptake in corneas after superficial scraping, but the uptake is considerably less than in corneas with epithelium removed.[10] In a noncomparative clinical study, riboflavin uptake enhanced with tromethamine and EDTA was, however, found to be effective in halting keratoconus progression.[15] In vitro, tetracaine was shown to be inefficient to permit penetration of riboflavin into the corneal stroma.[16]

CONCLUSIONS

Penetration of riboflavin into the corneal stroma depends on the integrity of the corneal epithelium. Complete debridement of the epithelium most effectively ensures proper imbibition of the corneal stroma with riboflavin. Some of the published chemical modifications of riboflavin solutions for performing transepithelial CXL are promising but should not be used routinely until safety and efficacy have been studied in detail.

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What is your preferred approach to CXL?

- ☐ Epithelium on
- ☐ Epithelium off
- ☐ Other
- ☐ I do not perform CXL

al reported a demarcation line 2 weeks after TCXL that was located approximately 100 µm from the corneal epithelium.[6] Using RTVue (Optovue Inc.) anterior segment OCT, Stojanovic et al[12] showed in 24 eyes that the mean demarcation line was located at the depth of 317 µm from the surface, which is similar to that seen in epithelium-off CXL.[13]

Another argument against TCXL is the concern that an intact epithelium blocks the transmission of UV-A light by 20% and therefore may result in decreased efficacy. Some studies have shown that epithelial UV absorption occurs only with wavelengths of less than 310 nm.[18-20] Nonetheless, in the worst-case scenario, if we assume a 20% reduction in UV-A absorption by the stroma, which might result in shallower crosslinking compared with epi-off CXL, the density of collagen fibers is much higher in the anterior portion of the corneal stroma, where we assume most of the collagen crosslinking would occur.[16,21]

Steps that can be taken to minimize surface absorption of and energy loss of UV-A light include washing the riboflavin from the corneal surface prior to initiating UV-A application.[13] Even with traditional epi-off CXL, the optimal UV-A irradiance and duration of treatment have yet to be determined. Therefore, future research in this aspect of CXL, including alterations in the UV-A irradiance level to overcome the physical barrier of an intact epithelium, may change our understanding of this procedure.

CONCLUSIONS

Modifications of traditional CXL have already begun to occur, and TCXL will undoubtedly continue to evolve. I firmly believe that the standardization of riboflavin loading of the cornea and further advances in UV-A irradiation technology will overcome the main objections to TCXL. As greater numbers of patients are treated worldwide with TCXL, we will have a better understanding of this exciting but, to date, relatively poorly understood procedure. TCXL will allow younger patients to undergo CXL and will facilitate bilateral treatments. Although keratoconus may be a small fish in the big pond of eye diseases, we have the potential to significantly affect the lives of these patients while maximizing their comfort, convenience, and safety.

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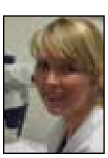

The Case for Epithelium-Off CXL

Epi-off CXL has shown evidence of success in halting the progression of keratoconus.


By Rebecca McQuaid, MSc; Arthur B. Cummings, MB ChB, FCS(SA), MMed(Ophth), FRCS(Edin); and Michael Mrochen, PhD

From the patient's perspective, there is no question that CXL without removing the epithelium (epi-on) is more comfortable, safer, and generally preferable to CXL with the epithelium removed (epi-off). However, the reason for performing CXL is to stabilize keratoconus, and the reported clinical outcome and experimental results of epi-on treatments demonstrate reduced efficacy: that is, less biomechanical stiffening of the cornea. Patient comfort is of secondary importance in this situation, and the primary outcome measure is whether or not CXL has been successful in stabilizing or even improving the corneal shape. This is the fundamental thought in the mind of the practitioner of epi-off CXL.

Clinically, epi-off CXL has been shown to stabilize corneal curvature in eyes with progressive keratoconus, with no significant change in the refractive index of the cornea.[1] Since its regulatory approval in the European Union in 2006, CXL has been widely practiced around the world as an effective procedure for halting the progression of keratoconus and corneal ectasia.[2]

Before the introduction of CXL, the only option to overcome keratoconus progression was keratoplasty. Due to the recent downturn in the economic climate, the high cost of surgical procedures, and long hospital waiting lists for corneal transplantation, a person's chance of receiving treatment is diminished,[3] giving crosslinking a significant advantage among options. CXL is less invasive, more cost-effective, and less stressful for the patient. CXL has a recovery period of 5 days, whereas 1 year of follow-up care is needed following corneal transplantation. The corneal transplant patient also faces potential graft rejection, something that does not affect the CXL patient. These factors are important when considering an effective treatment plan for a progressive disease.

WHY EPI-OFF CXL?

The Dresden protocol[4] was created in order to standardize the original CXL treatment in 2003. The protocol included epithelial removal before soaking the cornea with a dextran-based 0.1% riboflavin solution, followed by exposure with UV-A light for 30 minutes under an intensity of 3 mW/cm². The epithelium, approximately 50 µm in thickness, forms a barrier to both riboflavin and UV-A penetration. Removing the epithelium allows proper absorption of riboflavin into the cornea and anterior chamber in order for the UV-A light to efficiently illuminate the cornea.

For current techniques of epi-on CXL, soaking time can be up to 50 minutes before illumination, increasing treatment time and the risk of epithelial disturbance. Only 80% of UV-A exposure occurs in the stroma after the UV-A light penetrates the epithelium, creating a limited cross-linking effect compared with epi-off CXL.[5] Recently, clinical studies have investigated the use of higher-intensity UV-A light, consequently shortening treatment time and reducing the risk of corneal dehydration.

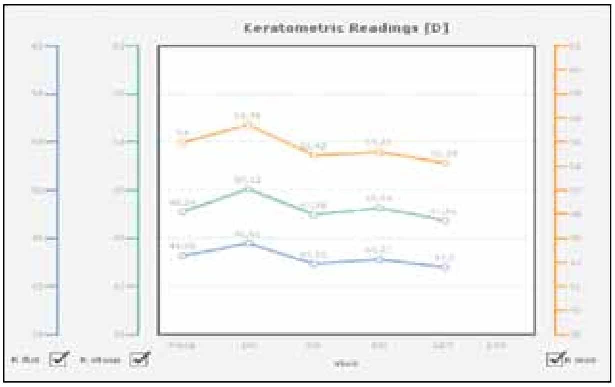

Figure 1. Clinical studies at the Wellington Eye Clinic have shown eyes treated with epi-off CXL to exhibit significant reduction in keratometry over time.

Clinical studies at the Wellington Eye Clinic have shown that eyes treated with epi-off CXL exhibit significant reduction in keratometry over time (Figure 1). An ongoing clinical trial (26 eyes) comparing two treatments—30 minutes at 3 mW/cm² using the UV-X 1000 lamp (IROC Innocross AG) versus 10 minutes at 9 mW/cm² with the UV-X 2000 lamp (IROC Innocross AG)—has shown similar safety with the two devices but increased efficacy with the UV-X 2000 device.[6] The observed difference in the two treatments may be due to the increased intensity with the UV-X 2000 lamp, but the device's optimized beam profile with additional depth in the peripheral part of the beam may be the primary cause for the increased efficacy.

In summary, both our own clinical experience over the past 6 years and a review of the literature[4] provide ample evidence that epi-off CXL is effective with low failure rates (less than 5%) and proven safety (less than 1% loss of BCVA of more than 2 lines). Numerous studies[7,8] have shown that the cornea flattens and regularizes to preoperative levels by approximately 3 months after the treatment. Visual acuity usually increases by 1 to 2 lines, and the cornea may flatten further over time.

EPI-ON CXL

The potential advantages of the epi-on approach are significant, but, to date, there is not sufficient evidence that it is effective.

Other methods such as iontophoresis have been investigated to achieve riboflavin delivery to the cornea with little or no disturbance to the epithelium.[9] This technique involves application of an electrochemical effect to the cornea, enabling a distribution of riboflavin similar to that with the epi-off technique and resulting in corneal strengthening after exposure to UV-A light. Although this method looks promising, more research is needed.

Kanellopoulos[10] has presented results with intrastromal riboflavin instillation via a femtosecond laser-created pocket along with application of higher-intensity UV-A light (7 mW/cm²). With follow-up time of 1.5 years (10 cases), he reported a reduction of 2.10 D in patients with refractive astigmatism and reduction of keratometry readings by 2.70 D. These results suggest that higher-intensity CXL with use of a femtosecond pocket instead of epithelial removal has the potential to be as effective as standard CXL.

CLINICAL RESULTS

To date, most clinical studies have focused on the success and failures of epi-off CXL. Investigators have shown that standard epi-off CXL affects the biomechanical properties of the cornea, increasing corneal rigidity by approximately 70%.[11] Laboratory investigations in human and porcine corneas examined the best treatment parameters for epi-off CXL, including riboflavin concentration, intensity and wavelength of UV-A light, and treatment duration.[7,12]

The largest clinical study to date to investigate long-term effects of standard CXL has been the Siena Eye Cross Study,[8] in which 363 eyes with progressive keratoconus were treated. In 44 eyes followed up for at least 4 years, long-term corneal stability was seen without relevant side effects.

Epi-on or transepithelial CXL has been reported to be less painful for the patient and to reduce the risk of infection postoperatively by keeping the epithelium intact. Although the short-term effects of epi-on seem positive, results reported to date do not provide significant evidence to suggest long-term success in halting the progression of keratoconus. A study with 3 years of follow-up found a reduction in steepest keratometry to be more prominent in corneas after epi-off CXL compared with epi-on CXL.[13]

Hafezi[14] found the stromal concentration of riboflavin to be lower by a factor of 40 during epi-on CXL compared with epi-off CXL, and the long-term effect of epi-on CXL on corneal shape was reduced. This corresponds with the findings of Wollensak et al,[15] who demonstrated a reduction in biomechanical changes with transepithelial CXL compared with standard epi-off CXL.

The Wellington Eye Clinic is conducting a comparative study of epi-on and epi-off CXL. New epi-on protocols currently under clinical investigation demonstrate encouraging results. Riboflavin diffusion occurs in the same amount of time as current epi-off techniques or less, and 1-month postoperative data demonstrate corneal flattening rather than the steepening typically seen at this interval with epi-off CXL. Visual recovery is very fast, with day 1 postoperative vision equal to preoperative vision. This level of recovery can take up to 3 months in epi-off CXL. As promising as epi-on may appear at this early stage, the final test will be the corneal shape at the 1-year postoperative interval.

CONCLUSION

It would be preferable to have epi-on CXL as a reliable surgical option, given its promise of faster recovery time and reduction in postoperative pain. In order to make epi-on CXL an effective and safe treatment method, longer-term results for a larger sample group will be required.

It has been suggested that epi-on CXL is worthwhile for eyes with thin corneas due to its inability to penetrate as deeply into the stroma as epi-off CXL. For the moment, however, epi-off CXL has shown evidence of success in halting the progression of keratoconus, and that is the most important factor for this disease. The efficacy of epi-on CXL still must be shown in a prospective clinical trial. For the moment, therefore, our preferred approach is epi-off CXL, a procedure with a proven track record. ■

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