Corneal Cross-Linking (CXL) is an established surgical procedure for the treatment of corneal disorders such as corneal ectasia and keratoconus. This method of treatment stabilises the corneal structure and increases rigidity, reducing the requirement for corneal transplantation. Since its development, many scientific studies have been conducted to investigate ways of improving the procedure. Biomechanical stability of the cornea after exposure to UV-A light, and the effect of shortening procedure time has been some of the many topics explored.

Key words: Corneal cross-linking, radiant exposure, ultraviolet-A

Advances in corneal cross-linking (CXL) shows the treatment to be at its peak in scientific research. It has become a reputable method for the treatment of keratoconus, or corneal ectasia. Since its introduction in 1997,[6] CXL has proven beneficial to halt the progression of keratoconus, potentially reducing the need for corneal transplantation,[2,3] as there is no direct evidence as yet to prove that collagen crosslinking reduces the need for a corneal transplant. CXL is followed using a standardized protocol,[4] which involves epithelial removal, followed by dextran-based 0.1% riboflavin solution applied to the cornea for 20 min. The cornea is then exposed to a ultraviolet-A (UV-A) lamp, under an illumination intensity of 3 mW/cm² for 30 min, with a radiant exposure of 5.4 J/cm². Recent studies are focusing on methods to improve the efficiency of the procedure and maximizing standard outcomes.

Corneal Cross-Linking

Recently, clinical studies have investigated the use of higher intensity UV-A light, consequently shortening treatment time and reducing the risk of corneal dehydration. A shorter procedure time would be beneficial for both patient and surgeon. If treatment time for CXL were to be reduced, the radiant exposure would remain the same, but with a shortened illumination time. Schumacher et al.[5] investigated the biomechanical stability of porcine corneas when exposed to 10 mW/cm², therefore reducing treatment time from 30 to 10 min. This study found an increase of corneal stiffness with higher intensity CXL, but specified further clinical investigation would be required to examine safety of the treatment. Kannellopoulos[6] investigated the safety of 7 mW/cm² with illumination time of 15 min. No adverse events or negative biomechanical effects were noted (ectasia/epithelial ingrowth). This confirms high intensity CXL can be performed, as long as the same radiant exposure of 5.4 J/cm² remains in place. Reduction in the surgical time seems to be associated with the same risks as in the standard protocol. Damage at the level of the corneal endothelium occurs at a threshold of 0.3 mW/cm² UV-A light.[5] Despite its safety and efficacy outcomes in the lab using porcine corneas, clinical data has not been published showing the effect of higher intensity CXL on human corneas as yet.

Clinical studies at the Wellington Eye Clinic have shown that eyes treated with standard CXL (3 mW/cm²) exhibit a significant reduction in keratometry over time [Fig. 1]. An ongoing clinical trial (26 eyes) comparing two treatments- 30 min at 3 mW/cm² using the UV-X 1000 lamp (IROC Innocross AG) versus 10 min 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[8] [Fig. 2]. 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.

Epithelial-on (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. Epi-ON or transepithelial CXL has been reported to be less painful for the patient and reduces 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 or standard CXL compared with epi-ON CXL.[9]

Other methods such as iontophoresis have been investigated to achieve riboflavin delivery to the cornea with little or no
disturbance to the epithelium.[10] 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.

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.

**Keraflex**

Keraflex KXS (Avedro, Inc., Waltham, Massachusetts) aims to cause significant flattening of the corneal surface using thermal heat below the corneal surface.[11] During a Keraflex procedure, the Verdera system delivers a single low-energy microwave pulse lasting less than 1 s. Energy is applied to the cornea using a dielectrically shielded microwave emitter, which noninvasively contacts the epithelial surface. Through capacitive coupling, the single pulse raises the temperature of the selected region of corneal stroma to approximately 65°C, shrinking the collagen, and forming a toroidal lesion in the upper 150 µm of the stroma below Bowman’s membrane. The treatment is then followed by corneal cross-linking (CXL) to “lock in” the flattening effect. Without performing CXL, the shape created through Keraflex would rebound to preoperative levels within 3 months. Clinical results at the Wellington Eye Clinic found the timing of performing cross-linking after Keraflex to be an important factor for a successful outcome. Cases treated with CXL directly after the Keraflex, all failed in the sense that 3 months later the corneal shape looked like it had never been treated with Keraflex at all. Those cases where the delay was longer than 5-6 h and even days and in one case, 3 weeks later, all demonstrated much more corneal stability over time. It appears as though there is a rebound effect after Keraflex and that if the CXL is applied while the cornea is rebounding, the newly formed links are simply broken by the stronger rebound effect and effectively, no CXL has taken place.

**Conductive Keratoplasty**

CK was used quite widely some years ago for the treatment of presbyopia and low degrees of hyperopia. It worked very satisfactorily, but the results were not long lasting. Most cases lost effect of conductive keratoplasty; induced corneal flattening within the first 12 months after surgery and some did so even earlier. CK has the benefit of being a spot application with properties very similar to Keraflex (about 65°C and a very brief application time, well less than 1 s) and to be used for the treatment of keratoconus, we believe that it too would simply regress if there was no concurrent treatment with CXL to stabilize the effect. Combining it with CXL, however does offer the potential of more stability and increased duration of benefit. CK is also delivered by means of a needle-tipped probe that allows accurate and direct placement of spots exactly where the effect is required. CK spots can be applied to the apex of the cone thereby flattening it, or to the superior peripheral cornea thereby steepening the superior paracentral area and making it more uniform with the steeper inferior area. CK has been used for keratoconus before, but without the concomitant use of CXL and the effect was only seen temporarily. We are currently conducting a CK and CXL clinical trial at the Wellington Eye Clinic and at this early juncture can report that the CK effect is indeed extended when compared to CK alone. At this point in time however, CK with CXL can certainly not be regarded as a permanent solution; but there is no doubt that it adds value to the CXL procedure by providing better quality of vision due to the improved corneal shape and an easier rigid glass permeable (RGP) or soft contact lens (CL) fit if required. An additional positive aspect of the thermal procedures is the fact that they do not use or ablate tissue. If more sophisticated procedures were to become available in the future, the patient can still avail of them as the cornea has not been ablated and made too thin.
SimLC

SimLC is an acronym for simultaneous laser cross-linking that was coined in an attempt to distinguish it from topography-guided photorefractive keratectomy (PRK)/CXL. The key difference is that with SimLC, the topography-guided element is always present but not necessarily the only treatment given with no refractive errors being targeted in the treatment. It is made very clear to the patient that the treatment is not designed to free them up from glasses or improve their uncorrected vision. Rather, the treatment is designed to improve the corneal shape before stabilizing it and thereby improve best corrected visual acuity (BCVA) and quality of vision. SimLC has been performed at the Wellington Eye Clinic since 2007 and the procedure can be regarded as being very stable with an average reduction in K-Max of 5.9 D. In our experience, the stability following SimLC has been excellent with no regression seen to date over the past 6 years. One potential reason may be the thorough riboflavin soak that is achieved due to the removal of Bowman’s membrane due to the laser ablation. The cornea typically soaks in 15 min where regular CXL, an adequate soak is typically achieved after 25-30 min of riboflavin exposure. Topography-guided PRK with CXL has been used for even longer in Athens by Dr. John Kanellopoulos who has been practicing this technique for close on 10 years with excellent stability. We use it in approximately 25% of cases where the BCVA is less than 6/12 (20/40 or 0.5), where the cornea is thick enough (>450 µm) and where the patient expresses a desire to improve the BCVA.

Discussion

CXL has proven its worth in the treatment of keratoconus and post-LASIK ectasia. Possible future applications, besides those of treatment of corneal infection and bullous keratopathy, may extend to the domain of refractive surgery. Many of the pioneers of CXL today believe that in time it will be possible to relatively accurately change the corneal power through the CXL process. In the case of epi-ON CXL, this would imply that a refractive procedure could be done without cutting or ablating the cornea and in fact, strengthening the cornea through the CXL effect and all without breaking the epithelium. This would result in an incredibly safe procedure and the benefits of this are enormous. Most patients that still opt not to have refractive surgery have made this decision based on their fear of the surgery. If this fear were removed due to the safety profile of epi-ON CXL, the numbers of patients undergoing refractive surgery would grow significantly. It is still very early in this research direction, but most believe that if it did work, that it would be suited to the lower myopia range in all likelihood. This happens to be the group that makes up the greatest proportion of laser eye surgery.

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