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ORIGINAL ARTICLE

Epithelium-on Corneal Cross-linking for Progressive Keratoconus: Two-year Outcomes

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ABSTRACT

Corneal cross-linking (CXL) has been established as a successful treatment tool for the treatment of progressive keratoconus in terms of slowing or halting progressive corneal steepening and thinning and even on some occasions, reversing the steepening. To date the Dresden epithelium-off protocol is regarded as the gold standard and the epithelium-on (epi-on) approaches have met with less success. Both doctors and patients would welcome an epi-on CXL procedure that provided good outcomes as the morbidity with epi-on CXL is so much less and the safety is enhanced. Patient comfort is greater with the epi-on techniques when compared to epi-off. This study looked at 82 eyes that had documented progression of keratoconus and then underwent epi-on CXL using the CXLO system. The results show that corneal steepening can be halted and even reversed over a 2-year follow-up period with no complications noted. Over the 24 months post treatment on average there was a decrease in all keratometry values, BAD and ISV when compared to before treatment with IHD being marginally increased.

Further studies over a longer follow-up period are required but recent publications using the same approach are validating the findings seen in this study.

Keywords: Accelerated corneal cross-linking, Blurred vision, Corneal cross-linking, Corneal ectasia, Corneal tomography, Corneal topography, Corneal transplant, Eye rubbing, Femtosecond-laser assisted DALK, Keratoconus, Steep corneas, Quality of vision, Vogt's striae.

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INTRODUCTION

Corneal cross-linking (CXL) has been established as a successful treatment for progressive keratoconus in terms of stopping or slowing progressive corneal steepening and thinning and even on some occasions, reversing the steepening.[1-4] To date, most success has been achieved with techniques based on the Dresden protocol: a 30-minute soak of riboflavin after removing the corneal epithelium followed by irradiation with UV-A at 3 mW for 30 minutes. Studies have followed on the Dresden protocol and shown that treatment times reduced to 10 minutes with 9 mW power have led to equivalent outcomes.[5] Although this epithelium-off technique is often described as "noninvasive" and safe, it is not infrequently complicated by delayed epithelium healing, sterile infiltrates, corneal infections and corneal scarring. Most ophthalmologists and all patients agree that being able to achieve similar outcomes with a procedure where the epithelium remains intact, would be a vast improvement on the current techniques, providing that it worked. The problem to date is that most of the reports on epi-on CXL suggest that it does not work. Possible reasons include the epithelium being a barrier to the penetration of the Riboflavin molecule, the diffusion of oxygen into the stroma and a barrier-filter to UV-A light. To complicate matters more, most epi-on protocols used the same techniques and components as are used in epi-off techniques and this may add to the failure rate.

For CXL to work effectively, three specific items are required:

1. Sufficient concentration of riboflavin in the cornea
2. Sufficient UV-A in the cornea
3. Sufficient levels of oxygen in the cornea

When an epi-off protocol is simply applied to an epi-on procedure, at least two of these are greatly affected. Less riboflavin gets into to stroma and less light gets into the stroma due to the epithelium, soaked in Riboflavin, filtering the UV-A light. When these are addressed specifically, then epi-on CXL can be more effective.

METHODS

Patients with progressive keratoconus as demonstrated by corneal topographies and tomographies at least 3 months apart and for the most part, 6 months apart, showing corneal steepening of at least 1 D were subjected to epi-on CXL with unique investigational protocols initiated under Ethics Board approval:

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Two separate sterile, proprietary investigational applicators designed to maximize contact between the riboflavin solution and the corneal surface were used.[5] First, eyes were gently brushed with minimal pressure in a circular motion over the entire cornea for ~10–20 seconds with the patent-pending applicator sponge. In earlier patients, a weck-cell sponge was used, and in later patients a patent-pending specially designed, sterile applicator (CXL Ophthalmics, Encinitas, CA) that had been fully saturated with proparacaine. This applicator is constructed of a nonabrasive porous material with patent-pending shapes, unique pore size, flexibility, and hydration properties specifically designed to enhance penetration of the unique riboflavin solution into the corneal stroma without disrupting the corneal epithelium. Eighty-two eyes were treated in this study of which 57.3% had the weck-cell sponge and 42.7% the specially designed, sterile applicator (CXL Ophthalmics, Encinitas, CA) was used. Unlike previously described techniques and devices, this device does not use the principle of inducing epithelial disruption to improve epithelial permeability. The intact nature of the epithelium has been confirmed on slitlamp examination by an independent laboratory.[6] Next, in each subject a sponge-like loading device (CXL Ophthalmics), shaped to conform to the cornea's curvature (including steep, cone-shaped corneas) and maximize contact with the cornea was saturated with the riboflavin solution and placed over the entire cornea.

The riboflavin being used to soak the cornea was augmented by 0.5% pure riboflavin (Streuhli). The absence of Dextran in the solution, the increased concentration and the unique sponge applicator system greatly increases the concentration and quality of the Riboflavin corneal soak.

The last 2 minutes of the 25-minute soak is dedicated to washing Riboflavin out of the corneal epithelium using BSS. When the eye is now examined on the slit lamp to determine the quality of soak, the epithelium appears clear/white while the stroma is green when using cobalt blue illumination.

The UV-A light is pulsed with 10-second cycles every 2 minutes to allow re-oxygenation of the corneal stroma that is depleted of oxygen during the CXL process. The lamps used included the IROC UV-X 1000 model that provides the required total energy by means of 3 mW for 30 minutes exposure and the IROC UV-X 2000 that provides the same energy over 10 minutes with 9mW power. The UV-lamp selected for each specific case was determined by the location of the cone: if the cone was centrally located, the UV-X 1000 was used, and if the cone was para-centrally located, the UV-X 2000 was used due to increased peripheral illumination.

Patients all had preoperative refractions and UDVA and BDVA assessments as well as pentacam (tomography) and placido disk (topography) examinations. These parameters were all repeated at subsequent visits at 1 month, 3, 6, 12, 18 and 24 months postoperatively. Table 1 shows the consistent increase in UDVA and CDVA over 12 months postoperative and the corresponding slight increase in myopia as the eccentric cone centralized.

Table 1: Average visual acuity values pre-epi-on CXL/AXL to 12 months post-treatment

Time (months)	*0*	*1*	*3*	*6*	*12*
CDVA	0.820	0.829	0.870	0.871	0.900
UDVA	0.357	0.378	0.338	0.399	0.419
SE	–1.34	–1.54	–1.60	–1.67	–1.73

RESULTS

Eighty-two eyes of 72 individuals (24 female, 48male) were treated in total. epi-on CXL (3 mW for 30 minutes) was used to treat 46 eyes and epi-on AXL (9 mW for 10 minutes) to treat 36 eyes.

The preoperative tomography and topography exams taken 3–6 months apart showed a significant increase in mean keratometry (K_{mean}) $p = 0.2754$, max keratometry (K_{max}) $p = 0.0008$, K2 $p = 0.0583$, Belin/Ambrósio enhanced ectasia display (BAD) $p = 0.004$, index of surface variance (ISV) p = 0.0026 and index of height decentration (IHD) $p = 0.0005$.

Following treatment over 12 months on average there was a marked decrease in BAD, ISV, IHD K_{max} and sphere equivalent (SE) and an improvement of both uncorrected distance visual acuity (UDVA) and corrected distance visual acuity (CDVA). Table 2 shows K_{mean} and K_{max} flattening over time and the improvements in other indices like IHD, ISV and BAD.

Over the 24 months post-treatment on average there was a decrease in all keratometry values, BAD and ISV when compared to before treatment with IHD being marginally increased.

For the 34 eyes examined at 24 months, 61.7% showed a decrease in BAD, with the average decrease being 0.77.

Table 2: Average tomography and topography values pre-epi-on CXL/AXL to 24 months post-treatment

Time (months)	*0*	*1*	*3*	*6*	*12*	*18*	*24*
Sample size	82	69	58	57	50	21	34
K_{mean}	45.35	45.5	45.08	45.39	45.21	44.90	44.97
K_{max}	54.37	54.27	54.71	53.52	53.32	51.59	53.27
K1	43.70	43.95	43.45	43.86	43.82	43.60	43.45
K2	47.19	47.18	47.17	47.07	46.72	46.32	46.61
IHD	0.11	0.105	0.1	0.098	0.097	0.12	0.12
ISV	88.08	80.93	84.02	79.75	79.52	71.85	84.59
BAD	8.61	9.20	8.55	8.26	8.37	8.22	8.94

A decrease of K_{mean} values lower than preoperative measurements was seen in 39% of eyes measured at 24 months.

Age at time of treatment was found to be a significant factor in the response to treatment with older patients having a greater reduction in K_{mean} p <0.0001, Kmax p = 0.0205, K1 p = 0.0002, K2 p <0.0001, BAD, IHD and ISV. Age was also significant in the improvement of both CDVA and UDVA.

AXL demonstrated more of an improvement than CXL of both CDVA p <0.0001 and UDVA p = 0.0019.

DISCUSSION

As these results demonstrate, a unique epi-on CXL technique (which is not yet commercially available) can be very effective through a 2-year follow-up for progressive keratoconus. Not only was progression halted in all cases, but 39% corneal steepening regressed. There were no extreme cases of corneal flattening like those seen on occasion with epi-off CXL cases. There were no complications, not even minor issues like a corneal epithelial defect. The safety profile of epi-on CXL can be called noninvasive while this does not apply to epi-off CXL.

During the early study experience, a weck-cell sponge was used to prepare the cornea for riboflavin loading. This was used in 57.3% of cases. The patent-pending specially designed, sterile applicator (CXL Ophthalmics, Encinitas, CA) was introduced later and has been used ever since, with 42.7% of the study eyes being prepared using the latter applicator technique as described in the methods section. With the weck- cell sponge the epithelium was sometimes disturbed but not interrupted and the surface often not pristine with lipid-like smearing of the epithelium. Using the specially designed, sterile applicator there has not been a single epithelial issue intraoperatively and the surface is typically pristine prior to commencing the Riboflavin soak.

A multicenter study in the USA conducted by the physician sponsored CXL-USA study group, made up of 17 centers across the country, evaluated Epi-On CXL.[7] Forme fruste keratoconus, post LASIK ectasia, pellucid marginal degeneration (PMD), forme fruste PMD, keratoconus or fluctuating vision after radial keratotomy all inclusion criteria for the study. In a single-center analysis[7] patients followed for 3–6 months showed approximately 50% of eyes treated with the epi-on CXL technique had gained 1 or more lines from baseline CDVA at both follow-up intervals or showed improved corneal topographic changes including reduction in K_{max} (approximately 1–1.5 D of flattening) and regularization of irregular astigmatism while 90% of eyes maintained their shape and did not progress. In a smaller cohort of eyes treated with the epi-off CXL technique, only about 25–30% had improved CDVA at these time points. Additionally, on postoperative day 1, 15–20% of patients experienced an improvement of 1–4 lines of UDVA.

Given that the corneal effect on flattening and the refractive effect is so gentle, epi-on CXL is also very useful for cases of PRK in suspect corneas where a topography-guided PRK can be performed to correct the refractive error and the topographic irregularities and then followed up and monitored for a few weeks to months until the outcome is optimal. At this point, epi-on CXL can be administered with little fear of any complication and significant corneal flattening or refractive changes.

Most cases of keratoconus are bilateral and often the second eye is still seeing well, often 1.0 or 1.2 UDVA. In these cases, patients and their parents are often keen to have this "good eye" stabilized to prevent it from going down the route of the more involved eye. epi-off CXL with its potential complications would pose a greater risk to such an eye than would epi-on CXL. We have performed epi-on CXL for such non-progressive eyes with no unwanted side effects and no signs of progression, certainly providing both the patient and their parents with peace of mind. It needs to be stated that before using epi-on CXL, I would not have treated a 1.0 CDVA eye with epi-off CXL to provide stability due to the greater risks associated with epi-off CXL.

Epi-on CXL, if done effectively, offers the benefits of CXL, including stopping the progression of keratoconus, improvement of corneal shape and improved vision with minimal to no risk.[8] Nawaz et al.[9] evaluated epi-on CXL compared to epi-off CXL and showed similar CDVA and topographic changes between the two groups. Two of the patients (10%) in the epi-off group, however, developed persistent stromal haze and the epi-on group showed superior comfort post-procedure.[9] Removal of epithelium, in addition causing significant pain,[7,9] is also associated with a longer recovery resulting in a long time before returning to contact lenses and daily living. Patients typically can return to contact lens wear within 48–72 hours of epi-on CXL. While there can be discomfort for the first 24 hours after epi-on CXL, after 2–3 days postoperatively most patients are fully functional and return to baseline. Additionally, epi-off CXL increases the risk of complications including pain, corneal haze, corneal melt, infection, and endothelial decompensation.[8-15] For these reasons, there is an incentive to perform epi-on CXL.

The list of potential complications with epi-off CXL is listed in Table 3 together with the complications noted in this epi-on study. Findings noted at the 3-month interval following CXL.

Table 3: Common (>1%) reported complications with epi-off CXL versus this epi-on CXL study

	Typical epi-off CXL (ref Avedro US-package insert)	*Epi-on CXL (the present study)*
Anterior chamber cells	2%	0
Anterior chamber flare	4%	0
Corneal disorder	3%	0
Corneal epithelial defect	24%	0
Corneal oedema	3%	0
Corneal opacity	65%	0
Corneal striae	24%	0
Dry eye	6%	2%
Eye pain	17%	2%
Eyelid edema	7%	0
Foreign body sensation	15%	3%
Lacrimation increased	5%	3%
Photophobia	11%	2%
Punctate keratitis	25%	3%
Vision blurred	16%	2%
Visual acuity reduced	10%	2%
Visual impairment	3%	0

There are several specific considerations with epi-on CXL. Because intact epithelium can slow penetration of riboflavin, adequate transepithelial saturation of riboflavin requires different techniques compared with epi-off. Loading times for epi-on can vary, depending on the concentrations of riboflavin, and may range from 25 minutes to 3 hours. Techniques to enhance penetration for epi-on CXL include the use of topical anesthetics, iontophoresis,[16] corneal sponge loading, and benzalkonium chloride-EDTA (BAC-EDTA) riboflavin-UVA TE-CXL.[17] The use of combinations of permeability enhancers may have an additive effect on epithelial riboflavin permeability and thereby increase riboflavin penetration into the corneal stroma.[18,19] The key is to proceed to UV light application only after complete riboflavin saturation of the corneal stroma

As with epi-off, UV light can be applied continuously or "fractionated," which is when the light is "pulsed" on and off.[8] The pulsed UV allows for a build-up of reactive oxygen species which are a key process for successful cross-linking[20] and additionally, allows oxygen to reaccumulate to be used in the next CXL cycle.

Corneal hysteresis is another potential measure of corneal biomechanics that can be assessed after epi-on CXL.[8] De Bernardo et al.[8] showed stabilization of patients with progressive keratoconus at 6 months after TE- CXL with minimal change in corneal hysteresis, while Lombardo et al.[21] also showed a biomechanical strengthening effect on donor globe eyes with TE-CXL. Torricelli et al.[17] showed that benzalkonium chloride-EDTA (BAC-EDTA) riboflavin-UVA TE-CXL statistically increased biomechanical corneal stiffening compared to the standard epi-off treatment in a rabbit model.

Epi-on treatments can be ideal for all age groups and varying degrees of disease.[22] Young patients, including children as young as 9 years old, tolerate the procedure well with fast recovery. Older patients (greater than age 35), as well as corneas with steep average keratometry, can also benefit as they may be slower to re-epithelialize with epi-off CXL compared to epi-on CXL. A study done by Koller et al.[23] showed that preoperative maximum K readings greater than 58D increase the risk for continued progression after epi-off CXL. Additionally, eyes of patients of age greater than 35 years undergoing epi-off CXL were at a clinically significant increased risk for complications afterward, defined by those eyes losing two or more Snellen lines.[22]

In summary, epi-on CXL can stop the progression of ectasia and result in improved UDVA, CDVA, corneal shape and reduction of K_{max} without the risk involved with epi-off CXL. It additionally resulted in the increased biomechanical strengthening of the cornea. Given the safety profile and results with epi-on CXL, it should be considered as a primary procedure when performing CXL. If epi-on CXL fails, there is no reason why epi-off CXL could not then be performed. Even though the consent form at the Wellington Eye Clinic clearly states that "in the event of epi-on CXL failing, then epi-off CXL will be provided at no cost to the patient", not a single patient in the last 5 years has needed to avail of this offer. For this very reason, almost all CXL treatments at the Wellington Eye Clinic today are performed using the epi-on CXL technique and the only time that epi-off is used is when the excimer laser has been used to remove the epithelium with either a PTK or in the topography-guided mode to first regularise the cornea before CXL.

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