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A comprehensive review on corneal crosslinking

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Abstract:

Corneal crosslinking (CXL) represents a paradigm shift in the management of corneal ectatic disorders. Before CXL was introduced, patients would need specialty contact lenses and possible corneal transplantation. CXL involves a biochemical reaction in which ultraviolet A light is used in conjunction with Riboflavin to form crosslinks in between corneal stromal collagen. This leads to strengthening and stabilizing of the collagen lamellae, resulting in mechanical stiffening of the cornea. Multiple protocols have been proposed including epithelium on versus off and varying light intensity and duration of treatment. All protocols appear to be safe and effective with few reported complications including infection, stromal haze, scarring, and endothelial toxicity. Overall, CXL has demonstrated to halt the progression of the disease clinically and in keratometry readings and improve the quality of life for patients. It is a minimally invasive, cost-effective procedure that can be performed in an outpatient setting with a fast recovery time and long-lasting results.

Keywords:

Cornea, cross-linking, ectasia, keratoconus, riboflavin

Introduction

Crosslinking is the process of forming chemical bridges between proteins and other molecules.[1] Corneal crosslinking (CXL) naturally occurs in the cornea by a reaction between transglutaminase and lysyl oxidase. This glycosylated crosslinking is responsible for increasing corneal stiffness with age.[2]

Riboflavin, also known as Vitamin B2, is a micronutrient important for maintaining healthy tissues. When exposed to ultraviolet A (UVA) radiation, riboflavin molecules absorb energy and reach an excited state. In its excited state, riboflavin it can either produce radicals or singlet oxygen species.[3,4] These active molecules can induce covalent bonds and therefore crosslink molecules.[5] Since 1970, investigators reported crosslinking reactions in collagen and elastin.[1] However, it was in 1997 that Spoerl *et al*. used this principle to increase corneal stiffness through crosslinking using UV light and riboflavin.[6]

Mechanism of Action

CXL is a complex biochemical reaction in which photo-oxidation occurs between UVA light and Riboflavin. This photochemical process occurs in an aerobic and an anaerobic phase. Riboflavin molecules absorb UVA light and gets excited to a triplet state. During the aerobic phase (Type II photochemical process), the excited triplet riboflavin interacts with oxygen in the atmosphere and forms reactive oxygen species including singlet oxygen. This singlet oxygen reacts with the collagen carbonyl groups, creating new bonds between the aminoacids and collagen molecules. During the anaerobic phase (Type I photochemical mechanism), the triplet riboflavin transfers electrons or hydrogen ions and forms riboflavin radicals. Both the radicals and the singlet oxygen specials will increase the formation of covalent crosslinks in between corneal stromal collagen.[7] This increases the

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strength of the cornea by increasing the diameter of the crosslinked Type I collagen fibers.[8]

The effect of crosslinking collagen fibers leads to strengthening and stabilizing the collagen lamellae, resulting in mechanical stiffening of the cornea. This in turn has been shown to improve corneal curvature that can be evidenced with keratometric and topographical parameters.[9]

In addition, crosslinking collagen fibers have also been shown to induce a high resistance to enzymatic digestion. This is important for many corneal disease processes as collagen degradation secondary to enzyme degradation (Typsin-2 and cathepsin K within the tear film) has been associated to thinning in keratoconus (KC) and corneal melting secondary to enzyme degradation can be seen in cases of infectious keratitis.[10]

Types of Crosslinking

Dresden protocol versus accelerated corneal crosslinking versus pulsed corneal crosslinking

The standard of treatment is based on the Dresden protocol that was described by Wollensak *et al*. in 2003 as a treatment option for KC. This technique is done under topical anesthesia and involves removing the central corneal epithelium (9 mm) by mechanical debridement, followed by the application of riboflavin solution (0.1% riboflavin in 20% dextran solution) to the de-epithelialized cornea for 30 min. The de-epithelized cornea soaked in riboflavin is afterward exposed to UVA light (370 nm) under a power of, 3 mW/cm^2 (5.4 J/cm^2) for 30 min. Riboflavin solution is continuously applied every 2–5 min during this irradiation process.[11,12] Usually, antibiotic drops are then administered postoperatively, and a bandage contact lens is placed for pain control.

To ensure an adequate corneal depth is obtained for the treatment in thin corneas, ultrasound pachymetry can be performed during initial Riboflavin instillation. If the cornea is thinner than 400 μm, then hypotonic riboflavin ophthalmic solution without dextran can be administered after which ultrasound pachymetry can be rechecked until a minimum of 400 μm is obtained.[13]

One issue with the Dresden protocol is the long treatment duration time. According to Bunsen-Roscoe's law of reciprocity, the same photochemical effect should be obtained with a reduced illumination time if the correspondingly irradiation intensity is increased.[14] Therefore, multiple protocols have been attempted with higher intensity of light to decrease the amount of exposure time. Accelerated CXL uses a higher intensity light of 30, 18, or 9 mW/cm^2 during a shorter amount of time 3, 5, or 10 min, respectively, for a cumulative irradiation dose of 5.4 J/cm^2. A meta-analysis performed comparing regular Dresden protocol with accelerated CXL, demonstrated standard CXL had a greater effect in terms of reduction in Kmax than accelerated CXL; however, accelerated CXL had less effect on central corneal thickness and endothelial cell loss.[15] Multiple studies have shown no significant difference between conventional and accelerated CXL regarding the uncorrected, best-corrected visual acuity (BCVA), and refractive outcome following treatment.[16]

Another proposed CXL protocol is pulsed CXL. Proponents state this may increase oxygen delivery to the cornea during treatment. Specially, during the aerobic phase that occurs during the first 10–15 s of continuous UVA illumination of a riboflavin-soaked cornea. Pulsating UVA radiation can lead to higher oxygen concentrations and therefore promoting an increase in the Type II photochemical mechanism.[17] When compared to the conventional protocol, pulsed light treatment seems to be able to possibly penetrate deeper in the corneal stroma, with a similar efficacy and safety profile.[18]

Epithelium-on versus epithelium-off crosslinking

The Dresden protocol removes the epithelium to increase the amount of riboflavin absorption into the cornea. The epithelium can be removed mechanically with a blunt hockey knife, blunt spatula, rotating brush, by simply wiping off the epithelium with or without the use of alcohol or by transpithelial phototherapeutic keratectomy.[9] De-epithelizing the cornea can lead to complications including corneal haze and pain. Transepithelial CXL or Epi-on is a newer option to promote faster healing, less patient discomfort, faster visual rehabilitation, and less risk of corneal haze.[19] Nonetheless, the epithelium essentially works as a barrier and thus decreases riboflavin penetration and oxygen availability.

Stulting *et al*. conducted a large prospective study in which 512 eyes of 308 patients with KC and 80 eyes of 55 patients with postlaser *in situ* keratomileusis (LASIK) ectasia were treated with trans-epithelium CXL using a proprietary transepithelial riboflavin formulation. Two hundred and twenty-nine were bilateral treatments. VA improved by 1–1.5 Snellen lines at 1 and 2 years postoperatively ($P < 0.0001$) and mean Kmax decreased by 0.48 D at 2 years postoperatively ($P = 0.0002$). They demonstrated no progression of ectasia and persistence of this effect at 1 and 2 years postoperatively, no vision threatening events and VA returning to baseline within 2 days with pain typically resolving within 24 h. These results demonstrated epithelium-on CXL could be used to halt KC and post-LASIK ectasia in a safer and faster manner.[20]

Nonetheless, there have been multiple studies comparing these two techniques. A Cochrane systemic review determined that no conclusion can be obtained between these methodologies given the lack of precision, frequent indeterminate or high risk of bias, and inconsistency in methods and outcomes among studies.[19] Further randomized, prospective studies are warranted to determine the superiority in efficacy or safety between epithelium on versus epithelium off CXL.

New emerging corneal crosslinking methods

Based on the same photochemical process, a variety of dyes have been studied. Recently, the spotlight has been on Rose Bengal (RB) dye excited with green light. It has been shown to increase corneal stiffness while having less cytotoxic effect in the deeper layers of the cornea.[21-23] This could be a promising treatment for thin corneas that are not candidates for CXL. Similarly, photosynthetic pigments (chlorophylls and bacteriochlorophylls) introduced into rabbit corneas were excited with near-infrared illumination with resulting increase in corneal stiffness.[24]

Applications

Keratoconus

KC is a spontaneous corneal ectasia that usually affects the younger population, and it is estimated to have an incidence of 1 in 2000. Vision is usually impaired because of the irregular astigmatism of the cornea. This is usually corrected with rigid gas permeable lenses or scleral contact lenses during the initial stages.[25] Penetrating keratoplasty is considered the gold standard when refractive correction is no longer possible due to severe irregular astigmatism, corneal scarring, or previous rupture of the Descemet membrane. Depending on the case, some patients can be candidates for lamellar keratoplasties including deep anterior lamellar keratoplasty, anterior lamellar keratoplasty, or intrastromal corneal ring segment.[26]

CXL halts KC progression by strengthening and stabilizing the collagen lamellae, resulting in corneal mechanical stiffening. This can reduce the irregular astigmatism caused by corneal chemical instability and therefore improve refractive errors while also avoiding further corneal steepening.[27] Keratometry readings demonstrate a flattening in Kmax as well as improvement in ocular aberrations after crosslinking.[28]

A randomized, controlled clinical trial of CXL versus control in KC, randomized 66 eyes of 49 progressive KCN patients into CXL treatment and control groups. At the 1-year follow-up, Kmax had been significantly reduced, with an average decrease of 1.45 diopters and improvement in BCVA was also observed. On the other hand, the control group showed a continuous deterioration in Kmax and BCVA.[29]

Although further studies must be performed, CXL is generally considered in cases of progressive KC. Progression is determined by was defined as one or more of the following changes over a period of 24 months: An increase of 1.0 D or greater in the steepest keratometry measurement, an increase of 1.0 D or greater in manifest cylinder, or an increase of 0.5 D or greater in manifest refraction spherical equivalent.[29]

Corneal ectasia

Corneal ectasias are a known complication of refractive surgery. This can occur following both LASIK, photorefractive keratectomy, and small incision lenticule extraction. Attempting to prevent this, both prophylactic CXL[30] as well as simultaneous treatment[31] has been proposed. Even though corneal stiffness improves cases of corneal ectasia, there appears to be less response to CXL in patients with postrefractive surgery ectasia compared to KC.[28] Pellucid marginal degeneration (PMD) is another indication of CXL. Interestingly, PMD is thought to affect the peripheral cornea and CXL usually has its effect on the central cornea.[32]

Corneal crosslinking in the pediatric population

The effectiveness of the CXL in the pediatric population is still a matter of debate. While some studies have shown an improvement of keratometric values with a reduction in the progression of the disease within the age group of 9–18 years, others illustrate adverse outcomes such as worsening of corneal thickness and topography values.[33-35] One of the largest studies was the Siena Pediatrics CXL study. It was a prospective, nonrandomized study conducted on 152 KC patients between 10 and 18 years of age. This study reported significant and rapid functional improvement in pediatric patients younger than 18 years with progressive KC and KC stability at the 36-month follow-up.[36]

Pain is another factor that must be considered in the pediatric population. In a large, prospective epithelium-on CXL study, 26 eyes of patients 18 years of age or younger were evaluated at 12 months after epithelium-on CXL for KC. There was a significant improvement in best corrected VA, high-order aberrations, Kmax and evidence of no disease progression.[20] Hence, epithelium-on CXL could be a more appropriate treatment for the pediatric population in an attempt to decrease pain related to epithelium-off CXL.

Considering most of pediatric cases will progress, with some cases even having "accelerated" progression as well as the risk of needing a penetrating keratoplasty in this population, some ophthalmologists argue that

CXL should be performed immediately after diagnosis is made.[34] While others believe not all children need CXL and documentation of progression should exist before deciding to perform CXL.[37] Given stabilization and possible improvement of visual and corneal parameters in a generally well-tolerated procedure.[38] CXL is becoming common practice in this population.

Infectious keratitis

CXL has also been used to treat severe, multidrug-resistant corneal ulcers.[39,40] The antimicrobial effects of riboflavin and UVA light[10] in conjunction to the increase resistance to enzymatic degradation, which prevents corneal melting, makes CXL a very attractive option for resistant infectious keratitis.[41]

Unfortunately, results have been controversial. CXL has been shown to be an efficient treatment stabilizing advanced melting corneal ulcers and to be useful in early infectious keratitis of bacterial origin. A meta-analysis demonstrated an 88% healing rate in bacterial keratitis with CXL but did not show to be effective in cases of viral keratitis and the procedure has exacerbated corneal melting in some cases.[39] In addition, it has been reported to have poor response to fungal and acanthamoebic infections. This is probably because of how deep these infections get into the corneal stroma.[42,43] A study comparing CXL for infectious keratitis versus standard antibiotic treatment in Egypt, Iran, and Thailand between 2010 and 2014, demonstrated there is not enough evidence that CXL with standard antibiotics is more effective than standard antibiotics alone for complete healing.[44]

Interestingly, Rose Bengal coupled with green light appears to have a more promising antimicrobial effect. An *in vitro* experiment comparing the effect of RB and riboflavin as photosensitizing agents for photodynamic therapy on *Fusarium solani*, *Aspergillus fumigatus*, and *Candida albicans* demonstrated Rose Bengal Photodynamic Therapy (RB-PDAT) successfully inhibited the growth of all three fungal isolates in the irradiated area, whereas riboflavin-mediated photodynamic therapy (PDT) did not have any inhibitory effect on the isolates.[45] Initial clinical experiments with RB-PDAT as a last resource for infectious keratitis with different etiologies (bacterial, fungal, and parasitic) demonstrated the therapy was able to avoid a therapeutic keratoplasty in 72% of the cases and could therefore be considered as an adjunct therapy for cases of severe, progressive infectious keratitis.[46] These results appear to persist in a longer-term follow-up and the crosslinking effect appears to increase graft survival at 1 year postoperatively.[47]

Other (bullous keratopathy and corneal burns)

CXL has been proposed as a possible treatment for bullous keratopathy. The links created between the corneal collagen stroma during CXL would make water filling more difficult and therefore decrease the amount of corneal edema. Studies demonstrated bullous keratopathy markedly improved after CXL, unfortunately, these effects disappeared about 3 months after the initial CXL treatment.[48]

Contraindications

Thin corneas

Since the beginning of the procedure until 1–3 months after treatment, CXL causes corneal thinning.[49] The corneal thickness starts improving after 3 months and recovers until getting to baseline by 12 months. Nonetheless, in thin corneas, this immediate decrease in corneal thickness can lead to endothelial damage.[50] As such, according to the Dresden protocol, a minimum of 400 μm corneal thickness is required to be suitable for CXL.

Prior herpetic infection

Herpetic keratitis may be triggered by CXL, even in cases with no history of the disease. Even though prophylactic systemic antiviral treatment in patients with a history of the herpetic might decrease the possibility of recurrence, CXL should be avoided in these patients.[51]

Other

Severe corneal scarring, neurotrophic keratopathy, past history of poor epithelial wound healing, severe dry eye, autoimmune disorders, and pregnancy are currently considered contraindication for CXL.[52]

Complications

Corneal infection

De-epithelization during epi-off techniques as well as bandage contact lens placement predisposes patients to corneal infections. Even though infection following transepithelial treatment is usually rare, infectious keratitis following CXL has been reported in all approaches.[53] Bacterial, acanthamoebic, herpetic, and fungal infections have all been reported.[5,53] As bacterial infections are the most common, routine antibiotic drops are given for prophylaxis following treatment.

Endothelial toxicity

CXL causes corneal keratocytes apoptosis and cell shrinkage of the anterior corneal stroma reaching a corneal tissue depth of 250–300 μm. These keratocytes repopulate within 3 months and CXL is therefore considered safe as the depth of apoptosis would not affect the corneal endothelium.[54] Nonetheless, direct UVA irradiation can harm the corneal endothelium and if the cornea is initially thinner or if it thins excessively

during the procedure, there is a potential risk of endothelial toxicity following CXL.

Stromal haze and scarring

The most common reported adverse event following CXL is stromal haze. This adverse effect can be clinically significant and can affect VA. It has been found to peak at 3 months and usually improves and resolves by 12 months.[55]

Demarcation line

Corneal stromal demarcation line is usually detectable in the slit-lamp examination as early as 2 weeks after CXL. It is thought that this line indicates the transition zone between cross-linked anterior corneal stroma and untreated posterior corneal stroma and is thus found at an approximately 300 μm depth. This line probably reflects the change in the refractive index and/or reflection properties of treated versus untreated corneal lamellae.[56]

Progression or excess flattening

Both progression as well as excess flattening has been described following CXL. Steeper Kmax preoperatively can be a risk factor for progression following CXL.[57]

Dry eye

Corneal subepithelial nerve fibers are affected following CXL treatment. A study demonstrated early regeneration of these fibers after 1 month following treatment and complete regeneration and sensitivity by 6 months.[58] However, another study described progression in the abnormal nerve migration even after 5 years of treatment.[59] This can lead to neuropathic cornea and worsening dry eye symptoms.

Conclusions

CXL represents a paradigm shift in the management of corneal ectatic disorders. Before CXL was introduced, patients would need specialty contact lenses and possible corneal transplantation. CXL is the first and only treatment that can stabilize the cornea and prevent further thinning. It is a minimally invasive, cost-effective procedure that can be performed in an outpatient setting with a fast recovery time and long-lasting results. We recommend adopting pediatric population screening to help identify the disease at an early stage and offer treatment to stop progression and the need for specialty lenses. Overall, CXL has revolutionized the management of KC by offering a safe and effective treatment option that can halt the progression of the disease and improve the quality of life for patients.

Data availability statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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