

SPECTACLES, CONTACT LENSES, AND CORNEAL AND LENTICULAR REFRACTIVE SURGERY FOR PRACTICE GROWTH

Putting the Brakes on Corneal Ectatic Disorders

Peter S. Hersh, MD

Collagen crosslinking can effectively slow or halt the progression of corneal ectasia. In routine clinical use abroad, collagen crosslinking is being refined to make the procedure both more effective and more efficient.

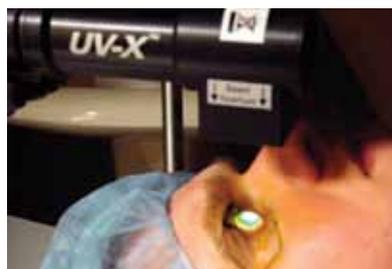


FIGURE 1 Keratoconic eye undergoing the crosslinking procedure. (Photo courtesy of Peter S. Hersh, MD)

A key feature of all corneal ectatic disorders—including keratoconus, pellucid marginal degeneration, and iatrogenic post-LASIK ectasia—is a weak, biomechanically unstable cornea that undergoes progressive stromal thinning. Over time, this structural change produces distortions of the corneal shape, which cause irregular astigmatism and significant loss of visual acuity.

We do not yet know which component of the corneal stroma is primarily affected in corneal ectasia, whether

it is the collagen, matrix sugars, or keratocytes, or interactions amongst these. But patients with keratoconus and pellucid marginal degeneration are believed to be genetically predisposed to biomechanical weakening

turn to **Corneal Ectasia** on page 26

INSIDE

- Contact Lens Wetting
- Refraction Without a Phoropter
- Prophylaxis for Resistant Bacteria
- Patient Selection for LASIK/PRK

DEPARTMENTS

DRY EYE
TECHNOLOGY &
PRACTICE



CORNEAL ECTASIA *continued from page 1*

of the cornea, possibly through mechanisms of localized inflammation, increased levels of lytic enzymes, and/or secondary oxidative stress. Eye rubbing, which stresses the corneal collagen lamellae, may also contribute to destabilizing the cornea.

Conceivably, post-LASIK ectasia could develop simply from excessive physical thinning of the stromal bed due to extreme tissue removal or an inordinately thick flap. More likely, though, patients who develop ectasia come to surgery with a natural predisposition to keratoconus; and the surgical insult pushes them to frank disease.

New Treatment Strategy

Surgeons now have a range of options for managing corneal ectatic disorders: contact lens fitting, intracorneal ring segments like Intacs®, thermokeratoplasty, and, should these be inadequate, partial or full thickness keratoplasty.

Most of these treatments aim for improvement in the corneal topography, astigmatism mitigation, and vision improvement. Procedures such as Intacs® and thermokeratoplasty do so by modifying the corneal shape and reducing optical irregularity to improve contact lens tolerance and spectacle-corrected visual acuity.

Recently, collagen crosslinking has emerged as an alternative approach to manage corneal ectasia.¹

This procedure allows surgeons to restore biomechanical stability to the cornea and prevent further progression of ectasia.

Crosslinking Procedure

In collagen crosslinking, surgeons expose the cornea to riboflavin (vitamin B2) and then ultraviolet A (UVA) irradiation at 365 nm (Figure 1). Riboflavin readily absorbs UVA; their interaction is believed to produce reactive oxygen species that cause covalent bonds to form within and between collagen molecules (crosslinks). These extra covalent bonds make the cornea stiffer and stronger, diminishing the

propensity for ectatic progression (Figure 2). When discussing the crosslinking procedure with patients, I often liken it to adding extra wires on a suspension bridge.

To date, most collagen crosslinking procedures that are performed utilize the traditional technique originally developed in Germany, in which the central corneal epithelium is removed before riboflavin is applied.¹ Intact epithelium is a biologic barrier that effectively blocks riboflavin penetration; epithelial removal allows the cornea to imbibe riboflavin, which is critical to the success and reproducibility of the procedure.



FIGURE 2 Corneal photographs before, during, and after collagen crosslinking. (a) Slit lamp photograph of a keratoconic cornea. Note the fine, white stripes in the corneal stroma. This is a cornea one month after crosslinking, showing fine stromal haze. (b) Cornea imbibed with riboflavin under UVA irradiation during crosslinking. (c) Slit lamp corneal photograph after initial riboflavin administration. Note riboflavin absorption through corneal stroma. (All images courtesy of Peter S. Hersh, MD)

Patients

Ectatic patients whose corneal condition is actively progressing may potentially gain the greatest benefit from crosslinking. We see disproportionately more young patients in our studies because keratoconus typically progresses early on and tends to stabilize with age.²

Because of the potential dangers of exposing corneal endothelium to UVA, patients with extremely thin corneas are ineligible for crosslinking. All patients in our study had a corneal thickness greater than 400 microns, and we found no signs of corneal endothelial damage.

Efficacy

In multiple clinical studies of collagen crosslinking, my colleagues and I have reported favorable outcomes in the great majority of patients, corroborating what has been reported from overseas.

In a study with 1-year follow-up, keratoconus was stabilized in over 95% of patients.³ In addition to stabilization, we found flattening of the keratoconic cone by an average of 1.7 D at 1 year and by 2.0 D at 2 years. Corneal topography showed significant improvement in a number of topographic indices at year 1, suggesting a general improvement in the corneal shape (Figure 3).⁴ We also found improvement in both total and corneal higher order aberrations, particularly coma.⁵ Visual acuity, both corrected and uncorrected, was significantly improved. The mean uncorrected visual acuity (UCVA) improved from 20/137 to 20/117.³ The mean best-corrected visual

COLLAGEN CROSSLINKING IN ECTASIA MANAGEMENT	
✓	Slows or stops the progression
✓	Can be combined with other approaches
✓	In routine clinical use abroad
✓	In clinical trials in the United States
✓	Crosslinking indications
	— Keratoconus
	— Pellucid marginal degeneration
	— Post-LASIK ectasia
✓	Patients
	— Early ectasia with active progression
	— Corneal thickness > 400 microns
✓	Clinical biologic effects
	— Transient corneal haze
	— Transient corneal thinning
✓	The crosslinking pipeline
	— Rapid crosslinking procedure
	— Transepithelial technique
	— Repeated crosslinking
	— Better outcome prediction

acuity (BCVA) improved from 20/45 to 20/34 at the end of the year, with over 20% of patients gaining two or more lines of BCVA.³

Progression was seen in 3.5% of patients, with each of the three patients who progressed losing two lines of BCVA. Slit lamp and topographic examination failed to reveal a clinical cause for this vision loss. The apparent loss of BCVA may reflect the difficulty of obtaining accurate acuity measurements in multifocal keratoconic corneas.

We have follow-up data on crosslinking performed overseas more than 5 years ago, and the beneficial effects appear to be holding up well. The cornea naturally stiffens as we grow older, and this age effect may be additive to the effect of the crosslinking procedure.

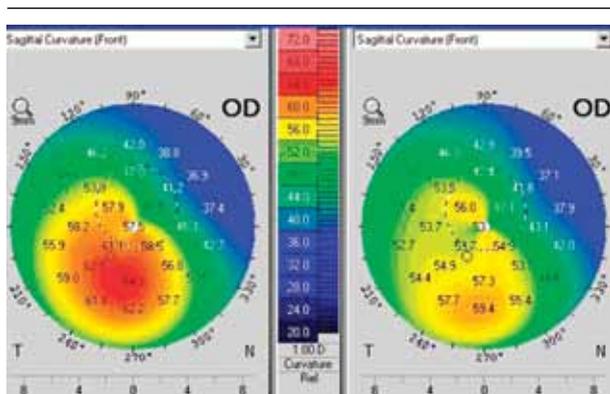


FIGURE 3 Topographic appearances of a keratoconic cornea before and after collagen crosslinking. Left: Sagittal curvature map before crosslinking. Right: Sagittal curvature map 1 year after the procedure, showing significant improvement in the keratoconus index. (All images courtesy of Peter S. Hersh, MD)

Clinical Biologic Effects

Overall, collagen crosslinking has proven to be a safe procedure. Epithelial removal creates a potential for slow healing and corneal infections, but we have not seen these (or any other dramatic adverse event) in our patients.

Our studies, however, did show that the crosslinking procedure can induce some short-term biological side effects, including corneal haze or slight corneal thinning. The corneal haze and thickness reduction are both transient phenomena that resolve on their own. Corneal haze after a crosslinking procedure usually peaks at about 1 month, plateaus at 3 months, and then slowly disappears until it is gone entirely by the end of the first year.⁶ Corneal thickness usually returns to baseline in the first few months.⁷

We have found that neither corneal haze nor the transient reduction in corneal thickness correlates with the clinical outcomes. These clinical biologic effects seem to be structural or cellular events set off by the crosslinking procedure. Keratocyte apoptosis, which can occur early on, followed by keratocyte repopulation, provides one possible explanation. There is no need to intervene, though surgeons need to be aware that these events are somewhat expected.

THE PHARMACEUTICAL REGIMEN

- **Preoperative**
 - Treat any ocular surface disease with artificial tears, cyclosporine drops, punctal plugs, and topical antibiotics as indicated
- **Perioperative**
 - Topical anesthetic, drop topical antibiotic
 - One drop 0.1% riboflavin solution every 2 minutes for 30 minutes before UVA exposure and every 2 minutes during UVA exposure
- **Postoperative**
 - Topical antibiotic and corticosteroid 4 times daily for 2 weeks
 - Remove bandage contact lens after 3 to 5 days
 - Nonpreserved artificial tears and topical non-steroidal antiinflammatory drops as need for discomfort

Combination Therapy

Since collagen crosslinking is the only modality that can halt ectatic progression, combining it with treatments that correct vision is a natural next step in ectasia management. One such promising strategy is to combine crosslinking with an implantable device like an Intacs ring segment to improve corneal shape. With this combined approach, we can both prevent progression and improve corneal optics. The more normal corneal shape created by the Intacs should make patients more contact-lens tolerant and improve their BCVAs.

My group is now in the midst of a clinical study of crosslinking combined with Intacs. Our goal is to find the optimal timing for the two treatments: is it best to do them together? Or should one implant the Intacs first and crosslink sometime later? Results of this trial will be available shortly.

The Future

Compared to most ophthalmic procedures, collagen crosslinking takes a long time, with 30 minutes of riboflavin uptake and 30 minutes of UV exposure in current protocols. There are ongoing efforts to develop more rapid crosslinking processes, which I think will be of benefit to both patients and surgeons.

The current “epithelium off” technique of crosslinking creates a challenge during the recovery period. The healing process can be slow, with the return of best vision taking as long as several weeks. The visual disability in this period, as well as time out of contact lenses, can create hardships for patients. To speed up recovery, a transepithelial approach to riboflavin delivery has been suggested and is now under development. In this method, the epithelium is left intact but manipulated with pharma-

cologic agents to break down the tight intercellular junctions and allow the riboflavin to penetrate to the stroma.

It is often asked whether the crosslinking procedure can be repeated for those few patients whose initial procedure failed to stop progression. There have been a few reports from overseas of patients successfully crosslinked in a second procedure, but until sufficient data is gained, this question will remain open.

A better approach may be to cull patients who are less likely to respond to crosslinking. In an effort to identify clinical markers for such patients, my colleagues and I recently performed a multifactorial analysis of our clinical trial data. By analyzing parameters including patient characteristics, corneal topography, steepness of the cone, cone location, and BCVA, we hope to find factors that predict clinical outcomes in crosslinking.

THE BOTTOM LINE

Utilizing a combination of riboflavin and UVA radiation, collagen crosslinking stiffens and stabilizes the cornea, diminishing the progression of ectasia. Encouraging results from ongoing clinical trials in the United States and overseas studies have found crosslinking to be an effective treatment for ectatic corneal disorders including keratoconus, pellucid marginal degeneration, and post-LASIK ectasia. The only treatment that can effectively prevent their progression, crosslinking fills the gaps in the management of ectatic disorders and further reduces the need for corneal transplants.

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