

Corneal Collagen Cross-linking

Current results are promising, and the procedure has the potential for expanded indications.

BY WILLIAM B. TRATTLER, MD, AND ROY S. RUBINFELD, MD

Corneal collagen cross-linking with riboflavin is currently performed internationally for the treatment of a variety of conditions, including keratoconus and pellucid marginal degeneration. Researchers are also studying the procedure's potential to treat conditions ranging from infectious corneal ulcers that will not heal to painful pseudophakic bullous keratopathy. With cross-linking expected to be approved and used frequently in the United States, now is a prime time for clinicians to learn more about its history, results to date, and potential future applications. This article also shares some tips for success.

BACKGROUND

Eberhard Spoerl, PhD, and Theo Seiler, MD, developed the cross-linking procedure in the late 1990s.^{1,2} The surgeon instills riboflavin (a B vitamin) drops on the cornea after removing the epithelium. Once saturated with riboflavin, the cornea undergoes irradiation with ultraviolet (UV) A light for about 30 minutes (Figure 1). This treatment stiffens abnormally weak

corneas, primarily in the anterior 200 to 300 μm , by creating strong bonds (or cross-links) between corneal collagen fibers.³ These bonds function much like the rungs that make a ladder structurally stronger and more rigid. Clinical research has shown that cross-linking not only stops the progression of keratoconus, but it also induces flattening of the cornea and visual improvement.³

TIPS

Preoperative Evaluation

During the preoperative assessment, it is important to determine whether a patient with keratoconus is an appropriate candidate for cross-linking. At the slit lamp, the cornea should be clear or at least not severely scarred. The clinician performs pachymetry to ensure that the cornea is sufficiently thick for treatment. After the epithelium's removal, the corneal thickness should be at least 400 μm . The instillation of hypotonic riboflavin drops can temporarily swell thinner corneas to make cross-linking safe. Studies have shown that the first 300 μm of



Figure 1. A patient undergoes corneal collagen cross-linking with riboflavin.

“During the preoperative assessment, it is important to determine whether a patient with keratoconus is an appropriate candidate for cross-linking.”

corneal tissue fully absorb the wavelength of UVA light used in cross-linking (approximately 370 nm), so the minimal amount of UV light that penetrates deeper is well within safe levels.³

Corneal topography and Scheimpflug photography or other advanced imaging allow ophthalmologists to determine the steepness of the cornea. Measurements greater than 60.00 D indicate that the cornea may not flatten enough to make cross-linking worthwhile. Other considerations include a history of corneal herpes simplex virus, which UV exposure may reactivate. Any pre-existing dry eye disease requires preoperative treatment, because the condition can delay epithelial healing.

In general, after a complete examination, patients with keratoconus can be advised on whether or not cross-linking has the potential to improve their corneal condition.

Surgery

Cross-linking is a straightforward procedure. After the instillation of topical anesthetic drops and the placement of a lid speculum, the surgeon manually removes the epithelium with a hockey-stick spatula. Some ophthalmologists use dilute alcohol to facilitate epithelial removal. The surgeon then removes the lid speculum, and an assistant instills liquid riboflavin in the eye (one drop every 2 minutes for 30 minutes). After this step is complete, the ophthalmologist performs a slit-lamp examination, which should reveal flare in the anterior chamber of the eye. This finding suggests that the riboflavin has saturated the cornea and the eye is ready for UV light treatment.

After placement of the lid speculum, the patient is positioned under the UV lamp, and the UV beam is centered on the cornea. During the next 30 minutes, an assistant places a drop of riboflavin solution on the eye every 2 minutes while the UV light remains centered on the cornea.

Upon the treatment's completion, the surgeon places a bandage contact lens and prescribes topical antibiotic and anti-inflammatory drops. At this stage, there are a lot of similarities to excimer laser surface ablation procedures such as PRK. The surgeon therefore selects a topical antibiotic that can reduce the risk of infection and

topical anti-inflammatory medications to decrease pain while avoiding delays in epithelial healing.

Postoperative Course

The patient should return 4 to 6 days after the procedure for removal of the bandage contact lens. He or she is instructed to continue the topical antibiotic drop for 7 to 10 days or until no epithelial defect remains. The patient continues using topical steroids for 2 to 4 weeks postoperatively.

CLINICAL RESULTS

In numerous European studies of the safety and efficacy of cross-linking for progressive keratoconus, the corneal shape has typically stabilized and is no longer becoming steeper by 3 months postoperatively. By 6 months, the cornea has become flatter (by as much as 6.00 D or more), and subjects' BCVA has improved in many cases.³ These improvements in corneal shape and changes in vision appear to continue for more than 6 years.³ After cross-linking, corneal thickness decreases as the tissue becomes stronger and more compact. This thinning becomes evident at 1 month and persists long term.³

In the United States, R. Doyle Stulting, MD, PhD, initiated a multicenter study in 2007. The preliminary results showed a stabilization of the corneal shape at 3 months and flattening by 6 months after treatment. In contrast, control eyes (which did not undergo cross-linking) continued to experience progressive keratoconus during this time period.⁴

Because cross-linking strengthens the cornea, patients may become eligible for laser vision correction. Preliminary results with PRK for these individuals have been favorable, with a significant improvement in UCVA and BCVA.⁴

FUTURE INDICATIONS

In addition to therapy for keratoconus and post-LASIK ectasia, corneal collagen cross-linking with riboflavin may play a role in the treatment of corneal infections. A recent in vitro study revealed that both riboflavin alone and UV exposure alone were inadequate at killing *Staphylococcus aureus*, methicillin-resistant *S aureus*, and *Pseudomonas aeruginosa*. The combined application of riboflavin and UV exposure, however, eliminated these organisms.⁵ In the future, cross-linking may serve as an adjunctive treatment for challenging corneal infections.

Research has also focused on the treatment of pseudophakic corneal edema in patients who may not be good candidates for corneal transplantation. Early studies have shown that cross-linking can induce a reduction in cor-

neal thickness. Investigators studied 10 patients with an average preoperative corneal thickness of 840 μm . On average, 9 months after treatment, the corneal tissue had thinned by 125 μm , and eyes had gained one line of BCVA.⁴ Cross-linking may prove more effective than corneal micropuncture at relieving the discomfort of patients with corneal edema.⁶

At present, cross-linking is an exciting procedure performed internationally that has the potential to help patients with a variety of clinical conditions. Surgeons are working hard to make this therapy available to patients in the United States. ■

Roy S. Rubinfeld, MD, is a clinical associate professor at Georgetown University Medical Center and on staff at The Washington Hospital Center in Washington, DC. He is in private practice with Washington Eye Physicians & Surgeons in Chevy Chase, Maryland. Dr. Rubinfeld may be reached at (301) 654-5290; rubinkr1@aol.com.



William B. Trattler, MD, is the director of cornea at the Center for Excellence in Eye Care in Miami. Dr. Trattler may be reached at (305) 598-2020; wtrattler@earthlink.net.



1. Sp̄r̄l E, Huhle M, Kasper M, Seiler T. Increased rigidity of the cornea caused by intrastromal cross-linking [in German]. *Ophthalmologe*. 1997;94(12):902-906.
2. Spoerl E, Huhle M, Seiler T. Induction of cross-links in corneal tissue. *Exp Eye Res*. 1998;66:97-103.
3. Kohlhaas M, Spoerl E, Schilde T, et al. Biomechanical evidence of the distribution of cross-links in corneas treated with riboflavin and ultraviolet A light. *J Cataract Refract Surg*. 2006;32:279-283.
4. Stulting RD. Update on riboflavin-UV crosslinking. Paper presented at: The ASCRS Symposium on Cataract, IOL and Refractive Surgery; April 6, 2009; San Francisco, CA.
5. Greebel GJ, Schrier A, Attia H, et al. In vitro antimicrobial efficacy of riboflavin and ultraviolet light on *Staph aureus*, methicillin resistant *Staph aureus* (MRSA) and *Pseudomonas aeruginosa*. *Invest Ophthalmol Vis Sci*. 2009;50:e-abstract 5117.
6. Rubinfeld RS, Laibson PR, Cohen EJ, et al. Anterior stromal puncture for recurrent erosion: further experience and new instrumentation. *Ophthalmic Surg*. 1990;21(5):318-326.