Collagen Crosslinking—An Evolving Procedure

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Abstract

Vitamin therapy combined with minimally invasive corneal surgery appears to be safe and effective in treating ectasias of varied etiology. Keratoconus, laser-assisted in situ keratomileusis (LASIK), radial keratotomy (RK), and marginal dystrophies have presented significant challenges in ophthalmic surgery. Ectasia resulting from progressive keratoconus, marginal degeneration, or any of several corneal surgical procedures has been successfully treated with riboflavin-activated ultraviolet light. These minimal surgical modalities are a major advance, and are discussed in this article.

Keywords

Cornea, ectasia, keratoconus, collagen crosslinking, riboflavin, UV

Femtosecond Laser for Corneal Eye Surgery

While there is no doubt that the microkeratome is a great tool for surgeons performing laser eye surgery, the femtosecond laser appears to be more accurate. But complications (transient light sensitivity, irregular flap with induced astigmatism, and ectasias) still occur. Dry eye syndrome is also a problem. The search for effective treatment continues (see Figures 2 and 3).

Method

The cornea is saturated with RF, then illuminated with UVA at a frequency of 365 nm, a wavelength that is strongly absorbed by the RF. The RF has a dual action of producing free radicals that cause crosslinking of the stromal collagen, creating new, stable bridges between collagen molecules, reinforcing the corneal structure, strengthening the cornea,
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Figure 1: Potential Applications of Collagen Crosslinking

Keratoconus and forme fruste post-laser-assisted in situ keratomileusis ectasia
Pellucid marginal degeneration
Marginal keratitis and ectasia

Figure 2: Femtosecond Laser-assisted in situ Keratomileusis

Figure 3: Corneal Changes with Laser-assisted in situ Keratomileusis

Figure 4: Stroma Before Crosslinking

Figure 5: Stroma After Crosslinking

Figure 6: Riboflavin/Ultraviolet Crosslinking

Figure 7: Riboflavin/Ultraviolet Crosslinking

Figure 8: Riboflavin/Ultraviolet Crosslinking

Figure 9: Riboflavin/Ultraviolet Crosslinking

Figure 10: Riboflavin/Ultraviolet Crosslinking

and acting as a shield to prevent significant levels of UV from penetrating deeper into the eye (see Figure 7).

Cases of irregular astigmatism caused by ectasia have been treated by initial crosslinking followed by custom topography-guided surface ablation, with restoration of vision and stabilization of the ectasia and improvement of patients’ visual, refractive, and topography outcomes.3,4

John Marshall has demonstrated that by increasing the power the effect can be the same in less time. He states, “We can play around with the power-time complex to deliver the same amount of energy to the cornea in less time” (see Figures 8–10).5

Validation

Leading experts have stated, in examining the data over the past 10 years, “If cross linking had been available in the United States as it was in other parts of the world, 50 % of the corneal transplants could have been avoided.” (Doyle Stulting, personal communication, April 2013.) It is apparent that if CXL had been readily available in the 1980s, RK could still be the procedure of choice for myopia and astigmatism today.
No medical or surgical procedure is perfect or complication free, but complications of CXL appear to be infrequent and manageable. Severe pain and visual loss may remain until epithelial regrowth occurs.

Several pioneers of crosslinking have reported, “The almost complete absence of adverse reactions to the treatment has been confirmed by several studies. The failure rate in my series is less than 3% and the complication rate is less than 1%.” (Theo Seiler, personal communication, January 2012.)

Joseph Colin wrote, “We remove the epithelium for better efficacy. However, investigators are now producing a new riboflavin preparation with modified physiochemical properties that will be able to penetrate the cornea through the epithelium.”

Stromal haze, present during the first few weeks, usually resolves within 3 to 6 months.

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Roberto Pinelli reports, “The epithelium does not significantly restrict the riboflavin penetration. In our series, RF 0.1% was applied to the cornea via a saturated Merocel sponge for five minutes before the start of UVA light administration, and reapplied every three minutes during the whole procedure. At six and nine months post-op there was no significant difference in the analyzed parameters between the depithelialized group and the non-depithelialized one.” (Personal communication, June 2012.)

Transepithelial CXL appears to be a major advance. RF is a hydrophilic compound and cannot easily cross the intact epithelial barrier. Buffers and ethylenediaminetetraacetic acid (EDTA) ‘enhancers’ are added to RF solution to help penetrate through intact epithelium. The addition of pulsed illumination with added oxygen has increased effectiveness in some studies (see Figure 11). (Francis Price, personal communication, July 2013.)

**Conclusion**

With continued refinement and improvement of technique, RF/UVA CXL may become the treatment of choice in stabilizing thinning or unstable corneas. FDA roadblocks should be reduced by shared information of an informed medical community. As additional applications and improved methodology are developed by investigators, transepithelial methodology will improve and become standard, and CXL will take its place as a method of choice in the treatment of ectasias of all etiologies.

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