Vitamin B2 in Corneal Surgery—Riboflavin and Collagen Cross-Linking

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Abstract

Cross-linking of collagen refers to the ability of collagen fibrils to form strong chemical bonds with adjacent fibrils. Corneal collagen cross-linking (CXL) with vitamin B2 activated by ultraviolet offers a new method for stabilization of unstable or weakened corneal tissue in cases of ectasia, dystrophy and irregular post-surgical healing.

Keywords

Vitamin B2, corneal surgery, limbal thinning, Riboflavin CXL

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Because of increasing numbers of cases with corneal and limbal thinning, ways to stop or reverse the degenerative changes induced by corneal surgery (radial incisions, laser-assisted *in situ* keratomileusis (LASIK), lamellar keratoplasty) and degenerative diseases such as keratoconus have become imperative. These include several surgical and non-surgical modalities (vitamin therapy, ultraviolet (UV) light therapy and cross-linking).

Originally developed as a new method to strengthen the weakened corneas of keratoconus, riboflavin CXL has been shown to strengthen the corneas in post-LASIK ectasias and in marginal corneal dystrophies.[1,2] Progressive irregular thinning (ectasia) is problematic and possible with any LASIK procedure.

Cross-linking of collagen refers to the ability of collagen fibrils to form strong chemical bonds with adjacent fibrils. Some naturally occurs in the cornea with aging (as in other parts of the body), but for immediate therapeutic effect, chemical agents (UV-activated riboflavin) are used.

In a number of studies, CXL has been shown to effectively stop the advancement of ectasia in eyes following excimer laser ablation. In an early German study with corneal cross-linking, the biomechanical status of the cornea was stabilized with a halting of the refractive and topographic progression of ectasia.[1]

In practice, the cornea is saturated with riboflavin, then illuminated with UVA at a frequency of 365 nm, a wavelength which is strongly absorbed by the riboflavin. The riboflavin has a dual action of producing free radicals which cause cross-linking of the stromal collagen, creating stable bridges between collagen molecules, re-inforcing the corneal structure, strengthening the cornea, as well as acting as a shield to prevent significant levels of UV from penetrating deeper into the eye (see *Figure 1*).

The photosensitizer riboflavin and UV irradiance lead to corneal tissue strengthening by increasing collagen covalent bonds, as in photopolymerization in polymers, leading to a significant increase in collagen fiber diameter and reduced elasticity.

Immunofluorescent confocal microscopy has shown a pronounced compacting of collagen fibers in the anterior stroma after riboflavin and UVA exposure (see *Figure 2*).

Cases of irregular astigmatism caused by ectasia have been treated by initial cross-linking followed by custom topography-guided surface ablation, with restoration of vision and stabilization of the ectasia, with improvement of patients' visual refractive and topographic outcomes. This method may eliminate the need for corneal transplantation.[3,4,6]

Doyle Stulting, MD, states: "If cross-linking had been available in the US as it was in other parts of the world, 50 % of the corneal transplants could have been avoided."[6,7]

Joseph Colin, MD, has stated: "In theory, the UVA light could be damaging to the inner endothelial cell layer of the cornea, and this is why the corneal thickness of the stroma needs to be at least 350 µm if a standard CXL treatment is to be undertaken. Although UVA is potentially damaging to the lens and retina, it is believed that riboflavin soaking the stromal layer blocks the UVA transmission to an extent that no measurable damage will occur."[6,8]

Figure 1: Technique of B2 and Ultraviolet Activation

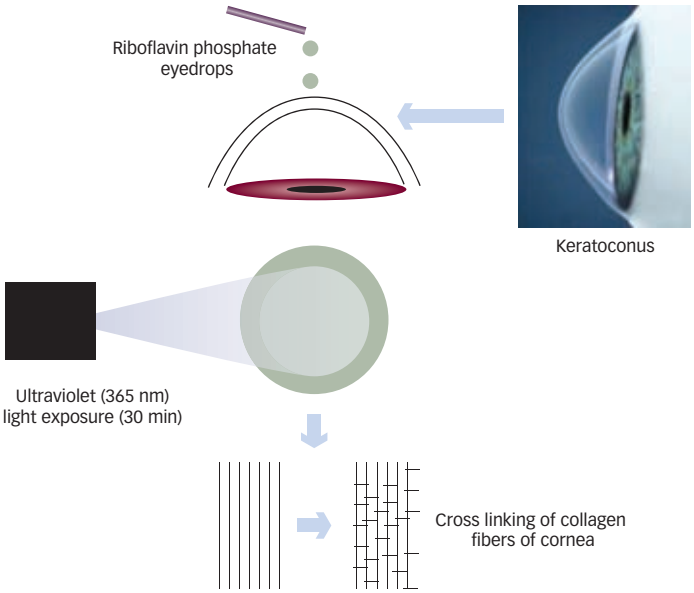
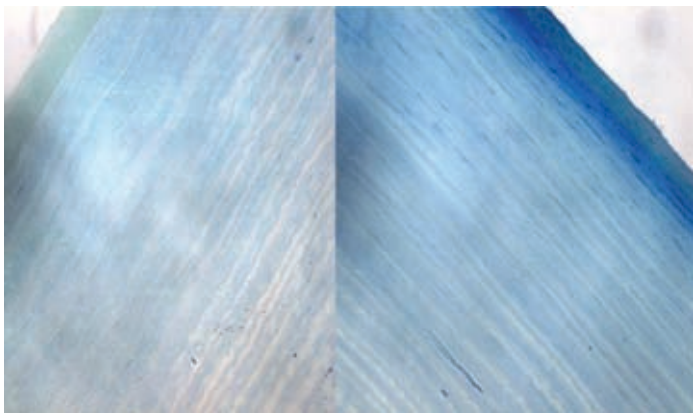


Figure 2: Riboflavin/Ultraviolet Cross-linking



Consistent improvement in coma and anterior corneal HOAs seem to indicate validity of the CXL procedure in ectatic cases.[9] Potential uses may include stabilization of corneal biomechanics early on, before further clinical progression of ectasia is noted.

Because of FDA restraints, further uses in the US are considered 'off-label'. The bureaucratic FDA will not recognize 'non-US' investigative results.

Possible complications with cross-linking may include diffuse lamellar keratitis, non-healing epithelium, infiltrates, stromal haze and endothelial disturbances.[6] Immediate post-operative hyperemia, foreign-body sensation, and photophobia usually resolve spontaneously.

Stromal hazy demarcation lines have been noted at depths of 100–300 um without significant visual effects. Theo Seiler states: "The almost complete absence of adverse reactions to the treatment has been confirmed by several studies. The failure rate is less than 3 % and the complication rate is less than 1 %."[7]

Raymond Stein, MD, states: "Transepithelial CXL appears to be a major advance. Riboflavin is a hydrophilic compound and cannot easily cross the intact epithelial barrier, so buffers, ethylenediaminetetraacetic acid (EDTA), or other 'enhancers' are added to riboflavin solution to help penetrate through intact epithelium."[6,10]

Roberto Pinelli states: "The epithelium does not significantly restrict the riboflavin penetration. In our series, riboflavin 0.1 % was applied to the cornea via a saturated Merocel sponge for five minutes before the start of UVA light administration, and re-applied every three minutes during the whole procedure. At six and nine months post-operatively, there was no significant difference in the analyzed parameters between the de-epithelialized group and the non-de-epithelialized one."[6]

Investigators are now producing a new riboflavin preparation with modified physiochemical properties that enhance penetration through the epithelium. These trans-epithelial riboflavin preparations are currently available from Leiter's Compounding Pharmacy (www.leiterrx.com) and Avedro KXL System (www.avedro.com), though neither is available in the US because of FDA restrictions.

For riboflavin corneal collagen cross-linking to become popular in the US, FDA acknowledgement of validity of European and other non-US studies is imperative. The author predicts that FDA roadblocks will be reduced by pressure of an informed medical community, and riboflavin/UVA corneal collagen cross-linking will become the treatment of choice in stabilizing thinning or unstable corneas, and will become as popular as was radical keratotomy in the latter part of the 20th century.[11]

Finally, the author predicts that transepithelial methodology will improve and become standard. ■

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