Corneal Collagen Crosslinking: Potential Pitfalls When Modifying the Technique

Surgeons should not emphasize modifying the technique but rather efficiently using it.

BY FARHAD HAFEZI, MD, PHD

The most important outcome of a corneal collagen crosslinking treatment with riboflavin and ultraviolet-A (UVA) is to stabilize the formerly progressive keratectasia in the absence of complications. Because crosslinking involves several steps that are potentially harmful to ocular structures, such as generation of free radicals and irradiation with UVA light, special attention should be given to the treatment's technical parameters. The currently accepted treatment protocol includes deepithelialization for efficient penetration of riboflavin into the cornea. This method has been successfully used for treatment of progressive keratoconus and pellucid marginal degeneration since 1999 and for iatrogenic keratectasia since 2003. Published and peer-reviewed data on the safety and efficacy of these parameters for crosslinking are available from numerous research groups, with long-term results of crosslinking for up to 6 years.[1-4]

Recently, some surgeons have suggested a modified crosslinking technique in which no epithelium is removed. They claim that this epithelium-on modification is an enhancement because it is painless for the patient and avoids complications of epithelial healing. At this time, no peer-reviewed data on this suggested modification are available.

TAKE-HOME MESSAGE

- The most important outcome of a corneal crosslinking treatment with UVA and riboflavin is to stabilize progressive keratectasia in the absence of complications.
- The surgeon's main concern should be to stop the progression of ectasia, not preserve patient comfort.
- Current treatment parameters show potential for optimization, but modifications must be first evaluated experimentally.

NO EPITHELIAL REMOVAL = NO PAIN = NO EFFECT?

A crosslinking procedure without epithelial removal would certainly be less painful than one with a large-diameter epithelial removal, and the epithelium-on modification would be ideal if it efficiently stabilized keratectasia. However, patients with progressive keratectasia are suffering from a potentially visually debilitating disease, and the surgeon's main concern should be to stop the progression of the disease—not necessarily the patient's comfort.

Several findings[5-8] raise serious concerns about the epithelium-on modification. First, riboflavin is a macromolecule (molecular weight, 376.37 grams per molecule), and the corneal epithelium represents a barrier that drastically decreases the absorption rate of riboflavin into the corneal stroma.[5] Another concern is that "corneas with a fully removed epithelium treated with riboflavin showed an abnormal dip in the transmission spectrum between 400 nm and 510 nm,"[6] which is indicative of the presence of riboflavin in the corneal stroma. In their research with porcine corneas, Hayes et al showed that complete removal of the epithelium is an essential component of crosslinking.[6] In epithelium-on corneas treated with riboflavin, the corneal spectral light transmission was identical to untreated controls even after frequent instillation of tetracaine drops to facilitate penetration.

Additionally, Baiocchi et al[7] recently investigated the concentration of riboflavin in the corneal stroma using high-pressure liquid chromatography in ex vivo human corneas. In epithelium-on corneas, only a limited stromal riboflavin concentration could be measured; it was 40-fold lower than in corneas with removed epithelium. Last month at the 2008 European Society of Cataract and

Refractive Surgeons (ESCRS) meeting, Wollensak reported that low concentration of riboflavin in epithelium-on corneas might cause a minimal crosslinking effect.[8] Whether or not this minimal crosslinking is sufficient to stabilize keratectasia in the long term remains to be seen.

NO EPITHELIAL HEALING = FEWER COMPLICATIONS?

Complications correlate to mismanagement of patients with delayed epithelial healing; however, any surgeon routinely confronted with deepithelialized corneas, such as surgeons who treat patients with previous PRK, will be able to manage crosslinking patients postoperatively.

CONCLUSION

From a medical perspective, the ongoing debate on whether or not to remove the epithelium during crosslinking is unnecessary. We agree that current treatment parameters show a great potential for optimization; however, we have serious doubts whether the epithelium-on modification is an improvement of the method.

Conclusively, any future parameter modifications should first be studied in the computational model of corneal saturation and then applied in experimental approaches. Only if these approaches show a proof of principle, then the modification can be applied in humans. ■

Farhad Hafezi, MD, PhD, is an Associate Professor of Ophthalmology at the Institute for Refractive and Ophthalmic surgery (IROC), Zurich, Switzerland. Dr. Hafezi states that he has no financial interest in the products or companies mentioned. He may be reached at tel: +41 43 488 38 00; fax: +41 43 488 38 09; e-mail: farhad.hafezi@iroc.ch.

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