Controversy continues

CXL: Epithelium on versus off?

Answer will depend on data from long-term studies of eyes treated with epithelium on

By Cheryl Guttman Krader
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Chicago—The debate over the need to remove the corneal epithelium when performing corneal collagen crosslinking (CXL) will continue until long-term data from peer-reviewed studies become available to answer the question of whether a procedure done with the epithelium on results in sufficient crosslinking for long-term arrest of ectasia progression, said Farhad Hafezi, MD, PhD, during refractive surgery subspecialty day at the annual meeting of the American Academy of Ophthalmology (AAO).


Dr. Hafezi

"The efficacy of the epithelium-off method is supported by a multitude of experimental data acquired since 1995 along with results from more than a dozen clinical studies, including a recent meta-analysis, with follow-up of almost 7 years," said Dr. Hafezi, professor and chairman, Department of Ophthalmology, University Hospitals, Geneva, Switzerland. "However, there is a lack of peer-reviewed, long-term data on the epithelium-on method."

In addition, results from experimental models investigating such issues as riboflavin penetration and concentration in the corneal stroma and the effects of the CXL procedure favor epithelial removal, he said.

However, the main question to be answered is how well the epithelium-on technique meets the primary therapeutic goal of achieving sufficient crosslinking to provide a long-lasting effect in arresting ectasia progression.

Parameters show potential

"Further study is needed, and the only conclusion that can be reached for now is that the CXL treatment parameters show great potential for optimization," Dr. Hafezi said. "Certainly, the way the procedure will be performed 5 years from now will be different [from] the technique used today."

The conventional method for CXL involves epithelial removal in order to increase riboflavin penetration into the corneal stroma, which is poor when the epithelium is intact because riboflavin is a high-molecular-weight macromolecule. Riboflavin is needed in the stroma for UVA-induced generation of oxygen free radicals that induce the crosslinking reaction.

Take-Home Message

Several lines of evidence support the conventional practice of removing the epithelium when performing corneal collagen crosslinking. However, the definitive answer on whether this is an essential step in the treatment protocol will depend on data from long-term studies of eyes treated with the epithelium on.

"The less riboflavin present in the stroma, the less oxygen radicals are generated and the less crosslinking that is achieved," Dr. Hafezi said. "Furthermore, the epithelium has a tendency to block the short-wavelength UVA light used for CXL, and while this barrier effect is not that great, it still reduces the amount of energy that reaches the corneal stroma."

As reviewed by Dr. Hafezi, available data from clinical trials and experimental models clearly show a benefit of the epithelium-off method for enhancing riboflavin bioavailability at its target site and increasing the depth and magnitude of the crosslinking effect.

For example, in an ex vivo study of human corneas, HPLC analysis showed a 40-fold lower concentration of riboflavin in the stroma when the riboflavin solution was applied with the intact epithelium on versus off.

In addition, findings from confocal microscopy and slit-lamp examination show that with the epithelium-off method, crosslinking occurs to a depth of 270 to 330 µm.

In contrast, findings from an animal model using confocal microscopy indicated the depth of crosslinking was only 50 to 80 µm when the procedure was performed with the intact epithelium on, and stress-strain measurements from a rabbit eye study showed the biomechanical effect of the epithelium-on method was only 20% of that achieved with conventional CXL.

"These data indicate that crosslinking occurs with the epithelium-on method, but the effect is shallower and less than when the epithelium is removed," Dr. Hafezi explained.

Dr. Hafezi noted to *Ophthalmology Times* that since the time of his presentation at the 2010 AAO meeting, interesting results presented by Eberhard Spörl, PhD, at the 6th International CXL Congress in Milan, Italy, in January 2011, provide some new insight about CXL with the epithelium on. Dr. Spörl is associate professor, Department of Ophthalmology, University of Dresden, Germany, and pioneered CXL with Theo Seiler, MD, PhD, professor of ophthalmology, Institute of Refractive and Ophthalmic Surgery, Zurich, Switzerland.


Dr. Spörl

According to his recent research, the concentrations of benzalkonium chloride, dextran, and sodium chloride in the riboflavin solution play important roles in the passage of the vitamin through the epithelium. In particular, dextran blocks the paracellular transport of substances through the epithelium.

"These findings indicate that the currently commercially available riboflavin solutions being used for transepithelial CXL may not be optimally formulated," Dr. Hafezi explained.

On but with modified epithelium?

Dr. Spörl told *Ophthalmology Times*, "The question is not epi-off or epi-on with the intact epithelium. This question was clearly answered with epi-off in the past. Now, we work at the question of epi-on but with modified epithelium. For that reason the conventional riboflavin solution with dextran and 0.9% sodium chloride cannot be used. A new riboflavin, without dextran, with benzalkonium chloride, and with a lower sodium chloride content is necessary for transepithelial CXL."

While there are disadvantages to the epithelium-off method relative to CXL with the intact epithelium on, these differences have relevance only to the secondary and

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Farhad Hafezi, MD, PhD

tertiary goals of the procedure, which are to maximize safety and patient comfort, respectively, Dr. Hafezi said.

Comfort and safety

Unquestionably the epithelium-on method is more comfortable. Regarding safety, the epithelium-off method has been associated with a number of complications. These have predominantly been described in case reports and, with the exception of a single case of localized endothelial damage in an eye with a very thin cornea, have primarily involved healing problems relating to the open corneal surface.

No such problems have been reported so far with the epithelium-on technique, acknowledged Dr. Hafezi.

"However, at least in my practice where I have almost 8 years of CXL experience, I have not seen a single case of severe infection," Dr. Hafezi said.

"Careful postoperative management is the key to reducing the risk of serious complications after CXL. Patients must be seen daily until the epithelium is closed, including on weekends," he concluded.**OT**

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