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Cross-linking can be performed at slit lamp

Corneal cross-linking, started by Theo Seiler and others, has changed the management of keratoconus. Guest columnist **Farhad Hafezi, MD, PhD, FARVO,** discusses how cross-linking performed at the slit lamp takes the procedure to another level.

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Over the last 20 years, corneal cross-linking (CXL) has grown from being a treatment to slow or halt the progression of corneal ectasia keratoconus to one that not only treats all corneal ectasias, but also Terrien's marginal degeneration and even sterile melting. In 2008, a second major indication for CXL was described: infectious keratitis, in a procedure termed by the cross-linking community as "photoactivated chromophore for keratitis-CXL" (PACK-CXL).

Cross-linking, irrespective of the indication, requires three hurdles to be cleared in order to work: saturation of the corneal stroma with riboflavin, UV irradiation to photoactivate the riboflavin and the presence of oxygen. Historically, all of these steps have been performed with the patient lying supine in an operating room. But is this necessary in every case? Absolutely not. We have recently published the technique of corneal cross-linking at the slit lamp. Let's examine what makes CXL at the slit lamp (Figure 1) outside of the OR an attractive option.

Figure 1. The C-Eye device (EMAGine), a portable slit lamp-mounted cross-linking device in use.

Source: Farhad Hafezi, MD, PhD, FARVO

Light, oxygen, riboflavin unaffected by gravity

It is a simple concept to grasp that when it comes to oxygen diffusion into the cornea and UV irradiation of the riboflavin present in the stroma, both are unaffected by the patient's position. Oxygen molecules diffuse into patient's cornea no matter whether they are sitting or lying down. If you shine a light on the

eye, the intensity of illumination is altered by distance, not direction. In other words, the photons emitted from the UV light source are similarly agnostic as to whether the patient is sitting upright at the slit lamp or supine on a bed.

As for riboflavin in the sitting position, we demonstrated and published in 2017 that saturation in the cornea remains homogeneous and stable for 1 full hour before any gravity-related changes in distribution appear. This is more than enough time to perform CXL, even using the long Dresden protocol.

CXL 'sterilizes' the cornea

One of the biggest concerns about taking a procedure out of the OR is the potential for an increased risk for infection, but the reason PACK-CXL exists is that cross-linking the cornea also reduces the microbial load without requiring antimicrobial agents to be used, which is becoming increasingly important as antimicrobial resistance becomes more prevalent.

When UV light interacts with the riboflavin present in the stroma, it produces photoactivated (reduced) riboflavin molecules and other reactive oxygen species (ROS), and these react in multiple ways (Figure 2). The first and intended effect when performing CXL to treat ectasia is that these molecules covalently bind and "cross-link" the molecules on the surface of stromal collagen fibrils and the proteoglycan extrafibrillar matrix, thereby strengthening the cornea. This process also means that there are fewer binding sites for matrix metalloproteinases to bind (a phenomenon called steric hindrance), which makes it harder for the proteases generated during inflammation or by pathogenic organisms to digest the stroma. But the third and fourth mechanisms are actively antimicrobial: Photoactivated riboflavin and ROS attack and damage cell membranes and intercalate and oxidatively damage nucleic acids.

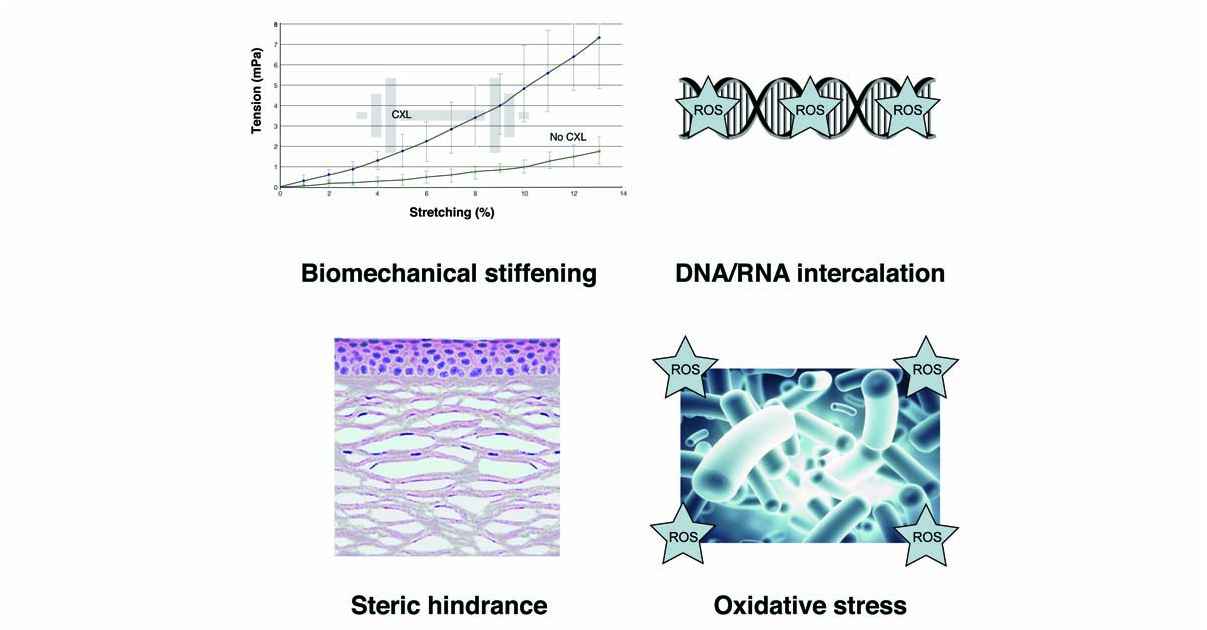

Figure 2. The four main effects of corneal cross-linking. Riboflavin, photoactivated by UV light, results in the generation of ROS, which causes covalent binding of stromal molecules together, resulting in biomechanical stiffening effects and a reduction in protease binding sites (steric hindrance). The ROS can also intercalate with pathogen nucleic acids and induce oxidative stress-related damage to pathogen cell membranes.

Given that CXL, in effect, "sterilizes" the cornea, and antibiotic prophylaxis is administered at the end of the procedure, it begs the question: Why do you need a sterile OR to perform the surgery? Further, when treating infectious keratitis with PACK-CXL, why would you bring an active infection into a sterile OR when you could treat it at a slit lamp elsewhere?

Make CXL more cost-effective

The OR is a resource that needs to be booked in advance, often in competition with other surgeons, and one that needs to be paid for because the costs of staffing, running and cleaning the OR are nontrivial. These resource costs have caused many doctors to rethink whether a procedure actually needs to be performed in the OR at all — perhaps in a clean but not sterile environment, such as a minor procedure room or, if safety can be maintained, even in the doctor's office. This is not news to medical retina specialists: Many administer intravitreal injections as an office-based procedure, and this does not compromise patient safety. One study showed that after more than 11,000 intravitreal injections, there was no difference in endophthalmitis rates when the procedure was performed in the office or an operating room setting, and a study involving 21,000 eyes showed that even cataract surgery can be performed as safely in an office setting as in the OR, in terms of not only visual outcomes, but also rates of adverse events and endophthalmitis.


Farhad Hafezi

There are "big picture" benefits to taking procedures out of the OR, too. ORs exist in hospitals. Hospitals exist in major population centers. In low- and middle-income countries (LMICs), this means that there tend to be precious few ORs in the remote, rural areas. Making a procedure less expensive and freeing it from the OR means more people can receive life-changing procedures, which in our case is sight-saving CXL or PACK-CXL.

Time is on your side

Thirty minutes can be a long time for some patients, especially children, to sit, trying to fixate on the UV light source. Would patients sitting at the slit lamp for extended periods remain comfortable and compliant? Our experience of CXL at the slit lamp is that patients find it comfortable, as we ensure that the height of the chair, table and chin rest on the slit lamp are all optimally positioned. The slit lamp has the added advantage of a red fixation light, which helps the patient to relax and fixate during the procedure.

The UV irradiation component of the now more than 20-year-old Dresden protocol for cross-linking requires a UV intensity of 3 mW/cm^2 to be delivered for 30 minutes, giving a total fluence (or "dose") of 5.4 J/cm^2. However, the intensity of 3 mW/cm^2 was a result of the limitations of UV lamps available at the time. Modern UV lamps can irradiate with much higher intensity; most can irradiate at 9 mW/cm^2 or even 18 mW/cm^2.

In the past, it was believed that the photochemical interaction between riboflavin and UV energy adhered to the Bunsen-Roscoe law of reciprocity. In other words, if the total light energy delivered into a photochemical reaction remains the same, the speed at which that energy (the total fluence) is delivered is irrelevant: The same amount of reaction should occur. In theory, therefore, 3 mW/cm^2 of UV energy delivered over 30 minutes should result in the same cross-linking effect as 9 mW/cm^2 delivered over 10 minutes.

However, the CXL reaction — for treating ectasia, at least — does not completely adhere to the Bunsen-Roscoe law. There appears to be a diminishing cross-linking effect as the protocols are accelerated. Increasing intensity beyond approximately 9 mW/cm^2 starts to result in less effective corneal stiffening compared with slower protocols, which may be explained by the fact that oxygen is consumed as part of the CXL photochemical reaction and does not diffuse into the stroma from the atmosphere at a rate fast enough at UV intensities much greater than 9 mW/cm^2. We believe that a good balance between the efficiency of the procedure and a patient-friendlier irradiation time is 9 mW/cm^2 UV intensity delivered over 10 minutes. A 10-minute treatment is therefore an attractive proposition for effective ectasia treatment, well within patients' comfort zone for sitting at a slit lamp.

PACK-CXL appears to be even less dependent on oxygen than CXL for ectasia, meaning that even highly accelerated treatments (as fast as 3 minutes with an intensity of 30 mW/cm^2) are not likely to compromise the treatment efficacy. A central point in the killing rate of microorganisms with PACK-CXL is the total energy used. We have learned that higher fluences are more effective at killing pathogens than the fluence delivered with the Dresden protocol and its derivatives, meaning that high-fluence PACK-CXL could be even more effective than we have seen in earlier clinical studies.

Summary

To summarize, CXL can be performed at the slit lamp outside of the OR because the procedure reduces the microbial load on the cornea to such an extent that it is now being used to treat bacterial and fungal corneal infections. The fact that the patient is sitting comfortably and upright during cross-linking for approximately 4 to 10 minutes rather than lying down on a reclining chair has no effect on riboflavin distribution, oxygen diffusion or UV irradiation.

There is little to argue against performing CXL safely and effectively at the slit lamp. The advantages of lowering costs, untethering CXL from hospitals and widening access to cross-linking to any location with a slit lamp are to be welcomed in any setting, but particularly in LMICs. The impact of PACK-CXL at the slit lamp has the potential to be even more transformative. Infectious keratitis is a leading cause of visual impairment worldwide, particularly in developing countries, where those who develop it are usually agricultural workers in the most productive years of their lives. An effective, and crucially, antibiotic-free option that can potentially treat infectious keratitis in a single sitting at the slit lamp in a rural doctor's office is an inviting proposition. This has been described as "democratizing cross-linking," and we believe that this is the greatest value that cross-linking at the slit lamp brings.

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