Corneal Cross-linking at the Slit Lamp

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ABSTRACT

PURPOSE: To describe a new surgical technique where corneal cross-linking (CXL) (to treat corneal ectasias) and photo-activated chromophore for keratitis-CXL (PACK-CXL) are performed while the patient is seated in an upright position at the slit lamp.

METHODS: Topical anesthesia is applied in the waiting room, 10 minutes before the procedure. Once in the office or procedure room, eyelids and periorbital areas are disinfected with chloramphenicol and the patient is seated at the slit lamp. Epithelial debridement is performed with a cotton swab soaked in freshly prepared 40% ethanol, using 70 seconds of tapping, followed by gentle pressure to remove the epithelium. The patient is placed in the supine position for riboflavin application for 10 minutes. Stromal thickness is assessed using ultrasound pachymetry after 5 and 10 minutes. Finally, the patient is returned to the slit lamp to receive ultraviolet irradiation.

RESULTS: CXL at the slit lamp is an easy-to-perform technique that substantially reduces the infrastructure needed to perform CXL and PACK-CXL procedures.

CONCLUSIONS: A significant advantage of allowing CXL treatment at the slit lamp is that CXL technology can now be used in clinics that do not have easy access to an operating room infrastructure. Slit-lamp CXL can also reduce procedure costs by eliminating the technical fees related to the use of an operating room, making this treatment not only more accessible for patients, but also affordable.

[*J Refract Surg*. 2021;37(2):78-82.] VIDEO

Corneal cross-linking (CXL) using riboflavin and ultraviolet-A (UVA) light is a commonly performed treatment and the only method to arrest corneal ectasias such as keratoconus and postoperative ectasia.[1,2] CXL involves saturating the corneal stroma with riboflavin, followed by a period of stromal irradiation with UVA light.[3] The resulting photochemical reaction creates reactive oxygen species that stiffen the cornea by predominantly covalently binding collagen fibril surface and the surrounding protein network.[4] This reaction also induces cell death of any living cells (and pathogens) by damaging cell membranes and nucleic acids.[5-7] This latter reaction has led to a second indication for CXL called photoactivated chromophore for keratitis-CXL (PACK-CXL) as a treatment for corneal infection of bacterial and/or fungal origin.[8-12]

To date, CXL and PACK-CXL are commonly performed in operating rooms, but with two major limitations. First, the use of CXL tends to be limited to areas that have access to an operating room infrastructure, restricting the procedure in more remote regions of the world. Second, the associated costs with the use of an operating room increase the overall price of the procedure.

To safely and effectively transfer CXL technology to be used at the slit lamp would greatly increase the accessibility to treatment globally and reduce overall costs related to the procedure. We present how this

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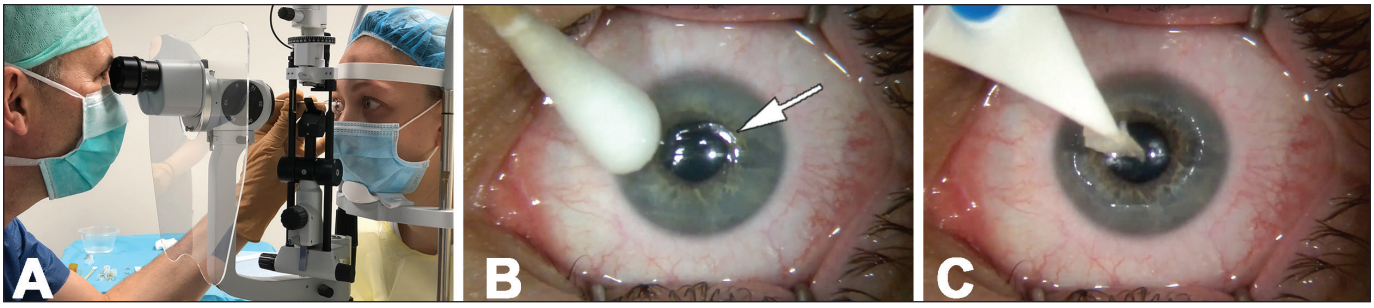

Figure 1. Corneal abrasion at the slit lamp. (A) An open-wire lightweight speculum is placed, and abrasion is performed using a sterile cotton swab first soaked in 40% ethanol. The cornea is tapped in a circular motion for 70 seconds. (B) After approximately 45 seconds, the first folds in the corneal epithelium appear. (C) After 70 seconds, gentle pressure is applied using a triangular sponge to remove the epithelium in a circular movement. Corneal cross-linking was performed with all parties wearing personal protective equipment per local legislation enacted to prevent the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in medical facilities.

corneal surgical technique can be safely performed using only the slit lamp for the required infrastructure.

SURGICAL TECHNIQUE

CXL was performed with all parties wearing personal protective equipment per local legislation enacted to prevent the spread of coronavirus 2 (SARS-CoV-2) in medical facilities.

Preparing the CXL Device

Prior to surgery, the UVA illumination device (C-Eye; EMAGine AG) was charged and calibrated by fully opening the aperture using a rotating dial, then placing the device onto a charging and calibration base (C-Base). A magnetic dock for the cross-linking device was fitted on the central mount present on the slit lamp and secured into place with a thumbscrew. **Video 1** (available in the online version of this article) describes every step of the procedure.

Anesthesia and Patient Preparation

For epithelium-off CXL and PACK-CXL procedures, topical anesthesia is administered in the waiting room, with one drop of oxybruprocaine hydrochloride (4 mg/mL, Théa Pharma SA) followed by one drop of tetracaine 1% (Théa Pharma SA), applied three times each over a 10-minute period. For the various epithelium-on procedures, the application of anesthesia is adapted according to the protocol of choice.

The patient is brought to the slit lamp (SL9900; CSO Italia), where the height of the chair and slit lamp are adjusted to ensure the patient's maximum comfort. This step is important because once comfortably seated, the patient will be able to more easily keep a steady position during irradiation. For that purpose, we also use a chair with two armrests rather than a simple stool. While the patient is in the sitting position, the eye and periorbital region are thoroughly disinfected with sterile cotton wool buds soaked in octenidine hydrochloride (Octenisept; Schülke & Mayr GmbH). A lightweight open-wire speculum (Kratz speculum, enclosed in the C-Eye Procedure Kit; EMAGine AG) is inserted and sterile surgical gauze is taped laterally to the temporal canthus to collect any riboflavin solution run-off (**Figure 1A**).

Abrasion

For epithelium-off CXL, several different approaches can be used to remove the epithelium, such as by means of a hockey knife or an Amoils brush. However, these surgical tools may be challenging to maneuver in the upright position. Additionally, special attention should be taken to not injure Bowman's membrane during the epithelial removal process. Therefore, we used an alternative approach to remove the epithelium. This approach is a modified laser epithelial keratomileusis (LASEK) approach[13] using a sterile cotton swab soaked with 40% ethanol. The epithelium-off process using the cotton swab and 40% ethanol is easy to perform, without potential harm to Bowman's membrane, rapid, and safe. Specifically, a sterile cotton swab is dipped in freshly prepared 40% ethanol solution, then gently tapped on the center and periphery of the cornea in a circular fashion for 70 seconds. After approximately 45 seconds of tapping, a loosening and folding of the epithelium can be seen (**Figure 1B**). After 70 seconds, gentle pressure is applied to the cornea with the cotton swab tip to wipe away the epithelium in a circular motion. An erosion of approximately 8 mm will appear (**Figure 1C**). Particular care must be taken that the 40% ethanol is not exposed to the air for prolonged periods of time prior to use. The evaporation of the ethanol from the solution will rapidly change the ethanol content within the solution and, ultimately, the effectiveness of the epithelium re-

Figure 2. Riboflavin instillation and ultraviolet-A (UVA) irradiation. (A) Riboflavin instillation is performed in a reclining chair, applying riboflavin every 2 minutes for 10 minutes. (B) UVA irradiation of the selected eye. Steady fixation is facilitated by presenting a red fixation target to the untreated eye (arrow). (C) Surgeon view of the irradiation zone through the ocular lens of the slit lamp. Corneal cross-linking was performed with all parties wearing personal protective equipment per local legislation enacted to prevent the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in medical facilities.

moval process. Finally, the cornea is rinsed with balanced salt solution using a syringe with an irrigation canula. For a PACK-CXL treatment, epithelial debris is removed over and/or around the infiltrate using a dry sterile triangular sponge.

Riboflavin Instillation

The patient is then moved to a reclining chair for riboflavin instillation. Corneal thickness is measured using an ultrasound pachymeter (SP-1000; Tomey). Reference points are used from preoperative corneal tomography measurements to ensure that the thinnest points are measured. A total of three measurements are taken, and the thinnest measurement of the three is recorded. Hypo-osmolaric 0.149% riboflavin solution (RIBOKER; EMAGine AG) is applied to the cornea every 2 minutes for a total period of 10 minutes, followed by a rinse with balanced salt solution (**Figure 2A**).

UVA Irradiation

The cross-linking device is switched on, and the appropriate cross-linking UV illumination protocol is selected (ie, 9 mW/cm² for 10 minutes). The device is placed on the adaptor that was previously attached to the slit lamp. The surgeon then focuses the beam of the slit lamp on the apex of the cornea, which equates to a working distance of 32 mm. The design of the optics of the cross-linking device allows a 5-mm distance margin of error where the cornea would still receive more than 95% of the intended UVA fluence. In other words, an unintentional focus on the iris rather than the apex of the cornea (approximately 3.5 mm from the corneal surface) would not result in excessive or insufficient corneal UVA irradiation. After confirming that the patient is sitting comfortably, the surgeon presses the UV button to start irradiation as per the preselected protocol. A red fixation target is offered to the untreated eye to facilitate steady fixation (**Figure 2B**). The surgeon can periodically check the status of the eye through the slit lamp during UVA irradiation. In the unlikely event of a patient excessively moving their eyes, the surgeon can easily readapt the irradiation zone by readjusting the slit lamp (**Figure 2C**).

Immediately Postoperatively

After irradiation at the slit lamp is complete, the patient returns to the reclining chair for postoperative corneal pachymetry measurements. Topical antibiotics moxifloxacin (Vigamox, 5 mg/mL; Novartis Pharma) and ofloxacin (Floxal; Bausch & Lomb Swiss) are administered and a bandage contact lens (Air Optix Night&Day; Ciba Vision AG) is used to cover the eye. Finally, the speculum is removed with care to avoid having the patient squeeze the newly placed contact lens from the eye.

DISCUSSION

Several concerns had to be addressed before CXL at the slit lamp could be safely and effectively performed. The two main concerns are (1) whether patients will tolerate the time sitting when their head is placed on the chin rest during irradiation and (2) whether risk for infection is increased when performing a CXL procedure outside the operating room.

Time Spent at the Slit Lamp

The original "Dresden protocol for keratoconus" uses a UVA intensity of 3 mW/cm² for 30 minutes.[14] In cases where a 30-minute irradiation is chosen, we recommend performing CXL in the supine position. However, several accelerated epithelium-off or epithelium-on CXL ectasia protocols with irradiation times between 4 and 10 minutes have been recently established both to provide efficient treatment and to be well-tolerated by patients at the slit lamp.[15-23]

There is the possibility that some patients (particularly young children and non-compliant individuals) will not tolerate sitting upright at the slit lamp, especially for extended periods of time. However, acceler-

ated CXL protocols, such as the 10 minutes of 9 mw/cm² UV irradiation used in the initial cases performed at the slit lamp, help minimize the time a patient has to sit at the slit lamp. Such an accelerated protocol only loses a negligible amount of corneal stiffening efficacy when compared to the Dresden protocol and can potentially be used in most keratoconus cases.[23-27] In any event, traditional cross-linking in the supine position can still be performed by docking the device into a table mount should it be necessary.

Risk for Infection

During every CXL procedure (standard CXL or PACK-CXL), the keratocytes of the cornea and pathogens (bacteria and fungi) are killed to a certain depth, depending on the protocol used.[9] The killing is due to two mechanisms: generation of oxidative stress (reactive oxygen species) and intercalation of photoactivated riboflavin with the DNA of pathogens, disabling replication.[12]

In CXL for keratoconus, the irradiated cornea must be free of pathogens at the end of the procedure. Additionally, prophylactic antibiotics and a bandage contact lens are administered. Therefore, it is highly unlikely that there is a sterility advantage of performing CXL in the operating room instead of an office or procedure room because the CXL procedure ultimately creates an antiseptic treatment.

In PACK-CXL for infectious keratitis, the cornea is already septic. As already mentioned with CXL for keratoconus, PACK-CXL is specifically used as an antiseptic procedure with an aim of reducing the pathogenic load on the cornea.[8,9] Thus, it is unnecessary and counterproductive to treat a septic eye in a sterile operating room to create an antiseptic procedure.

CXL in the Supine Position

Ultimately, CXL for keratoconus requires three factors: UVA light, oxygen, and a chromophore (eg, riboflavin). The propagation of UV light and the diffusion of oxygen are not impinged by the patient's position. For riboflavin, though, there was a theoretical concern that riboflavin might settle in the inferior part of the cornea due to gravity. However, experimental investigation has shown that even over the course of 1 hour (twice the duration of the classic "Dresden protocol"), the effect that gravity places on the riboflavin in the cornea is negligible.[24] Finally, another concern was that the supine position of the patient may theoretically entail a less steady fixation. We observed that by using a comfortable chair and providing a red fixation light on the untreated eye, the patient was able to fixate more easily than in a supine position.

We do not expect any difference in surgical outcomes between CXL performed in a sitting position at the slit lamp when compared to CXL performed in a supine patient. Notwithstanding, we do expect that this modification could facilitate the access of CXL technology to more patients, extending coverage in remote areas, and also allow treatments with reduced related costs and administrative burden of reserving, using, and maintaining an operating room.

AUTHOR CONTRIBUTIONS

Study concept and design (FH); data collection (OR, EAT-N, NLH); analysis and interpretation of data (FH, OR, EAT-N, MH, NLH); writing the manuscript (FH, MH); critical revision of the manuscript (FH, OR, EAT-N, MH, NLH); supervision (FH)

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