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A New Surgical Technique to Deliver Riboflavin Beneath Corneal Epithelium: The Corneal Cross-Linking Epi-Pocket

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Purpose: To describe a new technique to deliver riboflavin into the corneal stroma during Corneal Cross-Linking (CXL) without the removal of corneal epithelium.

Methods: Keratoconus patients underwent CXL for progressive keratoconus. Riboflavin was delivered by manually creating an epithelial pocket (CXL Epi-Pocket). Verbal rating scale was recorded postoperatively. Best-corrected visual acuity, keratometric indices, corneal thickness and corneal densitometry were recorded at baseline and at 12-month follow-up.

Results: Eighteen eyes of 18 patients were included in the study. At a 12-month follow-up, best-corrected visual acuity, K1, K2 and densitometry values were stable. Maximum keratometry (Kmax) reduced from 55.31 ± 6.21 (SD) to $52.34\text{d} \pm 4.12\text{d}$ (SD) (P value $= 0.032$). the thinnest point went from 441 ± 21.18 (SD) to 425.4 ± 19.02 (SD) um (P value $= 0.041$). The verbal rating scale at 1, 2 and 3 days postoperatively were 1.76 ± 0.19 (SD), 1.02 ± 0.51 (SD) and 0.28 ± 0.14 (SD).

Conclusions: CXL Epi-Pocket is able to deliver riboflavin to halt the progression of keratoconus at a 12-month follow-up.

Key Words: corneal epithelium, corneal cross-linking epi-pocket, keratoconus, riboflavin

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Corneal cross-linking (CXL) with epithelial debridement (CXL Epi-Off) is the gold standard for progressive keratoconus patients.[1–3] Debridement of the central corneal epithelium is a prerequisite in order to enable sufficient stromal diffusion of the photosensitizer riboflavin into the stroma bypassing the epithelial tight junctions.[4] However, debridement of epithelium increases pain and discomfort,[5] gives rise to a higher risk of corneal infection, and in thin corneas (<400 um) Ultraviolet-A (UVA) light may damage corneal endothelium.[6] Those are the main reasons why "Epithelial-On" CXL approaches have been proposed.[7–9] Unfortunately, without epithelial removal the stromal riboflavin absorption remains inferior to standard Epi-Off technique.[10,11] Intra-stromal riboflavin application after femtolaser stromal pocket creation has been an area of wide interest. However, the application of femtosecond laser cross-linking within public healthcare systems isn't affordable.[12,13] Here, we report a new surgical technique to aid riboflavin penetration into the stroma whilst preserving the integrity of the corneal epithelium via the creation of an Epithelial Pocket ("Epi-Pocket"). Our primary outcome was to evaluate the possibility to deliver riboflavin in CXL procedure via an epithelial pocket. Our secondary outcome measure was the postoperative pain and complications associated with this new technique.

METHODS

This retrospective case series was approved by the ethical committee at Ceuta Medical Center, Ceuta, Spain, and BMC Medical Center, Sesto Calende, Italy. The tenets of the declaration of Helsinki were followed. Informed consent was obtained from all individual participants included in the study. Patients with progressive keratoconus were recruited between May 2018 and April 2019. Patients were examined on the day of surgery and day 1, 3, 9, 28 followed by a 6 and 12-month follow-up. Patients underwent slit-lamp biomicroscopy, best spectacle-corrected visual acuity (BSCVA) on LogMAR, tonometry, fundoscopy, corneal tomography, pachymetry and 12 mm anterior, central and posterior stroma densitometry on Pentacam HR (Oculus). Standardized grayscale units were used for densitometric measurements.[14] The indication for inclusion was the presence of progressive keratoconus with an increase in the maximum cone apex curvature (Kmax) of at least 1.50 diopters or a decrease in corneal pachymetry of >15 microns in 2 consecutive visits within the previous 6 months. The exclusion criteria were: pregnancy/lactation, severe central opacity, a history of herpetic keratitis, active corneal infections, concomitant autoimmune diseases, any previous ocular surgery and corneal thickness less than 400 um.

Postoperative pain was measured immediately postoperatively at day 1, 2, 3, and 7. To measure postoperative pain we used the Verbal Rating Scale (VRS).[15] The different levels of pain were described with adjectives and the scores ranged from 0 to 4. "No pain" was marked as 0, "mild pain" as 1, "moderate pain" as 2, "severe pain" as 3 and "unbearable" as 4.[15]

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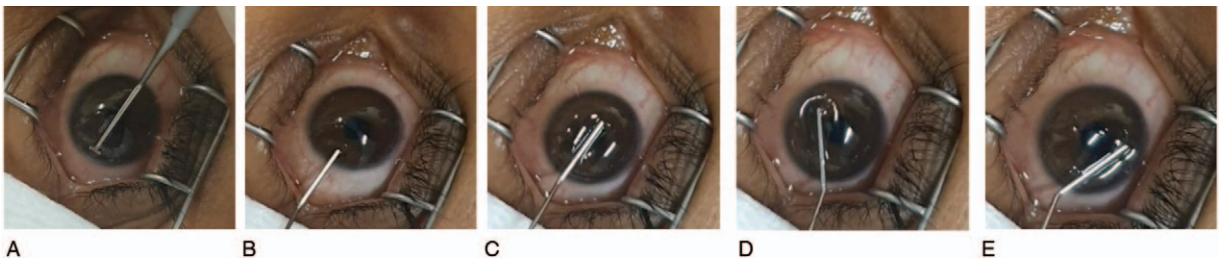

FIGURE 1. Step-by-step pocket photoshoot: (A) 1.5 mm linear epithelial opening (B) Insertion of riboflavin canula's tip under the epithelium. (C-E) Fine circumferential motions to create a 9 mm epithelial pocket.

Surgical Technique

Alcohol solution 18% was instilled into a 9.0 mm LASEK Epithelial Trephine (MicroSurgical Technology, 8415 154th Ave NE Redmond, WA). After 30 seconds a cellulose sponge was used to remove the alcohol. A balanced salt solution was then copiously instilled to wash out the ocular surface. In the temporal side of the cornea a 1.5 mm linear epithelial opening was created with an Epithelium Hoe–Flat–Malosa Medical Spatula (Ashday Works Business Park, Elland Rd, Halifax, Elland) (Figs. 1A and Fig. 2). The tip of the riboflavin canula is then inserted into this opening (Fig. 1B) and moved in fine circumferential motions to detach the epithelium and create a 9 mm epithelial pocket (Fig. 1C–E). Riboflavin (Riboflavin 0.1% (VibeX Rapid^{TM}, Avedro, Inc. Waltham, MA) solution was then injected directly into this pocket and topped up every 2 minutes for 15 minutes. To ascertain sufficient riboflavin fill within the pocket an intraoperative Optical Coherence Tomography (Casia-OCT) was performed (Fig. 3). Subsequently, the cornea was irradiated with an UVA 365 nm light for 15 minutes using the Avedro KXL system (Avedro, Inc. 30 North Avenue Burlington, MA) with an irradiance of 6 mW/cm^2 delivering a total of 5.4J/cm^2. At the end of the surgery one stat dose of Chloramphenicol 1% ointment and one drop of cyclopentolate 1% were instilled in the treated eye which is then padded for 12 to 24 hours. The surgical technique needs a learning curve of 6 cases. In 3 cases (16.7%), the creation of the pocket failed due to peripheral ruptures of the corneal epithelium. The ruptures didn't influence the procedure and the corneal epithelium remained in place. The postoperative regime consisted of chloramphenicol 1% ointment hourly for 1 week. After 3 days in the absence of epithelial defects, dexamethasone sodium phosphate 0.1% eye drops are applied 4 times a day for a month, and tapered down in the following 2 months.

Statistical Analyses

The collected data were analyzed using SPSS software (version 16, SPSS Inc., Chicago, US). Generalized linear model, generalized estimating equations, and repeated measures tests were used wherever appropriate.

FIGURE 2. Tip of Epithelium Hoe–Flat–Malosa Medical.

RESULTS

Eighteen eyes of 18 patients were included in the study. The mean age of the patient was 23.5 ± 1.98 (SD) years. 12 were females and 4 males. Nine patients had a history of atopy. All 18 patients with progressive keratoconus did not have any intra or postoperative complications. BCVA, keratometric and densitometry values are shown in Table 1.

The VRS at 1, 2, and 3 days postoperatively were 1.76 ± 0.19 (SD), 1.02 ± 0.51 (SD), and 0.28 ± 0.14 (SD).

DISCUSSION

In this present study, we showed the feasibility and efficacy of an alternative way to Epi-Off and Epi-On CXL to deliver riboflavin in CXL procedures. Our results show cessation of keratometric progression in a cohort of 18 eyes of 18 patients undergoing CXL with this novel technique with no adverse complications such as infectious keratitis or stromal haze over a 12-month follow-up. We supposed that the corneal epithelium provided a natural protection reducing the postoperative pain.

Several studies of Epi-On or Trans-Epithelial CXL have been published. However, evidence demonstrating efficacy long term to support this practice is still lacking or have not reported satisfactory results.[16] Compared to these techniques, Epi-Pocket CXL has the advantage to instill riboflavin directly onto the corneal stroma like in Epi-Off CXL. This may ease riboflavin penetration and avoids all disadvantages given by the barrier of the corneal epithelium. As a possible disadvantage, other than a steeper learning curve, the UV lights need to pass through the corneal epithelium during irradiation. Additionally, the pocket

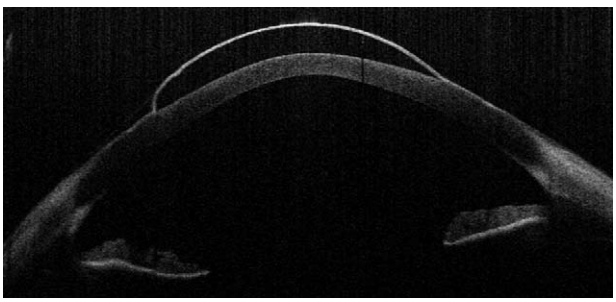

FIGURE 3. OCT scan showing the epithelial pocket filled with riboflavin. OCT indicates optical coherence tomography.

Table 1. Baseline and 12-month Follow-up Parameters After CXL Epi-Pocket

	Baseline	12-month FU post CXL Epi-Pocket	*P* value
BCVA (LogMAR)	0.38 ± 0.13	0.28 ± 0.36	= 0.74
Corneal thickness (um)	441 ± 21.18	425.4 ± 19.02	= 0.041
Kmax (D)	55.31 ± 6.21	52.34D ± 4.12	= 0.032
K1 (D)	44.73 ± 3.19	43.21D ± 3.22	= 0.61
K2 (D)	47.22 ± 4.21	46.19D ± 3.9	= 0.79
Mean densitometry (GSU)	15.78 ± 1.71	15.84 ± 1.81	= 0.82
Anterior densitometry (GSU)	21.38 ± 2.79	21.56 ± 1.56	= 0.79
Centre densitometry (GSU)	13.58 ± 1.77	14.17 ± 1.12	= 0.65
Posterior densitometry (GSU)	11.12 ± 1.21	11.41 ± 1.11	= 0.88

Data reported as mean ± SD.

BCVA indicates best corrected visual acuity; CXL, corneal cross-linking; D, Diopter; K1, flat keratometry; K2, steep keratometry; Kmax, maximum keratometry; FU, Follow-up; GSU, Gray Scale Unit.

could hinder oxygen diffusion. Randomized clinical trials are required to confirm these findings in the future.

Derakhshan et al[17] demonstrated in a study of 22 patients with 3 to 6 month follow-up utilising Epi-on CXL with a 30-minute Riboflavin induced a 100% halt in progression and improvement in mean keratometry in 77% of patients. Filippello et al[18] demonstrated in a group of 20 patients with bilateral progressive keratoconus that Epi-on CXL using an enhanced Riboflavin was effective in halting progression of keratoconus in comparison to the untreated eye.

However, penetration of riboflavin into the corneal stroma is believed to be a critical step in CXL.[19] The size of the riboflavin molecule plus the presence of epithelial tight junctions limits stromal penetration.[4] In vitro studies of corneal buttons excised during a penetrating keratoplasty in keratoconus eyes demonstrated a reduced stromal concentration of Riboflavin in eyes with corneal epithelium compared to those without epithelium.[4] This difference was affected by a longer exposure period to riboflavin.[20] Additionally, anterior segment imaging in patients undergoing CXL Epi-On versus Epi-Off demonstrate a deeper demarcation line in the latter, suggesting a deeper level of reaction within the cornea stroma CXL Epi-Off which may confer additional benefit.[21]

CXL Epi-Off procedures may carry a higher incidence postoperative pain due to exposure of the corneal nerves. To overcome this problem many advocate the use of a bandage contact lens after Epi-Off treatments but a study demonstrated a significant additional risk of infective keratitis with this practice.[22] We proposed the creation of an epithelial pocket (Fig. 3) that has the potential to reduce postoperative pain with no patients in our study reporting unbearable pain postoperatively.

One concern regarding CXL Epi-On is the UVA transmittance through epithelium. Some investigators suggested that the epithelium is not a barrier to UVA transmittance although others suggested a reduction of 20% in UV efficacy.[4] From our study, the presence of the epithelium didn't afflict the efficacy of the CXL procedure at stabilizing keratometry.

Densitometry level shows no statistically significant difference between baseline and after 12 months. Advantages of preserving the corneal epithelium during the CXL Epi-Pocket include less surgical trauma, reduced postoperative inflammation, less pain compared to CXL Epi-Off and reduced haze.[23]

Additionally, we didn't observe any epithelial sloughing, as it may happen in Epi-Lasik. Probably, the preservation of the Bowman membrane could play an active role.

The CXL Epi-Pocket technique may reduce postoperative pain and could be an alternative procedure to deliver riboflavin in the stroma to CXL Epi-Off. Considering the limitation in the low number of cases and the lack of a direct comparison with CXL-Off, further evaluation is needed. Epi-Pocket needs a learning curve steeper than previously described techniques, and we estimated it would take around 6 cases before acquiring proficiency.

In this study, we showed an alternative procedure to deliver riboflavin during CXL procedures. CXL Epi-Pocket is an effective intervention in halting progression of keratoconus at a 12-month follow-up with no adverse outcomes or complications reported in our small group of patients with progressive keratoconus. The intervention may be associated with reduced pain. Further long-term follow up involving studies in a larger cohort of patient with a control group is required to assess the long-term safety and efficacy of the CXL Epi-Pocket technique.

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