Sequential Versus Simultaneous CXL and Topography-Guided PRK

Simultaneous treatment appears to provide superior rehabilitation of keratoconus.

BY A. JOHN KANELLOPOULOS, MD

** Editor's note: The following three articles discuss the benefits of combining corneal collagen crosslinking with topography-guided PRK. Although it is safe to perform topography-guided PRK 6 months after CXL, some surgeons are also experimenting with a simultaneous approach, combining CXL and PRK in a single session. Share your approach: Send your response to lsuarez@bmctoday.com.*

Keratoconus is a bilateral, nonsymmetric, noninflammatory progressive corneal degeneration. Its reported incidence is one in 2,000 in the general population,[1,2] but the increased number of eyes undergoing laser refractive surgery screenings suggests the prevalence may be higher. It can be diagnosed at puberty, with up to 20% of eyes progressing to the extent that penetrating keratoplasty (PK) is indicated. Although spectacles and contact lenses provide useful vision in many cases, several surgical options are available for patients who can no longer benefit from them, including intrastromal corneal ring segments,[3,4] lamellar keratoplasty,[5] or, the gold standard, PK.[6,7]

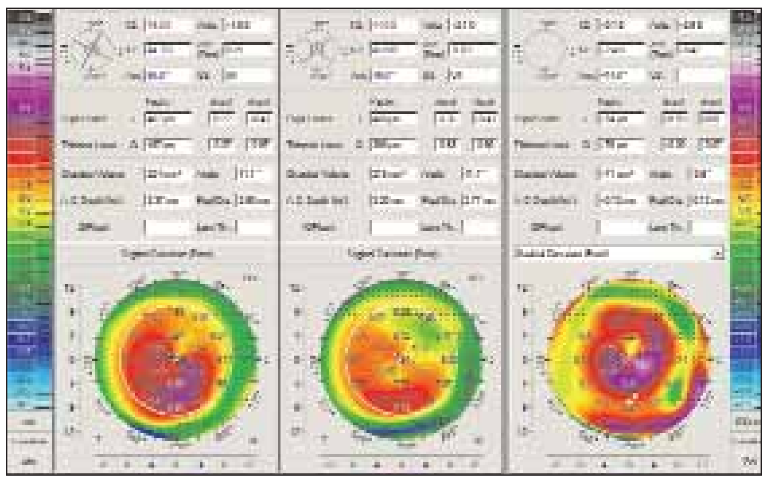

Figure 1. Representative corneal topographies from sequential exams are shown in a case from group B. One can appreciate the difference map (right) between pre- (left) and 2-year postoperative (middle). The data demonstrate the change of keratometric data from 49.00 and 44.30 X 60.9° to 44.00 and 41.80 X 46°. The acuity and refraction data of this 29-year-old patient who changed from UCVA 20/100 to 20/25 are: BCVA 20/30 with -2.75 -3.50 X 65° to BCVA 20/20 with +0.50 -1.00 X 35 at 2 years. The difference saggital topography illustrates the surface change achieved by the PRK and CXL combined technique. This change resembles a combined myopic PRK over the cone apex and a hyperopic PRK, an attempt by the topography-guided software to normalize the corneal irregularity with minimal central tissue removal. Some central area is flattened and some adjacent central area is steepened.

Other recently encountered iatrogenic ectatic corneal disorders, such as post-LASIK ectasia[8] and post-PRK ectasia,[9] require similar treatment approaches. Although PK for ectatic corneal disorders is highly successful, many eyes require contact lenses to correct the unpredictable topographic changes associated with sutures and post-suture abnormal corneal shapes. Sometimes, the contact lens is unsuccessful.[10] Additionally, long-term allograft rejection is a great concern in this young group of patients.

In recent years, basic laboratory studies and subsequent clinical studies have suggested that increasing the crosslinking of the corneal stromal collagen increases corneal stiffness, with attendant stabilization of this normally progressive corneal disorder.[11] Clinically, the use of topical riboflavin combined with UV-A irradiation to increase collagen crosslinking (CXL) has demonstrated a revolutionary potential for retarding or eliminating the progression of keratoconus and post-LASIK ectasia.[12-19]

TABLE 1. COMPARISON OF POSTOPERATIVE RESULTS								
	Preop UCVA	Postop UCVA	Preop BCVA	Postop BCVA	Sphere reduction	Mean K reduction	Haze cases	Follow-up time
Group A	0.12	0.35	0.42	0.68	2.50 D	2.75 D	17	48 months
Group B	0.11	0.5	0.41	0.78	3.20 D	3.50 D	2	32 months

MORE THAN 900 CASES

As I mention in *Surgical Visual Rehabilitation Techniques*, on page 60, I was inspired to try CXL after listening to Theo Seiler, MD, PhD, of Zurich, Switzerland, present his experimental results in 2002. Early on, I was impressed by the stability CXL created in the cornea. I found that visual rehabilitation was now possible in corneas that previously would have progressed to PK.

Of the more than 900 CXL cases I have treated, most have follow-up in the range of 6 years. Using CXL alone provided patients with stability; however, visual rehabilitation was often challenging in patients who were contact-lens intolerant. Several years ago, I performed topography-guided PRK in some of these patients, introducing the novel approach of a therapeutic partial topography-guided PRK on crosslinked cornea following post-LASIK ectasia or primary keratoconus. Outcomes have been satisfactory.[20-23] This technique normalizes the corneal surface by reducing irregular astigmatism and potentially the refractive error as well. Patients experience improved visual outcomes in addition to stabilization of the ectasia process.

Following employment of this technique for several years, we have recently devised a novel combined approach of simultaneous topography-guided PRK and CXL.[24] This article reviews the results of a study comparing the techniques of topography-guided PRK (Figure 1) performed 6 months after CXL (group A; n=117 eyes) and combined with CXL as a single procedure (group B; n=198 eyes). Mean follow-up was 36 months (range, 24–68 months).

DIAGNOSIS AND PATIENT SELECTION

A diagnosis of progressive keratoconus was made when the patient was under the age of 30 years and developed progressive corneal steepening associated with a documented increasing myopic and/or astigmatic refractive error for 3 or more months. These findings were combined with increasing inferior corneal steepening and thinning, no less than 350 µm, based on videokeratography and ultrasound pachymetry. Initial clinical data and topography were used as a baseline. Progression of myopic refractive error with or without progression of manifest astigmatism, decreasing UCVA, loss of BCVA, progressive inferior corneal steepening on topography, and/or decreasing inferior corneal thickness were found in all cases.

Once the diagnosis of keratoconus-related ectasia was confirmed, patients were presented with the options of contact-lens fitting, intrastromal corneal ring segment implantation, or PK; if these modalities did not serve the patient's needs, CXL was described as a possible technique to stabilize ectasia and prolong or prevent the need for PK.

Patients underwent manifest refraction, measurement of UCVA and BCVA, dilated refraction, slit-lamp examination to confirm the presence of keratoconus, keratometry readings, pachymetry, and specular microscopy. All received a verbal and written consent form prior to undergoing CXL and subsequent or simultaneous customized topography-guided PRK.

TAKE-HOME MESSAGE

- CXL alone provides corneal stability; however, it does not enhance visual rehabilitation.
- Simultaneous topography-guided PRK and CXL additionally reduces irregular astigmatism and potentially the refractive error.

DESCRIPTION OF THE TECHNIQUE

Sequential CXL and topography-guided PRK, as well as performing PRK at a later time,[21-22] have received the Conformité Europeéne (CE) Mark for clinical use within the countries of the European Union, including Greece. Topography-guided ablations with the WaveLight platform (Erlangen, Germany) and CXL have not received approval from the US Food and Drug Administration (FDA).

Step 1: Partial topography-guided PRK. We have described previously the topography-guided platform to normalize irregular corneas—and even ectasia—following treatment with CXL.[25-28] This technique is guided by topography images; it is completely different from wavefront-guided treatments. This proprietary WaveLight software utilizes topographic data from the Topolyzer (WaveLight) and averages data from eight topographies. The surgeon adjusts the desired postoperative corneal asphericity; inclusion/exclusion of tilt correction; and adjustment of sphere, cylinder, axis, and treatment zone.

The topography-guided PRK is performed in an attempt to reduce the irregular astigmatism and facilitate visual rehabilitation. In an effort to remove the minimum possible tissue, we decreased the effective optical zone diameter to 5.5 mm and partially treated the cylinder first, and if possible

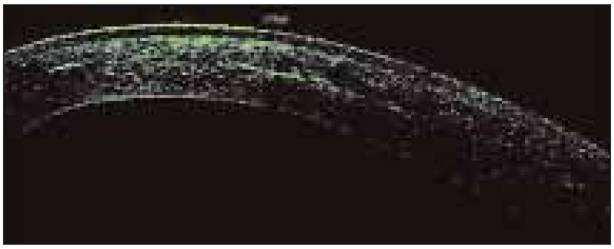

Figure 2. Corneal OCT demonstrating hyper-reflective intrastromal corneal lines at two-thirds depth corresponding with the clinical presence of CXL demarcation line in a patient from Group B, 3 years following the combined PRK/CXL procedure.

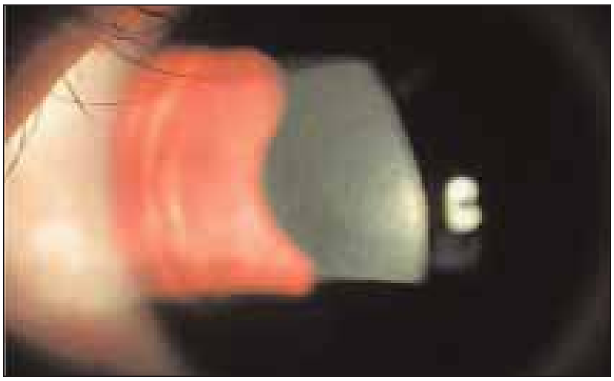

Figure 3. External corneal clinical picture at 6 months postop in a patient from group B demonstrates multiple fine intrastromal lines attributed by the author to CXL. The cornea haze score in this case was 0.

some of the sphere, so that we did not exceed 50 µm of planned stromal removal. For example, a refraction of -2.50 -4.50 X 85º had an attempted PRK of -1.00 -2.50 X 85º plus a customized ablation to normalize the cornea.

The epithelium was removed using 20% alcohol solution placed on the corneal surface for 20 seconds, after which the laser treatment was performed. A cellulose sponge soaked in mitomycin C 0.02% was applied over the ablated tissue for 10 seconds followed by irrigation with 10 mL of chilled balanced salt solution. Afterward, the riboflavin solution administration commenced.

Step 2: CXL. In the combined technique, following irrigation with mitomycin C and for the next 10 minutes, 0.1% riboflavin sodium phosphate ophthalmic solution (Priavision, Menlo Park, California) was applied topically every 2 minutes. Riboflavin facilitated CXL and protected the iris, crystalline lens, and retina from UV-A light exposure.

Following the riboflavin drops, four light emitting diodes, UV-A light of about 370 nm (range, 365–375 nm) and 3 mW/cm^2 radiance was projected onto the corneal surface for 30 minutes. A bandage contact lens was then inserted. A Keracure prototype device (Priavision), with a built-in beeper that resets at the beginning of the treatment, alerts clinicians every 2 minutes during the 30 minutes of treatment to instill the riboflavin solution in a timely fashion. A bandage contact lens was placed on the cornea at the completion of the two procedures.

After CXL, topical ofloxacin (Ocuflox; Allergan, Inc., Irvine, California) and prednisolone acetate 1% (Pred Forte, Allergan) were used four times a day for 60 days. Protection from all natural light with sunglasses was encouraged, along with oral 1,000 mg of vitamin C daily for 60 days. The bandage contact lens was removed on day 5, following complete reepitheliazation.

RESULTS

Patients were evaluated before and for least 2 years following the two procedures for UCVA; BCVA; refraction; topographic map and keratometry (K) indices, specifically mean keratometry, optical tomography and topography; and endothelial cell counts and morphology assessment.

Some patients in both groups complained of significant pain the first postoperative night, whereas others reported minimal discomfort. On average, reepithelialization took 4 days. Endothelial cell counts and morphology were unchanged in both groups (mean preop 2,650 ±150 vs postop 2,700 ±140 cells/mm^2). Results are noted in Table 1.

Group A. The mean improvements pre- to postoperatively were: UCVA, 0.12 ±0.3 to 0.35 ±0.25; and BCVA, 0.42 ±0.25 to 0.68 ±0.22. The spherical equivalent reduction was 2.50 ±1.20 D; mean keratometry reduction was 2.75 ±1.30 D. The mean postop haze score was 1.2 ±0.5, and the mean pachymetry reduction was from 465 ±45 to 395 ±25 µm.

Group B. The mean improvements pre- to postoperatively were: UCVA, 0.11 ±0.2 to 0.5 ±0.2; BCVA, 0.41 ±0.3 to 0.78 ±0.16. Spherical equivalent reduction was 3.20 ±1.40 D, and the mean postop haze score was 0.5 ±0.3. Mean K reduction was 3.50 ±1.30 D. Mean pachymetry reduction was 475 ±55 to 405 ±35 µm. Group B results were statistically superior in reference to BCVA (P<.001), spherical equivalent reduction (P<.005), corneal haze (P<.002), and mean K reduction (P<.005).

DISCUSSION

The mechanism of topography-guided ablation is fitting an ideal cornea shape, usually a sphere, under the present topography map, with tissue to be ablated in between. We employed simultaneous topography-guided PRK and CXL in this series for three reasons. First, the combination reduces the patient's time away from work. If the practitioner waits in between procedures, keratocytes replenish and, activated by fibroblasts after PRK, may cause more scarring even despite the use of mitomycin C.[31] Potential scarring from the PRK is minimized. When we delayed PRK at least 6 months following CXL, we encountered significant haze in 17 cases in spite of using mitomycin C.[28] CXL kills keratocytes as deep as 300 µm,[29] which may have prevented this late haze formation. Our experience suggests that when the therapeutic topography-guided PRK is performed first, the subsequent CXL procedure significantly reduces the keratocytes that induce the scarring mechanism.

Second, minimal haze formation was encountered when CXL was performed immediately after the PRK, with only two cases reporting significant haze.

Third, if one performs PRK following CXL, part of the crosslinked cornea—the strongest crosslinked tissue—is removed from the superficial cornea. It makes less sense to remove the crosslinked tissue, as we do with delayed PRK, because we are potentially removing a beneficial layer of the crosslinked ectatic cornea. Alternatively, performing the topography-guided treatment first compliments CXL and avoids corneal haze.

Keratoconus patients can have excellent visual results with the addition of PRK; however, completely removing a high level of refraction is not the goal. We have placed a ceiling on the amount of central tissue removal (50 µm) for safety reasons, anticipating that further thinning of an ectatic cornea may destabilize its biomechanical stability.

Special emphasis should be taken preoperatively in cases with minimal corneal thickness (ie, less than 350 µm) because of potential cytotoxic effects of UV-A on corneal endothelial cells.[29] The proprietary riboflavin solution is slightly hypotonic (340 mOsm), resulting in slight corneal swelling during CXL, thus adding protection to the corneal endothelium. This may be the reason we did not encounter corneal endothelial decompensation in any case.

We applied the laser treatment with caution, anticipating the refractive effect of corneal flattening after CXL, and elected to attempt significant under-correction of sphere and cylinder by at least 30%. At most, 70% of the measured sphere and cylinder may be attempted as a correction parameter when planning the excimer ablation, until the time that we can more accurately determine the new ablation rate of crosslinked stroma.

In some cases, the central epithelial surface took up to 1 month to smoothen and become lucent. It took between 1 and 4 weeks to detect stable changes in the keratometry and topography, which matched visual and refractive changes. We did see a specific demarcation line in the cornea separating the suspected crosslinked collagen from the deeper cornea (Figure 2). However, the crosslinking effect was assessed at the slit lamp by the presence of ultra-thin, curved white lines in the anterior and mid-stroma in most of the corneas within the 9 mm of the treated area (Figure 3). These lines do not appear to affect vision and tend to fade by 12 months.

CONCLUSION

Sequential topography-guided PRK and CXL appear to provide superior rehabilitation of keratoconus compared with other methods. (See *Surgical Visual Rehabilitation Techniques* on page 60 for further details on this topic.) Patients experience enhanced CXL because riboflavin penetrates through the ablated stroma. Additionally, the absence of Bowman's membrane further enhances results—the riboflavin-soaked Bowman's may have shielded UV-A light during CXL, preventing deeper UV-A penetration and more efficacious CXL. Finally, crosslinking a more normal corneal shape, as in keratoconic eyes pretreated with topography-guided PRK, may provide resistance to factors influencing ectasia progression.

As we perform more CXL procedures, we hope to learn which candidates might best benefit from the procedure. How much ectasia can we safely and predictably correct? Is there a minimum pre-CXL corneal thickness that will not respond to the procedure? Does one type of ectasia have a different outcome when the cause is different: For example, an eye with no preoperative risk factors versus an eye with preexisting keratoconus or pellucid marginal degeneration? We need to develop strategies for determining the attempted PRK correction as part of this process. The proper concentration of riboflavin and its delivery within the corneal stroma, the proper UV-A exposure, and duration of exposure will need to be adjusted as we move from animal model studies into clinical procedures. Perhaps this modality can be employed prophylactically in laser refractive surgery.

Based on our experience, our findings suggest better results with the performance of partial topography-guided PRK as a therapeutic intervention in extreme corneal irregularity followed by CXL immediately thereafter to stabilize the cornea as opposed to CXL followed by PRK. Our main goal was to stabilize the ectasia to delay or avoid corneal transplantation. This appears to have been successful in a large number of young patients with advancing keratoconus. I perform few grafts for keratoconus if patients present with minimum corneal thickness over 400 µm. ■

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