Transepithelial Corneal Cross-linking in Pediatric Patients: Early Results

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ABSTRACT

PURPOSE: To report 18-month follow-up after transepithelial cross-linking (CXL) in young patients.

METHODS: Thirteen eyes with keratoconus were evaluated (mean patient age: 14.4±3.7 years [range: 8 to 18 years]). Corrected distance visual acuity (CDVA); spherical equivalent refraction; keratometry (K); coma, spherical aberration, and higher order aberrations (HOAs) for a 5.0-mm pupil; and thinnest point were measured preoperatively and 1, 3, 6, 9, 12, and 18 months postoperatively by Scheimplug camera. Endothelial cell density and anterior segment optical coherence tomography were also evaluated. Paired Student t test was used to compare preoperative and 12- and 18-month postoperative data. P<.05 was considered significant.

RESULTS: Eighteen months after treatment, CDVA improved significantly, whereas K readings and HOAs showed statistically significant worsening (P<.05). Spherical equivalent refraction, sphere and cylinder, coma, spherical aberration, thinnest point, and endothelial cell density did not show statistically significant changes (P>.05). The mean demarcation line depth was 105 μm. No side effects were observed.

CONCLUSIONS: Transepithelial CXL appears to be a safe treatment in children. Although improved CDVA was noted 18 months after treatment, this technique does not effectively halt keratoconus progression in children compared to standard CXL. [J Refract Surg. 2012;28(11):763-767.]
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its debridement. Trometamol and sodium ethylenediaminetetraacetic acid (EDTA) when combined, as in Ricrolin TE (Sooft Italia SpA, Montegiorgio, Italy), may enhance epithelial permeability of hydrophilic macromolecules.

The features of the transepithelial procedure could prove to be particularly suitable for less cooperative patients such as children. Clinical results of transepithelial CXL in pediatric patients have not yet been reported in the peer-reviewed literature. We present our results at 18-month follow-up after transepithelial CXL in children.

**Patients and Methods**

In this prospective, observational case series, 13 eyes from 13 patients (12 boys and 1 girl) with keratoconus (stage 2 or 3 according to Amsler-Krumeich classification) were evaluated. Mean patient age was 14.4 ± 3.7 years (range: 8 to 18 years). Patients with corneal scars or opacities and anterior segment pathology were excluded from the study. All treatments except 1 (an 8-year-old) were performed using topical anesthesia.

All experimental investigations reported herein were performed with informed consent and followed all guidelines for experimental investigation with human subjects required by the institutions with which both authors are affiliated. Corrected distance visual acuity (CDVA) analyzed as the logMAR value; spherical equivalent refraction; maximum keratometry (Kmax, the steepest meridian with its curvature expressed in diopters [D]); minimum keratometry (Kmin, the flattest meridian with its curvature expressed in D); average keratometry (Kavg, the mean curvature between Kmax and Kmin); coma, spherical aberration, and higher order aberrations (HOAs) for a 5.0-mm pupil; and thinnest point were measured preoperatively and 1, 3, 6, 9, 12, and 18 months postoperatively by Sirius Scheimpflug camera (CSO, Florence, Italy). The Sirius software displays a series of indices describing the morphology of the cornea, which are useful in the diagnosis of keratoconus and its follow-up. The steepest point of the anterior surface (AKf–Apical KeratometryFRONT) and the steepest point of the posterior surface (AKb–Apical KeratometryBACK) were evaluated.

Endothelial cell density was assessed using a non-contact specular microscope (CSO), and anterior segment optical coherence tomography (Spectral OCT SLO; OPKO/OTI, Toronto, Canada) was performed to evaluate the demarcation line depth.

**Surgical Procedure**

The enhanced riboflavin solution was instilled 30 minutes before UVA exposure, with one drop being instilled every 2 minutes thereafter. The enhanced riboflavin solution is an aqueous solution of 0.1% riboflavin containing trometamol (Tris-hydroxymethyl aminomethane) and sodium EDTA as excipients and epithelial penetration enhancers. To reduce the risk of UV exposure of retroirideal eye structures, miosis was induced with pilocarpine 1.0% 30 minutes before the procedure. Thirty minutes before UV radiation, the cornea was anesthetized with single-dose anesthetic eyedrops (oxybuprocaine hydrochloride 0.2%), one drop every 4 minutes, repeated four times. All treatments were performed by the UV source (CBM X-linker VEGA, CSO) with the power set at 3.0 mW/cm² and a circular spot diameter of 8.0 mm in an outpatient setting. The cornea was irradiated with UVA for 30 minutes. During the irradiation, a blepharostat was applied and a homogeneous level of the enhanced riboflavin solution was constantly maintained by adding one drop every 3 to 5 minutes. At the end of the procedure, all residue of the enhanced riboflavin solution was rinsed away with a sterile physiologic salt solution. Immediately postoperatively, the treated eye was medicated with one drop of single-dose antibiotic-steroid association.

The cornea was examined with a slit lamp to assess the integrity of the epithelial layer, and the patient was given a prescription for single-dose antibiotic, one drop three times a day and sodium hyaluronate 0.15% with amino acids, one drop three times a day for 20 days.

**Statistical Analysis**

A paired Student t test was used to compare pre- and 12- and 18-month postoperative data. P < .05 was considered significant.

**Results**

Table 1 shows refractive outcome. Corrected distance visual acuity improved throughout 18-month follow-up, with significant increases noted at 12 and 18 months (P < .05). Spherical equivalent refraction did not change significantly (P > .05) at 12 and 18 months after CXL; the same was true for sphere and cylinder (P > .05).

All topographic derived data (Table 2) showed progressive statistically significant worsening at 12- and 18-month follow-up (P < .05).

Table 3 shows corneal aberration changes. The root-mean-square coma and spherical aberration values did not change significantly 18 months after transepithelial CXL (P > .05), although they showed statistically significant worsening until 12-month follow-up (P < .05). Higher order aberrations showed significant worsening (P < .05) at 12 and 18 months after treatment.

The mean thinnest point (445 μm preoperatively; 446 μm at 1 and 3 months; 445 μm at 6 months, 452 μm at 9
months, 451 μm at 12 months, and 449 μm at 18 months postoperatively) did not change significantly (P>.05). Endothelial cell count did not show significant changes (P>.05) 18 months after treatment (preoperative mean density 2901±216 cells/mm² vs 18-month postoperative mean density 2874±217 cells/mm²). Optical coherence tomography analysis showed a dense linear area (demarcation line) in the corneal stroma (not present before treatment), on average 105 μm from the corneal epithelial layer. No postoperative complications were observed.

**DISCUSSION**

In this study, transepithelial CXL did not halt the progression of keratoconus in patients younger than 18. In the literature and clinical practice, the progression of keratoconus is generally defined as an increase in the maximum K value by 1.00 D over 6, 12, or 24 months.10,11,14 Our data show a statistically significant worsening of all K readings that demonstrates the progression of keratoconus.

In younger patients, the progression of keratoconus
is generally fast and the risk of requiring keratoplasty is high. Corneal collagen CXL with the use of riboflavin and UVA irradiation is the latest technique being proposed for the stabilization of ectatic disorders such as keratoconus. The basic principle of CXL is the induction of cross-links in the corneal stroma, producing a stiffening effect and increasing corneal strength and stability. Caporossi et al suggested that CXL is most indicated in young patients, especially those younger than 26 years with both clinical and instrumental documented evidence of keratoconus progression. The standard protocol includes, for safety purposes, a minimum corneal thickness of 400 μm and biomicroscopic evidence of clear cornea (absence of scars and accentuated Vogt striae) after epithelial removal, which is necessary for an effective CXL treatment. Recently, some authors reported a significant improvement in CDVA, corneal asymmetry, and aberrometric pattern after CXL in pediatric patients.

Transepithelial CXL is performed without the need for epithelial debridement. Baiocchi et al observed that the human corneal epithelium complete with basement membrane naturally absorbs 30% to 33% of UVA radiation and with substantial concentrations of riboflavin in the epithelium, it seems to block approximately 85% of the dose of UVA administered; the authors found that consequently this high epithelial absorption reduces the risk of endothelial toxicity of UVA, but gives rise to doubts about the efficacy of transepithelial passage. Moreover, they reported that stromal concentrations of riboflavin, one hundredth of those recorded in debrided corneal stroma, would greatly reduce production of singlet oxygen and limit cross-linking.

Some authors, however, reported that the improvements in keratometry provided by transepithelial CXL appeared comparable to those published for standard CXL. Koppen et al evaluated the effect of benzalkonium chloride–assisted transepithelial CXL in eyes with progressive keratoconus complete with basement membrane naturally absorbs 30% to 33% of UVA radiation and with substantial concentrations of riboflavin in the epithelium, it seems to block approximately 85% of the dose of UVA administered; the authors found that consequently this high epithelial absorption reduces the risk of endothelial toxicity of UVA, but gives rise to doubts about the efficacy of transepithelial passage. Moreover, they reported that stromal concentrations of riboflavin, one hundredth of those recorded in debrided corneal stroma, would greatly reduce production of singlet oxygen and limit cross-linking.

Our findings show that in pediatric patients 18 months after treatment, CDVA significantly improves in contrast to the worsening of topographic data. The corneal higher order aberrations evaluated demonstrated no change in coma and spherical aberration whereas higher order aberrations showed significant worsening at 18 months. Filippello et al suggested that anterior transepithelial CXL could be effective, at least in part, because the density of collagen fibers in corneal stroma is higher in the anterior portion, where most of the collagen cross-links develop. The depth of the demarcation line, whose origin is not yet well known and differs from the value reported with the epithelial debridement of approximately 300 μm, was measured to be approximately 105 μm from the epithelial surface, which could support this opinion.

The variability of our results appears high 18 months after transepithelial CXL. The small size sample, the interindividual differences, as well as the young age of the patients enrolled in this study may have an affect on the individual responses. Another possible limitation of the procedure could be the application of the blepharostat during the treatment; its removal in fact could avoid the riboflavin meniscus that could mask the cross-linking effect. However, the poor cooperation of the majority of our patients did not allow the use of a ring-shaped silicone container, the alternative to blepharostat, designed for riboflavin refill, which resists the pressure of the eyelid and allows minimum lid adjustments. However, as rapid disease progression is usually observed in pediatric patients affected by keratoconus, the significant improvement in CDVA appears meaningful. Additional follow-up will clarify the true progress of the aberrometric pattern. It is important to note that in patients affected by keratoconus, CDVA could improve simply because with repeated measurements the refraction could shift due to the subjective and objective effect of irregular astigmatism. However, in this series of patients, the same ophthalmologist (L.B.) performed all visual acuity measurements, thereby reducing the variability of the CDVA examination.

Transepithelial CXL is a safe and comfortable procedure for pediatric patients but its effectiveness remains doubtful. To date, this technique does not appear to stop the progression of keratoconus, and our findings, similar to those reported by Koppen et al although for a different patient age group and transepithelial CXL technique, seem to show a limited effect. Further studies, a larger sample of patients, and longer follow-up are needed to evaluate the true efficacy of transepithelial CXL. This procedure could be considered complementary to traditional CXL, especially for less cooperative patients for whom epithelial debridement may be distressing as well as for eyes with a minimum preoperative corneal thickness <400 μm.

**AUTHOR CONTRIBUTIONS**

Study concept and design (L.B.); data collection (G.P.); analysis and interpretation of data (L.B.); drafting of the manuscript (L.B.); critical revision of the manuscript (L.B., G.P.)
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