

Safety and Efficacy of Transepithelial Corneal Collagen Cross Linking in Keratoconic Eyes with Very Low Corneal Thickness

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Abstract

Aim of this Study: The aim of this study is to assess the safety and efficacy of transepithelial corneal collagen crosslinking as a treatment modality for Keratoconus with corneal thickness less than 400 μm .

Patients and Methods: This study was carried out on two hundred eyes having keratoconus with corneal thickness less than 400 μm . All eyes included in the study were treated with transepithelial corneal collagen cross linking with riboflavin and ultraviolet irradiation. All eyes included in the study had underwent complete ophthalmic examination with corneal topography and specular microscopy preoperatively and 1 day, 1 week, one month, six months and one year postoperatively.

Results: Transepithelial cross linking could enhance significant improvement in best corrected visual acuity in LogMAR (0.96 ± 0.14 preoperatively versus 0.61 ± 0.19 postoperatively, $p = 0.03$), spherical equivalence ($-7.8 \pm 2.4\text{D}$ preoperatively versus $4.6 \pm 1.9\text{D}$ postoperatively, $p = 0.03$) and mean keratometric readings ($51.5 \pm 2.6\text{D}$ preoperatively versus $48.6 \pm 3.1\text{D}$ postoperatively, $p = 0.04$). No complications were encountered during the study.

Conclusion: Transepithelial corneal collagen crosslinking is a safe and effective technique in keratoconic eyes with very low corneal thickness less than 400 μm .

Keywords: Transepithelial; Corneal Collagen Cross Linking; Keratoconus; Low Corneal Thickness

Introduction

keratoconus is a bilateral, non-inflammatory and progressive corneal ectasia that affects nearly one person in 2000. Progressive corneal thinning and progressive irregular astigmatism, corneal fibrosis and visual deterioration are challenging. In early stages, spectacles and soft/rigid contact lenses may be effective. However, other modalities of treatment are considered in more advanced cases [1].

Corneal collagen cross-linking (CXL) is a promising treatment that may slow or stop the progression of keratoconus. Corneal rigidity was proved to increase by about 70% after corneal exposure to riboflavin and irradiation with ultraviolet light. Riboflavin with photo activation can generate active oxygen and superoxide radicals leading to corneal stromal collagen aggregation [2,3]. Wollensak firstly reported the halting of the progression of 23 moderate to advanced keratoconus as long with visual and topographic improvements. Since then, it has been thoroughly explored. CXL has been shown to decrease the steepness of the cone and improve uncorrected (UDVA) and corrected (CDVA) distance visual acuities as well as subjective visual symptoms in some cases [4].

Classically described, CXL was preformed after removing the central 7 - 9 mm of the epithelium. However, postoperative pain and infection potentiality raised the need for an alternative. Transepithelial CXL could get over the former downsides while maintain similar efficacy. Different studies have been conducted comparing both modalities, with comparable outcomes [2,5,6].

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Over years, CXL was limited to cases with corneal thickness of at least 400 μm . This was due to the danger of the toxic effect of ultraviolet light on the corneal endothelium, crystalline lens, and the retina. This threshold had limited the performance of corneal stromal collagen crosslinking in eyes with advanced corneal ectasia. Also, unfortunately, many cases of keratoconus have corneas that are thinner than the 400 μm [2,7].

Aim of the Study

In this study, we aim at exploring how transepithelial CXL safe and effective for keratoconic eyes with thickness less than 400 μm . We believe that this study could highlight an important, yet missed, aspect in keratoconus treatment. In addition, in-depth exploration of safety and efficacy of CXL in different circumstances are critical for such promising modality.

Patients and Methods

All patients with keratoconus with corneal thickness less than 400 μm , confirmed with Pentacam, in El-Hikma Eye Center were evaluated. To be enrolled, no ocular pathology other than keratoconus was considered so, eyes having opaque cornea, history of herpetic corneal affection, history of any ocular surgery, active ocular inflammation or infection, autoimmune disease, diabetes, pregnancy, and lactation were excluded from the study.

From January 2016 to January 2018, 180 patients were eligible for the study. They were counselled for enrollment in the study. Enrolled patients signed a well-informed consent and underwent through clinical examination including UCVA, BCVA, IOP and fundus examination. Optical pachymetry and corneal topography were performed before as well as day 1, week 1, 1 month, 6 months and 1 year after the procedure. Specular microscopy was done preoperatively, 6 months and 12 months postoperatively.

All study procedures were carried out in accordance with declaration of Helsinki and were approved by the institutional ethical committee.

Surgical techniques

Transepithelial CXL with riboflavin and ultraviolet irradiation was performed in the operative theatre under complete sterile conditions. All eyes had received topical anesthesia with benoxinate hydrochloride 0.4% (Benox[®]) eye drops just before the procedure. Pilocarpine 2% eye drops were instilled 30 minutes before the procedure to induce pupillary constriction during ultraviolet irradiation to protect the lens and retina from the toxic effect of ultraviolet irradiation. An eyelid speculum was used to retract the eyelids and provide complete corneal exposure during riboflavin installation and ultraviolet irradiation. Riboflavin hypotonic solution 0.25% containing benzalkonium chloride to enhance epithelial penetration (Medio-Haus, Medizinprodukte, GmbH) was instilled onto the cornea without epithelial debridement for 30 minutes (one drop per minute), then ultraviolet irradiation was delivered.

The irradiation level was calibrated to 9.0 mW/cm^2 which is equal to 5.4 J/cm^2 surface area at the specified working distance. Ultraviolet irradiation was applied to the central 9 mm of the cornea for 10 minutes (as the usual safe standard protocol for laser application) and riboflavin solution was instilled every 2 minutes during irradiation. At the end of the procedure, the eye was washed with balanced salt solution and a therapeutic soft contact lens was applied.

The postoperative regimen for all eyes was a combination of moxifloxacin 0.5% eye drops instilled q.i.d, prednisolone acetate 1% eye drops q.i.d and lubricant eye drops instilled six times/day for one week then the dose is gradually tapered over the next 3 weeks. Follow up visits were arranged at 1 day, 1 week, 1 month, 3 months, 6 months and 12 months after the procedure. At each visit, UCVA, BCVA, SE and corneal topography was performed. Specular microscopy was done at 6 and 12 months postoperative. The 12-months' outcomes were the target to report and discuss.

Statistical analysis was performed with IBM SPSS for Windows (Version 22.0, Armonk, NY: IBM Corp). Categorical data was expressed as numbers and percentage, while numerical variables were expressed as mean \pm SD. Normality of data variables were checked. For normally distributed data, paired student t-test was used to compare the means pre- and postoperatively. Chi-square test was used to compare the categorical variables between both groups.

Results

Two-hundred eyes of 170 patients were enrolled in our study, including 90 males and 80 females. The age of patients range from 20 to 28 years with the mean age was 24.3 ± 2.1 years.

Regarding safety, no intra- or postoperative complications were detected. for both groups (no persistent corneal ulcer no infection no cataract development no retinal phototoxicity no significant decrease in endothelial density no IOP changes). Complete epithelial healing had occurred for all eyes in the first postoperative day. The mean preoperative IOP level was 15.2 ± 2.54 mmHg 15.4 ± 2.51 mmHg preoperatively and 12 months after the procedure ($p = 0.5$). No IOP spikes (defined as IOP ≥ 21 mm hg) were detected at any visit.

Regarding visual and refractive outcomes, transepithelial CXL could significantly improve both BCVA and SE, which was maintained for 12 months postoperatively. BCVA (LogMAR) significantly improved from 0.96 ± 0.14 preoperatively to 0.61 ± 0.19 at 1 year after the procedure ($p = 0.03$). SE has significantly decreased from -7.8 ± 2.4 D preoperatively to -4.6 ± 1.9 at 12 months after the procedure ($p = 0.03$).

Regarding topographic outcomes, mean K has significantly been reduced from 51.5 ± 2.6 D preoperatively to 48.6 ± 3.1 D at 1 year after the procedure ($p = 0.04$). Steepest K has significantly been reduced from 53.5 ± 2.5 D preoperatively to 49.8 ± 2.4 D at 1 year after the procedure ($p = 0.039$). Specular microscopy values didn't show significant difference before and after the CXL (3050 ± 125 and 3025 ± 120 cells/mm² respectively, $p = 0.4$).

No significant changes were detected in endothelial cell density.

No significant changes were detected in central corneal thickness. The mean preoperative central corneal thickness was 381 ± 16 microns and the mean postoperative central corneal thickness at 12 months postoperative was 379 ± 14 microns (P value 0.31).

The 12-months' outcomes were the target to report and discuss.

Discussion

Collagen crosslinking is a promising treatment to halt the progression of keratoconus as well as different forms of corneal ectasia. In addition, visual and topographic improvements are reported. Classically, epithelium is removed from central 7 - 9 mm that may result in infection after the procedure [2,3]. In transepithelial CXL, the corneal epithelium is not removed with a reduced risk for infection as well as better patient comfort and faster visual recovery. Another potential advantage for maintenance of the epithelium is to decrease corneal thinning during the CXL procedure and allow treatment of more severe disease in cases in which corneal thickness may otherwise preclude treatment [8-10].

Conventional technique was limited to corneas with thickness of at least 400 μ m. While this is justified with the potential ultraviolet irradiation on corneal endothelium, crystalline lens, and other intraocular structures, this braked the CXL benefits to cover the whole disease spectrum. It was found that ultraviolet irradiation of 0.37 mW/cm² is cytotoxic to corneal endothelial cells. The absorption coefficient of the cornea is 70 cm⁻¹ and the desired surface irradiation is 3.0 mW/cm² so, the toxic level of ultraviolet irradiation which is 0.37 mW/cm² will penetrate the cornea to a depth of 300 μ m while at a depth of 400 μ m, the irradiation level will be 0.18 mW/cm² which is only half of the toxic damaging irradiation dose. Therefore, corneal thickness of 400 μ m is considered to be protective for the corneal endothelium and the intraocular structures from the toxic effects of ultraviolet irradiation [5,11,12].

In addition, postoperative significant decrease in endothelial cell count was encountered with corneal stromal collagen crosslinking done for corneas with pachymetry less than 400 μ m. The previous findings had limited the use of corneal stromal collagen crosslinking in corneas with pachymetry less than 400 μ m and so, the technique of iatrogenic corneal swelling before ultraviolet irradiation had been developed to benefit from corneal stromal collagen crosslinking in thin corneas [13].

In our study, we aimed at exploring safety and efficacy of trans-epithelial CXL in such corneas. In this study, the final outcomes at 12 months were analyzed. Including 200 eyes, this study is among the largest prospectively analyzed transepithelial treatment groups to date. In our study, transepithelial CXL showed significant improvements of BCVA, SE and mean K readings, that were maintained at 1 year follow up. Moreover, no IOP spikes nor significant changes of IOP were encountered with the procedure.

Literature review for transepithelial CXL efficacy shows variable results. Additionally, different techniques such as riboflavin formulations and adjunctive agents were applied. In agreement with our results, Filippello, *et al.* used isotonic riboflavin with dextran, EDTA, and trometamol and found statistically significant improvement in UDVA, CDVA, and all topographic-derived values [14]. Stojanovic, *et al.* used hypotonic riboflavin without dextran, increased the concentration of riboflavin to 0.5%, used BAK, and used mechanical disruption of the superficial epithelium. They report a statistically significant improvement in the UDVA, CDVA, and maximum K value [9].

On the otherside, Caporossi, *et al.* reported initial improvement in CDVA that returned to baseline and worsening of the maximum K value at 24 months of follow-up [15]. Koppen, *et al.* found a significant improvement in CDVA at 12 months but with a statistically significant worsening of the maximum K value [11]. Salman used isotonic riboflavin with dextran, EDTA, BAK, and trometamol and found a statistically significant improvement in UDVA and the maximum K value in a pediatric population [16].

A limitation of this study is the lack of a control group or treatment group with epithelial removal and/or corneas of at least 400 μm to emphasize the comparison. Moreover, longer follow-up is essential to assert the stability of gained benefits. Extending the spectrum of CXL to include other ectatic corneal conditions can provide in-depth understanding and delineation for safety and efficacy margins for CXL.

Conclusion

Trans-epithelial corneal CXL is a safe and effective technique in keratoconic eyes with pachymetry less than 400 μm . Concerning safety, no complications were encountered during our study. Also, no toxic effect was noted on corneal endothelial cells by specular microscopy. Concerning efficacy, transepithelial corneal stromal collagen crosslinking in our study had performed statistically significant improvement in visual acuity, SE and mean keratometric readings.

Conflict of Interest

None.

Funding

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