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Full Length Research Paper

Comparison between Corneal Collagen Cross-Linking with Epithelial Removal and Transepithelial for Management of Progressive Keratoconus

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This study aim to compare the efficacy and safety of corneal cross linking (CXL) with and without removal of epithelium for treatment of progressive keratoconus. One eye of 16 patients with bilateral progressive keratoconus was randomly treated by corneal cross linking (CXL) with epithelium removal (group I) while the fellow eye underwent corneal cross linking (CXL) without epithelium removal (Transepithelial CXL group II). Visual acuity, refraction, corneal topography was evaluated at after 3, 6, and 12 months. In both groups uncorrected and corrected distance visual acuity improved significantly after treatment. There was a significant improvement in topographic outcomes, spherical equivalent and astigmatism in both groups at one year postoperatively. Postoperative pain was significantly less and shorter in duration in group II. The most significant difference between epithelium removal CXL and intact epithelium CXL (Transepithelial CXL) was short recovery as regard pain and epithelium healing. Both techniques were equally safe and effective in stabilization of keratoconus.

Keywords: Corneal Collagen Cross-Linking, CXL, Transepithial, Keratoconus.

INTRODUCTION

Keratoconus is a degenerative, non inflammatory disease of the cornea with onset generally at puberty. It is progressive in 20% of cases and can be treated by lamellar or perforating keratoplasty. Its incidence in the general population is reported to be about 1/2000. It characterize by stromal thinning and cone shaped steepening of the cornea that result in irregular astigmatism and refractive myopia (Rabinowitz. 1998). Incidences of 1/600-1/420 seem more in keeping with current diagnostic capacity. Changes in corneal collagen structure (Cheng et al., 2001), organization and intercellular matrix (Kenney et al., 1997), as well as apoptosis (Wilson 1998) and necrosis of keratinocytes prevalently or exclusively involving the central anterior stroma and the Bowmann lamina, are documented in the literature (Zaldaway et al.,1992).

Corneal collagen cross-linking (CXL) with riboflavin and ultraviolet-A (UVA) is a new technique of corneal tissue strengthening by using riboflavin as a photosensitizer and UVA to increase the formation of intra and interfibrillar covalent bonds by photosensitized oxidation. The major indication for the use of CXL is to inhibit the progression of corneal ectasias, such as keratoconus and pellucid marginal degeneration. (Spoerl et al., 1998; Wollensak et al., 2003; Kohlhaas et al., 2005; Caporossi et al., 2006; Mazzottaet al., 2007).

Standard CXL with epithieal removal, however, may lead to serious complications like postoperative infection (Zamora and Males, 2009): (stromal haze (Mazzotta et al., 2007), and corneal melting (Eberwein et al., 2008) Hence, a CXL technique that does not require epithelial removal may be preferable to increase the safety of the procedure. For this reason, and for the assumed increase in patient comfort, transepithelial CXL was proposed(Boxer et al., 2010) Thereafter, several approaches have been pursued to solve the major limitation of the transepithieal CXL—an inadequate and inhomogeneous riboflavin penetration (Baiocchi et al., 2009). These include partial grid-like pattern deepithelialization (Samaras et al., 2009), the replacement of the isotonic by hypotonic riboflavin solution (Raiskup et al., 2011), and chemical enhancers such as benzalkonium chloride (BAC) (Filippello et al., 2012), trometamol and ethylenediaminetetraacetic acid

(EDTA) (Hayes et al., 2008) tetracaine (Coskunseven et al., 2009) and ethanol (Samaras et al., 2009).

The aim of this study was to compare epithelium removal and transepithieal CXL by comparing their safety and efficacy in eyes with progressive keratoconus.

PATIENTS AND METHODS

This prospective interventional case series comprised thirty two eyes of sixteen patients. Inclusion criteria were moderate progressive keratoconus diagnosed by corneal topography (Progressive change of corneal thickness and change of posterior surface parameter) with clear central cornea, a BSCVA of 20/30 or better, minimum central corneal thickness of 400 µm and steepest keratometry ≤ 51 D. Exclusion criteria were as follows: (1) history of herpes virus keratitis; (2) severe dry eye; (3) concurrent corneal infections; (4) previous ocular surgery; and (5) hard contact lens wear ≤4 weeks before the baseline examination. Preoperative examinations included UCVA, BSCVA, manifest refraction, slit lamp biomicroscopy, dilated fundus examination, corneal topography and ultrasonic pachymetry.

Sixteen patients (Thirty two eyes) with bilateral progressive keratoconus was randomly managed by corneal cross linking (CXL) one eye of 16 patients treated with epithelium removal (group I) while the fellow eye underwent corneal cross linking (CXL) without epithelium removal (Transepithieal CXL group II).

Surgical technique

Cross-linking with removal of the epithelium (Group I)

Abrasion of the corneal epithelium out to 8 mm is performed under topical anesthesia. Prior to the treatment itself, ultrasound pachymetry should be performed at the thinnest point of the deepithelialized cornea, to ensure a minimal corneal thickness of 400 µm riboflavin 0.1% drops were applied every 3 minutes for 30 minutes. we performed slit-lamp inspection, using blue light for riboflavin shielding, followed by irradiation with the UV-X Corneal Cross linking System (Iroc Medical, Zurich, Switzerland; distributed by Peschke GmbH, Nuremberg, Germany). For the 30-minute treatment, the parameters were: 370 nm, 3mW/cm2, 5.4 j/ cm2.

Transepithelial CXL (Group II)

Several substances have been used to loosen the tight junctions of the epithelial layer and thus increase the penetration of riboflavin. One is a riboflavin solution containing benzalkonium chloride (BAK), the most commonly used preservative in ophthalmic medications. two drops of proparacaine and two drops of hypotonic 0.5% aqueous riboflavin solution without dextran (Vitamin B2; Streuli, Uznach, Switzerland) were applied alternating every 30 seconds until the riboflavin saturation was verified by the slit-lamp inspection of the cornea and by determination of presence of riboflavin flare in the anterior chamber followed by irradiation with the UV-X Corneal Cross linking System (Iroc Medical, Zurich, Switzerland; distributed by Peschke GmbH, Nuremberg, Germany). For the 30-minute treatment, the parameters were: 370 nm, 3mW/cm2, 5.4 j/ cm2.

In both groups balanced saline solution was applied, along with ofloxacin 0.3% and one drop of diclofenac ophthalmic eye drop and a bandage contact lens. Postoperative medications include oflaxacin 0.3% four times/daily, fluorometholone four times/daily and lubricating eye drops every two hours.

Patients were reviewed on the first and seventh postoperative days, and subsequently at 4 weeks, 3 months, 6 months and one year. At each examination, unaided and aided visual acuity was determined, and the cornea was examined by the slit lamp. Autorefractometry as well as manifest subjective refraction were performed; Post operative corneal topography was performed at the 3 months 6 month and one year.

RESULTS

This study comprised thirty two eyes of 16 patients 38% patients were male and 62 % of patients were female (Figure 1) the mean age of study patients was 19(range 16 to 36 years old) (Table 1). All of the 16 patients included in the study were available for evaluation.

The mean UCVA in group I improved from 0.3 ± 0.14 preoperatively to 0.6 ± 0.12 at 12 months (P=0.055). The improvement was statistically significant. In group II the mean UCVA improved from 0.3 ± 0.15 preoperatively to 0.6 ± 0.13 at 12 months (P=0.057). The improvement was statistically significant.

The mean BSCVA in group I improved from 0.95 ± 0.16 preoperatively to 1.0 ± 0.12at 12 months (P0.005). The improvement was statistically significant at 12 months. In group II the mean BSCVA improved from 0.95 ± 0.15 preoperatively to 1.1 ± 0.11at 12 months (P0.045). The improvement was statistically significant at 12 months.

None of the eyes lost lines of BCVA, while 40% of the eyes in group I and 45% of the eyes in group II gained 1 or more lines.

Manifest refraction spherical equivalent

The mean spherical equivalent (SE) refraction in group I

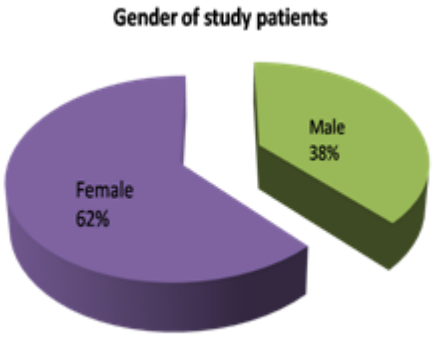


Figure 1. Gender

Table 1. Age of Patients.

Mean	**19 yrs**
Minimum	**16 yrs**
Maximum	**36 yrs**

decreased significantly from -3.25 ± 2.21 D preoperatively to -2.55 ± 1.59 D (P=0.013). The changes in spherical equivalent (SE) were statistically significant at 12 months. In group II the mean spherical equivalent (SE) refraction decreased significantly from -3.55 ± 2.60 D preoperatively to -2.75 ± 1.62 D (P=0.015) . The changes in spherical equivalent (SE) were statistically significant at 12 months.

Manifest refraction cylinder

The mean manifest refraction cylinder in group I decreased from -1.55 ± 1.67 D preoperatively to -1.00 ± 1.5 D (P=0.015) at 12 months (Table 2). In group II the changes in manifest refraction cylinder were significant at 12 months. The mean manifest refraction cylinder decreased from -1.50 ± 1.61 D preoperatively to -.95 ± 1.55 D (P=0.020) at 12 months. The changes in manifest refraction cylinder were significant at 12 months (Table 2).

The mean corneal thickness was 445.0 ± 33.6 microns in group I compared to 450 ± 42.4 microns in the group II. Postoperatively The mean corneal thickness was 450.0 ± 39.3 microns in group I compared to 455 ± 47.2 microns in the group II(P=0.055) at 12 months. The changes were not significant at 12 months (Table 2).

Keratometry

In group I the mean average K-value decreased from 45.04 ± 2.17 D preoperatively to 43.15 ± 1.72 D at 12 months (P=0.045). The maximum K-value decreased from 51.0 ± 2.93 D preoperatively to 47.15 ± 1.81 D at 12 months (P=0.040). The astigmatic K-value decreased from 2.22 ± 0.97 D preoperatively to 1.89 ± 0.72 D at 12 months (P=0.045). The changes in all k-value were significant.

In group II the mean average K-value decreased from 45.26 ± 2.19 D preoperatively to 43.21 ± 1.77 D at 12 months (P=0.044). The maximum K-value decreased from 51.0 ± 2.96 D preoperatively to 47.90 ± 1.84 D at 12 months (P=0.040). The astigmatic K-value decreased from 2.72 ± 0.99 D preoperatively to 1.92 ± 0.92 D at 12 months (P=0.045). The changes in all k-value were significant (Table3).

No significant difference was found in visual acuity (UCVA and BCVA), refraction measurements, astigmatism and keratometry between the two groups at any follow-up point.

Evaluation of pain

There was no significant difference in the pain however, the pain was less and had a shorter duration due to rabid healing of epithelium in group II (Table 4).

No significant differences were found in the measurements of topography features or wavefront aberrations between the two groups at any follow-up point. No postoperative complications were recorded. (Figure 2).

DISCUSSION

Wollensak et al. 2003 described the standard CXL-protocol by including mechanical removal of the corneal epithelium in a diameter of 7 mm and use of 0.1% isotonic riboflavin solution in 20% dextran as a photosensitizer. This protocol proved to be effective in the stabilization of keratoconus and improved the

Table 2. Shows UCVA, BCVA, Spherical equivalent, Astigmatism and Central corneal thickness preoperative and postoperative.

Preoperative	***UNCVA**	***BCVA**	***Sph. Eq**	***Astigma.**	***CCT(um)**
Group I	0.3	0.95	- 3.25D	-1.55D	445
Group II	0.3	0.95	- 3.55D	-1.50D	450
Postoperative	*UNCVA	*BCVA	*Sph. Eq	*Astigma	*CCT(um)
Group I	0.6	1.0	- 2.55D	-1.00D	450
Group II	0.6	1.1	-2.75D	-0.95D	455

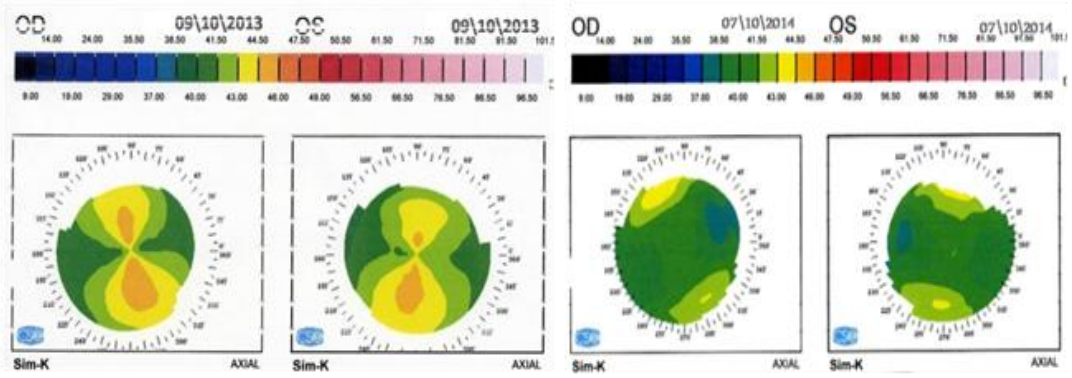
*UNCVA=Uncorrected visual acuity *BCVA=Best corrected visual acuity *Sph. Eq=Spherical equivalent. *Astigma=Astigmatism
*CCT(um)=Central corneal thickens

Table 3. Represent K reading as regard the mean K, the maximum K and astigmatism by K in dioptre(D)

Preoperative	**K .READING**		
	Mean k (D)	**Max.k (D)**	**Astigm.K (D)**
Group I	45.04	51.0	2.22
Group II	45.26	51.0	2.72
Postoperative	Mean k (D)	Max.k (D)	Astigm.K (D)
Group I	43.15	47.15	1.89
Group II	43.21	47.90	1.92

Table 4. Scale for pain after CXL in group I and group II

Intensity of the pain	**Description of the pain**	**Number of eyes**	
		group I	**group I I**
No pain	No pain or discomfort	0	0
Very little	Discomfort (foreign body sensation, dry eye)	2	1
Little	Mild pain	4	2
Moderate pain	Intermediate, released by closing the eyes or by artificial tears	5	5
Much Severe pain	relieved by use of oral analgesics	3	5
Very much severe pain	must use oral analgesics and local anesthetic drops	2	3



Preoperative Postoperative

Figure 2. Shows preoperative and one year postoperative topography for one of study patient (RT eye CXL with epithelium removal LT eye with Transepithelial CXL).

refractive and topographic features in most cases.

Transepithelial CXL was introduced in 2010 with the rationale of eliminating the complications related to deepithelialization; such as decreasing postoperative pain, making CXL possible on thin corneas and in less cooperative patients, increasing vision during the initial postoperative period, and lowering requirements for a sterile environment (Boxer et al., 2010).

The results of this study showed visual improvement (UCVA and BCVA) and no progression of keratoconus after the treatment and throughout the 12-month follow-up period in both groups. Also there was improvement of topographic feature (steep MaxK decreased from 51.0 D to 47.15 D in group I and to 47.90 D in group II), No significant difference between the groups was observed at any point. Wollensak and Redl found a significant increase in corneal rigidity after Transepithelial CXL. (Wollensak and Redl, 2008). Filippello et al. 2012 showed stabilization of keratoconus with improvement of all visual, topographic (steep Sim decreased from 51.02 D to 48.05 D), and aberrometric parameters.

In this study the pain score reported by the two groups showed little significant difference the pain was less and shorter in course in group II. Pain or discomfort may be attributed to damage of anterior stromal nerve fibers caused by toxic effects of CXL (Bakke et al., 2009). Corneal denervation may lead to dry eye-related problems due to the decreased blinking rate and increased tear evaporation and exposure of corneal surface. However, Kontadakis et al. 2013 reported no significant change in Schirmer's test and tear film break-up time after 1 month post CXL. Raiskup et al. 2009 found pathologic staining with fluorescent and Rose Bengal, as well as tear film height at 3 and 6 months after CXL, to be comparable to preoperative measurements. These findings revealed that dry eye does not seem to be a significant complication after CXL in patients with keratoconus. No patient complained about symptoms of dry eye after 4weeks postoperatively.

No postoperative complications were recorded in this study. In a retrospective study of 163 eyes of 127 patients with stage 1-3 keratoconus, 8.6% developed a clinically significant haze after 1-year follow-up (Raiskup et al., 2009). No long follow up period more than one year for this study.

Mazzotta et al. 2007 have also presented two cases of post-operative corneal haze among a cohort of 40 eyes of 39 keratoconus patients. In two cases, stromal haze appeared 2-3 months post-operatively and was resistant to topical steroid treatment. Repeated examination of the pre-operative confocal studies of these patients revealed a reticular pattern of stromal microstriae that may imply advanced keratoconus. However, even with the haze, BSCVA in these patients was improved. Additional case reports describe diffuse lamellar keratitis (Kymionis et al., 2007) and a reactivation of herpetic keratitis (Kymionis et al., 2007) following CXL. In both cases, prompt diagnosis and treatment resulted in favorable resolution. In another report, Koppen et al. 2009 reported four cases of keratitis and corneal scarring from a total of 117 eyes treated with CXL where patients experienced delayed (more than 24 hr) symptoms and signs of inflammation.

CONCLUSION

Corneal cross linking mediated by riboflavin and UVA either with epithelium removal or transepithieal appears to be a safe and efficacious procedure in management of progressive keratoconus. CXL reduces spherical equivalent refraction and refractive cylinder in eyes with progressive irregular astigmatism due to keratoconus.

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