Original Article

Evaluation of the outcomes of corneal collagen cross-linking in progressive keratoconic eyes

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Abstract

Background: Corneal collagen cross-linking (CXL) is gaining popularity as a treatment in arresting the progression of keratoconus. It is a relatively new therapy using ultraviolet-A (UVA) with a photosensitizer to increase corneal stiffness. The purpose of this study was to evaluate visual, keratometric and topographic outcomes after corneal CXL in progressive keratoconic eyes.

Materials and Methods: In this prospective nonrandomized clinical study, 140 eyes of 110 patients with progressive keratoconus were treated by combined riboflavin/UVA CXL. Mean sphere, mean cylinder uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), manifest refractive spherical equivalent, corneal topography, pachymetry, and endothelial cell morphology were examined preoperatively and 12–24 months postoperatively.

Results: The preoperative mean sphere was −3.33 ± 3.13 diopter (D) and decreased to −3.09 ± 3.09 D ($P = 0.007$). The preoperative mean cylinder was −4.05 ± 2.29 D and changed to −3.79 ± 2.23 D ($P = 0.011$). UDVA changed from 0.95 ± 0.64 logarithm of the minimum angle of resolution (logMAR) to 0.85 ± 0.59 logMAR ($P = 0.003$). Thirty-five eyes (25%) gained one or more lines of preoperative UDVA, 87 eyes (62.1%) did not change and 18 eyes (12.8%) lost one or more lines of the preoperative UDVA. CDVA in 80% of the patients remained stable (no lines lost). Statistical analysis of keratometry, pachymetry, and endothelial cell count did not show the significant difference after surgery.

Conclusion: Our study showed improvement in visual and refractive results of the corneal CXL and confirmed that CXL is the safe and effective procedure.

Key Words: Collagen cross-linking, progressive keratoconus, ultraviolet irradiation

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INTRODUCTION

Keratoconus is a progressive, noninflammatory corneal disorder due to the weakness of the corneal stromal structure that can lead to progressive protrusion of the cornea.[1,2] Because of the young age of onset; this condition often has a significant negative effect on quality of life.[3] In patients with keratoconus visual acuity can decrease because of severe myopia, corneal irregular astigmatism and corneal scaring.[4]

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Common techniques for visual acuity improving in these patients include spectacle, rigid gas-permeable contact lenses, intracorneal ring segments implantation,[5-7] and lamellar or penetrating keratoplasty in the most severe cases. These techniques just correct the refractive errors of keratoconic patients, but do not change the underlying pathophysiological mechanism and cannot stop the progression of the disease.[8]

Recently, it has been shown that the progression of the disorder can be halted by corneal collagen cross-linking (CXL).[8,9] CXL increases corneal biomechanical rigidity by the combined action of a photosensitizing substance (riboflavin) and ultraviolet-A (UVA) light.[10-14] By selection of the spatial wavelength of the UV light the treatment is limited in corneal stromal tissue and exposure to the surrounding structures is minimized.[15-18]

The riboflavin irradiated with UVA light create free radicals to induce new chemical bands through the corneal stroma that improve the biochemical stability of the corneal tissue.[15] The stiffening effect is concentrated in anterior 200–300 μm depth of the cornea due to the high absorption of UV light in this area.[16]

Previous clinical studies on CXL have reported that CXL is an effective and safe method to stabilize keratoconus.[10,17,18] However, to the best of our knowledge few studies have investigated the stability of visual, refractive, and topographic outcomes of the cornea after CXL during 12–24 months follow-up. To address this issue and very limited clinical study in our population, we conducted this study in eyes with progressive keratoconus.

MATERIALS AND METHODS

In this prospective clinical study, 140 eyes of 110 patients (61 male and 49 female) with progressive keratoconus were treated by combined riboflavin-UVA CXL.

Inclusion criteria in this study were corneal ectasia and corneal thickness of ≥400 μm at the thinnest point. All procedures were performed by a single surgeon. Informed consent was obtained from all subjects. Exclusion criteria included pregnancy, a history of herpetic keratitis, severe dry eye, concurrent corneal infections, concomitant autoimmune diseases, and any previous corneal surgery such as corneal ring insertion. Furthermore, patients with diabetes mellitus, patients with poor compliance, and patients with corneal transplantation were excluded.

The criteria for progression of keratoconus were at least one of the following:

An increasing in maximum keratometry (by 1 D or more) on serial corneal topography, changing in refractive error (decreasing minus sphere by ≥0.50 D and minus cylinder by ≥1.0 D), deteriorating visual acuity (loss of corrected distance visual acuity [CDVA] two lines or more).

These criteria were chosen by the Food and Drug Administration (FDA) for their clinical trial on keratoconus. Preoperative corneal thickness was at least 400 μm. Preoperative examinations included slit lamp examination, fundoscopic examination, and measurement of uncorrected distance visual acuity (UDVA), CDVA, manifest refraction, corneal topography (Oculus, Pentacam, Germany), pachymetry and endothelial cell morphology (Specular Microscope, Tomey Corp., Japan). The Institutional Ethics Committee approved the study, and all of the patients provided written informed consent.

Surgical technique

Collagen CXL was performed in the operating room under sterile conditions and topical anesthesia (tetracaine 1% eye drops). The central 6–8 mm of the corneal epithelium was then removed manually. This was done to ensure penetration of riboflavin in the corneal stroma. Photosensitive riboflavin solution 1% was repeatedly instilled every 5 min for 30 min until the cornea was completely soaked and then the cornea was irradiated with UVA light every 5 min for 30 min. UVA irradiation was performed using a commercially available UVA system (UVX, Peschke Meditrade, Switzerland). Before treatment, the correct irradiance density (3 mw/cm^2) and dose (5.4 J/cm^2) were checked using UVA meter (LaserMate-Q, LASER 2000, Germany). During this procedure, riboflavin solution was applied every 5 min to saturate the cornea, and balanced salt solution (BSS) was applied every 3 min to moisten the cornea. After treatment, the ocular surface was washed with BSS solution and one drop of topical antibiotic was instilled. At the end of surgery, a soft bandage contact lens was placed for at least 5–6 days (until epithelium healing was completed).

Postoperative regimen included ciprofloxacin (Ciplex) 0.3% eye drops 4–6 times daily for 1-week, betamethasone 1% eye drops 4–6 times daily for 3–4 weeks and artificial tear drop for approximately 1-month.

A postoperative follow-up examination was done between 12 and 24 months after CXL (mean duration

was 13.51 ± 5.42 months). Postoperative progression of keratoconus (safety and effectiveness of the CXL) was assessed by measuring the UDVA, CDVA, manifest cylinder/sphere, keratometry, pachymetry, and endothelial morphology (cell density, coefficient of variation [CV] and percentage of hexagonal cells).

The postoperative progression of the keratoconus was evaluated based on FDA clinical trial criteria for keratoconus over the entire follow-up period.

Statistical analysis

Statistical analysis was performed using SPSS software (version 18, SPSS Inc., IL, USA). All measured parameters were analyzed pre- and post-operatively. The data was analyzed using the paired *t*-test for each parameter. Data is expressed as the mean ± standard deviation (SD) and mean changes from pre- to post-operative. $P < 0.05$ is considered to be statistically significant.

RESULTS

In this study, 140 keratoconic eyes of 110 patients (61 male, 49 female) were evaluated. The mean age of the participants was 22.97 ± 4.51 years (range: 14–37 years). Tables 1 and 2 show the preoperative and postoperative studied parameters in all patients.

Visual acuity

Visual acuity was measured using the decimal equivalent and transformed into the logarithm of the minimum angle of resolution (logMAR) for further statistical analysis as recommended by Holladay.[19] Visual acuity data is expressed as logMAR ± SD (Snellen value).

The preoperative mean UDVA was 0.95 ± 0.64 logMAR and changed to 0.85 ± 0.59 logMAR. This change was statistically significant ($P = 0.003$). Thirty-five eyes (25%) gained one or more lines of the preoperative UDVA, 87 eyes (62.1%) maintained the preoperative UDVA, and 18 eyes (12.8%) lost lines of the preoperative UDVA.

The preoperative mean CDVA was 0.26 ± 0.24 logMAR and changed to 0.25 ± 0.21 logMAR. There was no statistically significant change from the preoperative values ($P = 0.282$). Postoperatively CDVA improved at least one line in 35 eyes (25%), 77 eyes (55%) had no change in CDVA, and 28 eyes (20%) experienced lost one to three lines of CDVA.

Refractive error

The preoperative mean sphere was –3.33 ± 3.13 D and decreased significantly to –3.09 ± 3.09 D ($P = 0.007$). The preoperative mean cylinder was –4.05 ± 2.29 D and changed to –3.79 ± 2.23 D. These changes were statistically significant ($P = 0.011$) [Table 1].

Postoperatively, manifest sphere improved in 54 eyes (38.6%) by ≥0.5 D, and remained stable in 58 eyes (41.4%). Twenty-eight eyes (20%) showed a progression of ≥0.5 D in the manifest sphere over the follow-up period. The manifest cylinder improved by ≥1.0 D in 27 eyes (19.3%), no changed in 96 eyes (68.6%) and decreased by ≥1.0 D in 17 eyes (12.1%).

Keratometry

Table 1 shows postoperatively, there were not statistically significant changes in keratometry (*K*) values (K_{min}, $K_{average}$ and K_{max}) compared to preoperative ($P > 0.05$ for all comparisons).

The mean preoperative and postoperative K_{min} was 45.32 ± 3.27 D and 45.32 ± 3.14 D, respectively. The mean change was –0.007 ± 1.05 D that was not statistically significant ($P = 0.936$).

The mean preoperative K_{max} of the apex of keratoconus was 49.11 ± 4.11 D and this value remained unchanged and was 49.10 ± 3.88 D postoperatively ($P = 0.943$).

Table 1: Preoperative and postoperative visual and refractive parameters

Parameter	Mean±SD (range)		Change (post-pre)	*P*
	Preoperative	Postoperative		
UDVA (LogMAR)	0.95±0.64 (2.0–0.0)	0.85±0.59 (2.0-0.0)		0.003
CDVA (LogMAR)	0.26±0.24 (1.0 - −0.1)	0.25±0.21 (1.0 - −0.2)		0.282
Mean sphere (D)	−3.33±3.13 (−17.00-0.50)	−3.09±3.09 (−14.50-1.75)	0.24±1.04	0.007
Mean cylinder (D)	−4.05±2.29 (−10.00-0.00)	−3.79±2.23 (−9.00-0.00)	0.29±1.35	0.011
MRSE (D)	−5.35±3.53 (−19.00 - −0.50)	−4.99±3.43 (−17.50-0.00)	0.38±1.33	0.001
$K_{average}$ (D)	47.03±3.33 (39.3-59.8)	47.10±3.36 (39.7-58.3)	0.071±0.87	0.338
K_{max} (D)	49.11±4.11 (39.9-62.3)	49.10±3.88 (40.6-62.0)	−0.006±1.08	0.943
K_{min} (D)	45.32±3.27 (38-59.5)	45.32±3.14 (38.4-55.4)	−0.007±1.05	0.936
Pachymetry (μm)	471.39±41.53 (427-557)	469.09±35.58 (424-540)	−2.35±27.67	0.343

UDVA: Uncorrected distance visual acuity, CDVA: Corrected distance visual acuity, D: Diopters, MRSE: Manifest refractive spherical equivalent, K: Keratometry, LogMAR: Logarithm of the minimum angle of resolution, SD: Standard deviation

Table 2: Endothelial characteristics of cornea pre- and post-operative

Parameter	Mean±SD (range)		*P*
	Preoperative	Postoperative	
ECD (cells/mm²)	2743.43±233.54 (2290-3344)	2703.49±232.09 (2124-3288)	0.967
CV (%)	38.77±10.33 (25-86)	39.46±9.96 (25-83)	0.671
Hexagons (%)	53.90±11.78 (11-77)	53.34±9.05 (22-73)	0.90

ECD: Endothelial cell density, CV: Coefficient of variation, SD: Standard deviation

The K_{max} value decreased in 17 eyes (12.14%) by ≥ 1.0 D, remained stable in 77 eyes (55%) within ± 0.50 D and 16 eyes (11.43%) showed a progression of ≥ 1.0 D in K_{max} over follow-up period.

Pachymetry

The preoperative and postoperative mean pachymetry were 471.39 ± 41.53 μm and 469.09 ± 35.58 μm, respectively. There was no statistically significant difference between pre- and post-operative corneal thickness values (P = 0.343)

Endothelial cell morphology

The endothelial cell morphology analysis included: Cell density (cells/mm²), polymegethism (CV) and pleomorphism (% of hexagonal cells). The overall characteristics of the initial endothelial cell analysis of all eyes are detailed in Table 2.

Preoperatively, mean endothelial cell density determined by specular microscopy was 2743.43 ± 233.54 cells/mm², percentage of hexagonal cells were 53.90% ±11.78%, and the CV of endothelial cell area was 38.77% ±10.33%. These differences were not statistically significant postoperatively (all $P > 0.05$). The mean cell count decreased from 2743.43 ± 233.54 cells/mm² to 2703.49 ± 232.09 cells/mm² (P = 0.976).

Complications

In our study, 5 eyes (5.2%) of 3 patients developed permanent haze. In 3 eyes (3.12%) there was mild haze without decrease vision and in 2 eyes (2.1%) there was moderate haze with decreasing visual acuity one line of Snellen chart. The opacity in 4 eyes (4.16%) was deep posterior and in 1 eye was anterior.

DISCUSSION

Corneal CXL is a new technique for the treatment of progressive keratoconus, the procedure consists of photopolymerization of stromal collagen fibers induced by combined action of a photosensitizing substance (riboflavin or Vitamin B_2) and UVA light that increases the rigidity of cornea.[15,20]

CXL Collagen is also effective in other conditions such as postrefractive surgery keratectasia,[21-23] corneal melting lesions or corneal ulcers.[24] We performed CXL in a group of progressive keratoconus patients that were referred to our clinic to evaluate efficacy and safety of this procedure. The primary goal of the treatment was to stabilize the progression of keratoconus. The progression was defined based on keratometric and refractive outcomes. In our study, the preoperative mean sphere was −3.33 ± 3.13 D and decreased significantly to −3.09 ± 3.09 D (P = 0.007). Also, the preoperative mean cylinder changed significantly from −4.05 ± 2.29 D to −3.75 ± 2.23 D (P = 0.011). Our study showed postoperative UDVA improvement that was statistically significant (P = 0.003). 122 eyes (88.2%) maintained the preoperative UDVA or gained one or more lines of preoperative UDVA. It seems that increasing in postoperative UDVA is associated with improvement of postoperative refractive errors. Similar results were found by other previous studies for example Vinciguerra *et al*.[20,21] reported significant improvement in UDVA and CDVA most likely by significantly reducing corneal asymmetry and total abrasions. In Caporossi *et al*.[17] study a reduction of about 2.50 D was showed in the mean spherical equivalent postoperatively. Our results are similar to the research of Saffarian *et al*.,[25] that was also done on the Iranian population in 2010. This study showed a statistically significant decreasing of cylindrical power ($P < 0.001$) and decline of −0.18 ± 0.79 diopter (D) in spherical power ($P > 0.05$). In 2008, Raiskup-Wolf *et al*.[26] described what remains the largest published series comprising 241-eyes followed in Dresden for up to 6 years after cross-linking. This uncontrolled, retrospective study confirmed earlier findings with statistically significant improvements in astigmatism, best corrected visual acuity, and maximum simulated keratometry values (K_{max}) at 12 months. Flattening was observed in 54% of eye with a mean change in K_{max} of −1.91 D ($P < 0.01$) In our evaluation, there was no statistically significant difference between pre- and post-operative K values (K_{min}, $K_{average}$, K_{max}) ($P > 0.05$ for all comparisons) and corneal thickness values (P = 0.343). No statistically significant difference occurred in postoperative corneal endothelial cell counts compared with preoperative (P = 0.967). Different previous studies have shown that keratometery reading have decreased significantly after cross linking while in our study keratometry of our patients did not change significantly pre- and post-operative. Despite this fact, refraction and visual acuity parameters were improved significantly. This results is not clear for us and should be investigated. Previous studies had improvement of visual acuity accompanied by improvement of K reading.[18] One explanation may by the improvement

of optical aberrations which were not measured in our study but some other studies have evaluated the effect of improving high order aberrations after CXL.[19] However, the duration of patients follow-up in the present study were longer than most previous studies. This is another strength point of the present study.

CONCLUSION

According to our study, CXL was safe and effective in this group of progressive keratoconus patients. This procedure also improves mean visual acuity in a portion of the Iranian population. We have not observed any significant complications and adverse effect in corneal endothelial cells during follow-up. However, additional studies with longer follow-up are needed to assess the long-term effectiveness of this procedure.

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Conflicts of interest

There are no conflicts of interest.

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