Two-Years Corneal Collagen Cross-Linking Outcomes in Patients with Keratoconus

Mitra Zamani[1], Asghar Heidarian[2], Mohammad Sadegh Mirdehghan[3]

[1]Associate Professor, [2]Tutor, [3]Resident of Ophthalmology, Department of Ophthalmology, Imam Khomeini Hospital and Infectious Ophthalmologic Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

Abstract

Aims: This study aimed to report refractive, topographic, and tomographic outcomes of 2-years corneal collagen cross-linking in patients with progressive keratoconus.

Materials and Method: This prospective study was conducted on76 eyes of 40 patients with progressive keratoconus and a corneal thickness of at least 400µm. After the baseline examination, cross-linking was performed using riboflavin 0.1% and ultraviolet irradiation (370 nm, 3 mW/cm2) for 30 min. Uncorrected visual acuity (UCVA), best spectacle-corrected visual acuity (BSCVA), manifest refraction spherical equivalent (MRSE), cylinder, keratometric readings, and corneal thickness were evaluated at baseline, 6, 12, and 24 months after corneal collagen cross-linking.

Results: Results showed that at a 24-month follow-up, mean BSCVA, and UCVA had significant improvements. Changes in MRSE and cylinder were not significant during the two years of follow-up. At a 2-years follow-up, the mean values of minimum keratometry, maximum keratometry, and average keratometry decreased significantly to0.75, 0.97, and 0.52 D, respectively, compared to their baseline values. Anterior best fit sphere (BFS) also had significant difference at 24-month follow-up compared to base line evaluation. The central corneal thickness decreased significantly up to38 µ after 2 years.

Conclusion: Corneal collagen cross-linking is an effective treatment to stop the progression of keratoconusas shown by reduced keratometry and improved vision.

Keywords: *Collagen cross-linking, Keratoconus, Ultraviolet, Riboflavin*

Introduction

Keratoconus is a bilateral, asymmetric corneal degeneration that causes steepening and thinning of the central corneal tissue, resulting in irregular astigmatism, myopic progression, and reduction of visual acuity.[1]

The incidence of this disease is usually at the age of puberty,[2,3,4] and accordingly, it has a significant effect on the quality of life.[5,6] The main causes of biomechanically weak corneas include alteration in the corneal collagen cross-links and higher pepsin activity than normal.[7]

Chemical and immune histochemical studies of the corneal tissue in normal and keratoconic eyes determined the increased expression of proteolytic and lysosomal enzymes,[8,9] reduced the diameter of collagen fibers,[8] and decreased the level of protease inhibitors concentration.[10] Common options for vision correction in keratoconic eyes include spectacles, rigid contact lens, intra corneal ring segments ,and lamellar keratoplasty. Keratoconus is the most frequent cause of keratoplasty in the past three decades.[11]

Collagen cross-linking was first introduced for the treatment of keratoconic eyes by Wollensak et al. in 2003.[12] The purpose of treatment was not only the improvement of visual acuity but also the prevention of the underlying pathophysiologic mechanism of the

Corresponding Author:
Asghar Heidarian,
Department of Ophthalmology, Imam Khomeini Hospital and Infectious Ophthalmologic Research Center. Tel:+989173050945

disease.[13,14,15] The method of corneal collagen cross-linking (CXL) uses the photosensitizer riboflavin 0.1% and after corneal saturation exposes cornea to ultraviolet-A (UV-A) for approximately 30 min.[16] The riboflavin creates new covalent bonds between collagen fibers and improves the biomechanical strength of the cornea.[17]

Confocal microscopy studies indicate the apoptosis of keratocytes in anterior and intermediate corneal stroma and a gradual repopulation of the keratocytes.[18,19] The stiffening effect of riboflavin and UV-A is approximately 200-300μ in the anterior cornea.[13] Due to the possible increase of corneal endothelial cell damage, CXL is recommended in eyes with a corneal thickness of>400 μm.[20] This study aimed to report refractive, topographic, and tomographic outcomes of 2-years corneal collagen cross-linking patients with progressive keratoconus.

Materials and Method

Population

This prospective, nonrandomized, single-center study was conducted on 76 eyes of 40 patients with progressive keratoconus and a corneal thickness of at least 400 μ. The patients referred to the cornea service of the Ophthalmology Department of Apadana Hospital, Ahvaz, Iran, from December 2013 to December 2015.

Patients who had an increase in maximum keratometry (K-max) of 1.00 diopter in one year, loss of more than2 lines of best corrected visual acuity, and the need for new contact lens fitting more than once in 2 years were enrolled.[21] The exclusion criteria included corneal thickness less than 400μ at the thinnest point,[20] previous ocular surgery, herpetic keratitis, concomitant autoimmune diseases, pregnancy, breastfeeding, severe dry eye, central and paracentral opacities, and patient with poor compliance. All procedures were performed by a single surgeon.

Preoperative evaluation

Patients with hard lenses and those with soft lenses were required to stop wearing their contact lens at least 3 weeks and 3 days before the preoperative eye examination, respectively. Afterwards, all patients were subjected to the evaluation of slit-lamp and fundus examinations, as well as UCVA, BSCVA, manifest refraction, corneal topography, and corneal pachymetry.

Collagen Cross-linking procedure

The CXL was performed under sterile conditions in the surgical room. After topical anesthesia (tetracaine 0.5% ophthalmic drops, Sina Darou Co, Iran), the central 9mm corneal epithelium was abraded with a surgical blade. Riboflavin with dextran(0.1% riboflavin, 20% dextran, MedioCROSS D-Simovision BVBA, Belgium) was applied in the eye every 3 min for half an hour before the irradiation, which led to the sufficient saturation of the stroma. Using a slit-lamp with the blue filter, the surgeon ensured the penetration of riboflavin into the anterior chamber. Next, an 8 mm diameter of central cornea was exposed to UV-A light at a wavelength light (370 nm; PESCHKE CXL System, System Vision, Germany), and an irradiance of 3 mw/cm2 for 30 min. During the procedure, the riboflavin solution was instilled every 3 min.

Post operation regime

After the surgery, Levofloxacin Ophthalmic Solution 0.5% (Sina darou Co, Iran) was instilled and a soft bandage contact lens was applied until the completion of re-epithelialization. Topical Levofloxacin 0.5% and betamethasone 0.1% (Sina Darou Co, Iran) were administered 4 times a day for a weak. The patients were examined on 3 and 7 days after the surgery to evaluate epithelial healing. Follow-up examinations were performed at baseline, 6, 12, and 24 months after the procedure. At each visit, slit-lamp examination, cyclo refraction, BSCVA, UCVA, corneal topography (TMS-4N, TOMEY, USA) and pachymetry(Bausch & Lomb Orbscan2, Bausch & Lomb Co, USA) recorded.

Statistical Analysis

The analysis of data was performed using SPSS software 20 through paired t-test and repeated-measure ANOVA. P-value less than 0.05 was considered statistically significant .

Results

The mean age of patients was 22±3.54 and 42% of the participants were male.

Vision results

The UCVA and BSCVA data are summarized in Figure1 and Table1. The visual acuity results were reported through the logarithm of the minimum angle of resolution. The baseline mean values of UCVA and

BSCVA were 0.47±0.01 and 0.16±0.14 Log MAR, respectively. During the 24-month follow-up, post-CXL mean values of UCVA and BSCVA were 0.41±0.01 and 0.12±0.10 log MAR, respectively. These improvements in UCVA and BSCVA were statistically significant (P<0.05) after2-years follow-up, compared to those at the baseline.

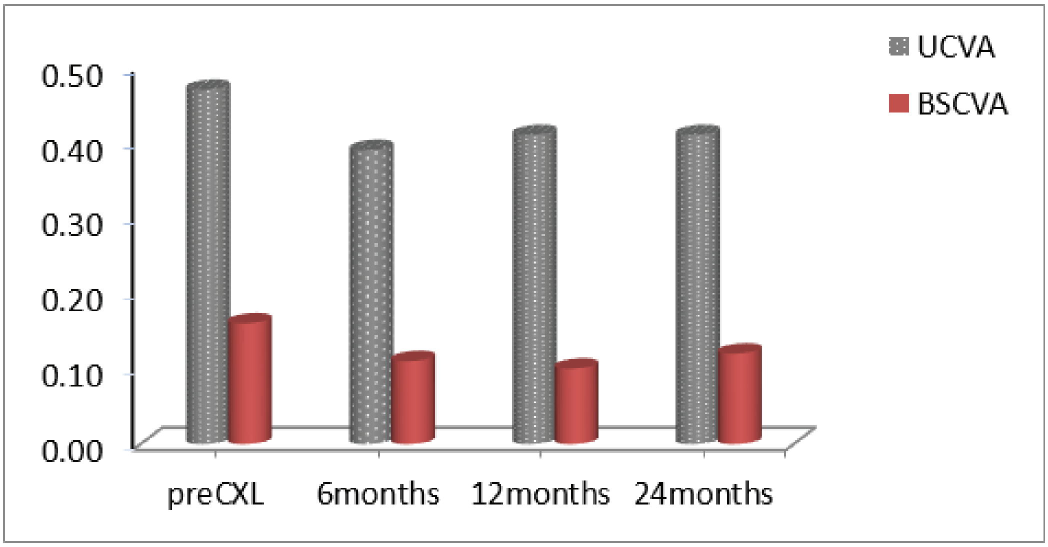


Figure1. Changes in visual acuity based on the logarithm of the minimum angle of resolution during the 2-yearfollow-up

BSCVA: best spectacle-corrected visual acuity

UCVA: uncorrected visual acuity.

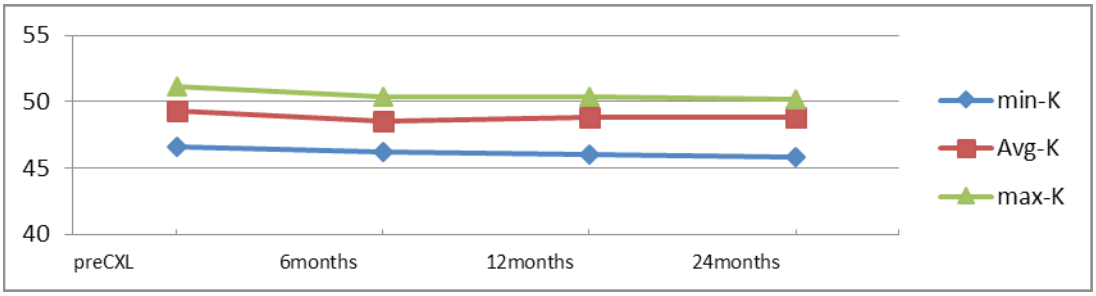
Table 1. Average measures during the 2-year follow-up

Indexes	**Pre CXL**	**6 months**	**12 months**	**24 months**	**P value**
UCVA(logMAR)	0.47±0.01	0.39±0.01	0.41±0.1	0.41±0.01	0.035
BSCVA(logMAR)	0.16±0.14	0.11±0.07	0.1±0.08	0.12±0.10	0.001
MRSE (D)	-5.39±4.23	-4.86±3.65	-5.18±3.86	-5.22±3.80	0.426
Cylinder (D)	-4.95±2.67	-4.78±2.78	-4.74±2.62	-4.67±2.71	0.243
Max-K (D)	51.1±4.94	50.36±4.66	50.4±4.80	50.13±4.8	0.000
Avg-K (D)	49.34±4.55	48.57±4.31	48.8±4.33	48.82±4.40	0.049
Min-K (D)	46.56±3.69	46.18±3.58	46.01±3.54	45.81±3.52	0.000
CCT (um)	454±39	367±74	411±71	416±70	0.000
AnteriorBFS(mm)	7.65±0.32	7.68±0.3	7.69±0.29	7.69±0.31	0.006
Posterior BFS(mm)	6.19±0.41	6.02±0.3	6.09±0.29	6.15±0.31	0.459
Irregularity5 mm (D)	5.42±2.08	5.26±2.04	4.92±1.88	4.75±1.78	0.000
Irregularity3 mm (D)	5.11±2.15	4.96±2.08	4.60±1.52	4.48±1.53	0.001

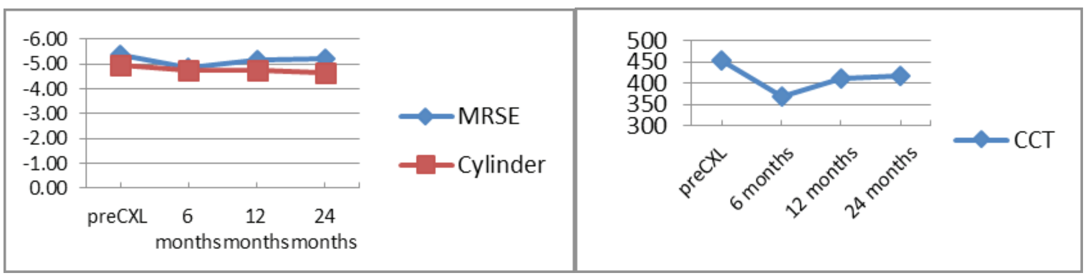
UCVA: uncorrected visual acuity; BSCVA: best spectacle-corrected visual acuity; logMAR: alogarithm of the minimum angle of resolution; MRSE:manifest refraction spherical equivalent; K-max:maximum keratometry; K-min: minimum keratometry; K-avg: average keratometry; D: diopter; CCT: central corneal thickness; BFS: Best fit sphere

Refractive results

The baseline mean values of MRSE and cylinder were 5.39±4.23 and 4.95±2.67 D, respectively. There was a mean reduction in MRSE of 0.17 D and a mean reduction in a cylinder of 0.28 D at the 2-year follow-up compared to baseline. There was no significant difference, 24 months after the procedure. The mean value of MRSE improved significantly 6 months after CXL and remained unchanged during 12 and 24 months (Figure2 and Table1).



(A)



(B) (C)

Figure 2.Changes in (A) keratometeric reading based on diopter, (B) cylinder and manifest refraction spherical equivalent based on diopter, (C) central corneal thickness based on micrometer. K-Min: minimum keratometry, K-avg: Average keratometery, K-max: maximum keratometery, MRSE: manifest refraction spherical equivalent, CCT: central corneal thickness

Topographic results

Table 1 also shows the comparison of the difference between pre-CXL and post-CXL keratometric values, anterior and posterior best fit sphere (BFS) and changes in the irregularity of 3mm and 5mm zones of the cornea at baseline (Figure C), 6 months,12 months and 24 months respectively. The improvements in the irregularity of 3mm and 5mm zones of the cornea were statistically significant throughout the entire postoperative period, compared to preoperative levels (P<0.05). The baseline mean values of the irregularity in 3mm and 5mm zones of the cornea were 5.11±2.15 and 5.42±2.08, respectively, which decreased to 4.48±1.53 and 4.75±1.78, respectively, after 24 months (Table1).

The baseline mean values of the surface regularity index, irregular astigmatism index, surface asymmetry index, and keratoconus prediction index and post-CXL follow up (6, 12 and 24 months) changes in these indices were not statistically significant (Table2).

Table 2. Changes in Klyce Indices

	Pre CXL	6 months	12 months	24 months	p-value
Surface regularity index	0.92±0.47	0.90±0.50	0.84±0.51	0.89±0.50	0.141
Surface asymmetry index	2.33±1.28	2.29±1.41	2.10±1.21	2.21±1.29	0.116
Irregular astigmatism index	0.43±0.09	0.43±0.10	0.44±0.10	0.49±0.27	0.107
Keratoconus prediction indexa	0.39±0.11	0.37±0.11	0.38±0.10	0.38±0.12	0.107
Keratoconus index	0.72±0.30	0.70±0.28	0.71±0.01	0.70±0.28	0.687

A significant relationship between CCT, ANT DIFF, POST DIFF, K max, K min, K avg, Irregularity zone 3, and Irregularity zone 5 indexes was observed 24 months after operation (P<0.05)(Table 3).

Table 3. Correlation of post-operative indices

		BCVA	ANT DIFF	POST DIFF	cct	Min.K	Max.K	Irreg. zone.3	Irreg. zone.5	Avg.K
UCVA (logMAR)	Correlation	-0.04	0.148	0.01	0.03	-0.05	-0.11	-0.19	-0.151	-0.09
	P-value	0.67	0.201	0.87	0.75	0.66	0.33	0.08	0.192	0.404
BSCVA (logMAR)	Correlation	1	-0.053	-0.15	-0.01	0.11	0.102	0.03	0.120	0.11
	P-value		0.647	0.19	0.88	0.33	0.38	0.78	0.303	0.33
Anterior BFS (mm)	Correlation	-0.05	1	0.49	0.29	-0.47	-0.51	-0.36	-0.403	-0.43
	P-value	0.64		<0.005	0.01	<0.005	<0.005	0.001	<0.005	<0.005
Posterior BFS(mm)	Correlation	-0.15	0.49	1	0.37	-0.37	-0.43	-0.31	-0.416	-0.39
	P-value	0.19	<0.005		0.001	.001	<0.005	0.005	<0.005	<0.005
CCT (um)	Correlation	-0.01	0.294	0.37	1	-0.39	-0.38	-0.26	-0.33	-0.34
	P-value	0.88	0.01	.001		<0.005	0.001	0.02	0.003	0.002
K-min (D)	Correlation	0.11	-0.47	-0.37	-0.39	1	0.87	0.43	0.76	0.81
	P-value	0.33	<0.005	.001	<0.005		<0.005	<0.005	<0.005	<0.005
K-max (D)	Correlation	0.1	-0.519	-0.43	-0.38	0.87	1	0.52	0.809	0.88
	P-value	0.38	<0.005	<0.005	0.001	<0.005		<0.005	<0.005	<0.005
Irregularity 3 mm (D)	Correlation	0.03	-0.361	-0.31	-0.26	0.43	0.52	1	0.801	0.55
	P-value	0.78	0.001	0.005	0.02	.000	<0.005		<0.005	<0.005
Irregularity 5 mm (D)	Correlation	0.12	-0.403	-0.41	-0.33	0.76	0.8	0.801	1	0.82
	P-value	0.3	<0.005	<0.005	0.003	<0.005	<0.005	<0.005		<0.005
K-avg(D)	Correlation	0.11	-0.43	-0.39	-0.34	0.81	0.88	0.55	0.82	1
	P-value	0.33	<0.0005	<0.0005	0.002	<0.005	<0.005	<0.005	<0.005	

UCVA: uncorrected visual acuity; BSCVA: best spectacle-corrected visual acuity; log MAR: alogarithm of the minimum angle of resolution; MRSE: manifest refraction spherical equivalent; K-max: maximum keratometry; K-min: minimum keratometry; K-avg: average keratometry; D: diopter; CCT: central corneal thickness; BFS: Best fit sphere

Discussion

In recent years, CXL has developed as an effective therapeutic modality for the treatment of corneal ectasia[22] and progressive keratoconus.[12] In the past few years, a small number of studies on animals demonstrated that collagen cross-linking significantly increased corneal rigidity in porcine and rabbits cornea.[13,23] On the basis of the results, BSCVA and UCVA improved significantly to 0.04 log MAR and 0.06 log MAR, respectively, at the 2-years follow-up compared to baseline. Similar results were also reported by Hashemiet al. at a 2-year follow-up.[24] The findings of the previous studies were indicative of a significant reduction in the manifest refraction spherical equivalent and cylinder after cross-linking.[25,26] The results of the current study during the 24-month follow-up revealed that here was no significant change in the manifest refraction spherical equivalent and cylinder in the course of time. The same results were observed by Viswanathan with a mean of 14.38±9 months.[27] Likewise, in two longitudinalstudies performed by Hashemi[24] and El-raggal,[28] there was no significant change in the cylinder five years after the CXL. The reduced values of the corneal curvature and the K-max were important parameters indicating the success of collagen cross-linking. Previous studies have shown a decrease in max-K after the CXL.[25,27,29,30]

Conclusion

According to present study, collagen cross-linking can be combine with procedures, such as rigid contact lenses, ring segments, and surface customized refractive surgery to correct vision partially in keratoconic eyes. In a long term, this therapeutic treatment seems to be much safer compared to corneal grafting with many complications, including infection, glaucoma, cataract, and graft rejection. In addition, cross-linking is a cost-effective and minimally invasive option to the treatment of ectasia compared keratoplasty.No major complications were observed in the current study.

Conflict of Interest: Authors have declared that no competing interests exist.

Ethical Clearance: Ethical clearance taken from ethical committee of Ahvaz Jundishapur University of Medical Sciences.

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