

## MYORING IMPLANTATION ALONE VERSUS CORNEAL COLLAGEN CROSS-LINKING FOLLOWING MYORING IMPLANTATION FOR MANAGEMENT OF KERATOCONUS: 1 YEAR FOLLOW UP

SAHAR MOJALED NOBARI<sup>1</sup>, CONSUELO VILLENA<sup>1</sup>, KHOSROW JADIDI<sup>2</sup>

<sup>1</sup>PhD candidate of Optometry, Master in Optometry and Vision, Department of Optics II (Optometry and Vision), Complutense University, Madrid, Spain - <sup>2</sup>Consuelo Villena: PhD, Professor of Optometry, Department of Optics II (Optometry and Vision), Complutense University, Madrid, Spain - MD, Ophthalmologist, Associate Professor of Ophthalmology, Bina Eye Hospital Research Center, Between Sayyad-e Shiraz and Imam Ali Highways, Resalat Highway, Tehran, Iran

### ABSTRACT

**Purpose:** To compare combined MyoRing implantation with previously corneal collagen cross-linking (CXL- MyoRing) versus MyoRing implantation alone in patients with keratoconus.

**Methods:** This retrospective, comparative, cohort study included 33 eyes of 33 patients with keratoconus stage II and III according to Amsler-Krumeich classification. Two groups were performed for this study with 1 year follow up. The group 1 received MyoRing implantation and the group 2 received CXL approximately 12 months before MyoRing implantation. All patients had a complete pre and post-operative examination including visual, refractive and keratometry examinations.

**Results:** In Group 1 at the end of follow up the mean UDVA and CDVA improved by 9 and 4 lines of logMAR. In Group 2 the mean UDVA and CDVA improved by 8 and 2 lines of logMAR. There was not observed a statistically significant difference between mean UDVA of two groups postoperatively ( $p = 0.142$ ) whereas the mean CDVA in Group 2 was significantly better than mean Group 1 at the end of follow up ( $p = 0.018$ ). Spherical equivalent error and refractive astigmatism were significantly reduced in both groups which no statistically significant differences was noted in these refractive parameters between two groups. The mean keratometric values also were reduced in both groups at the end of follow up which no statistically significant difference was observed between two groups.

**Conclusion:** Both MyoRing implantation alone and combined MyoRing implantation with previously CXL were safe and effective methods for moderate and severe keratoconus and resulted in similar clinical outcomes after one year follow up. Exclusively MyoRing implantation alone demonstrated better outcome in mean CDVA.

**Key words:** Corneal Collagen Cross-linking, MyoRing, Keratoconus, Intracorneal Ring Segment implantation

Received February 05, 2016; Accepted March 02, 2016

### Introduction

Condition in which the cornea becomes thin and loses tensile strength, and subsequently develops warpage and irregular astigmatism, are referred to as corneal ectasias. Ectatic condition of the cornea can cause very poor vision<sup>(1)</sup>.

Keratoconus (KCN) is a progressive, non-inflammatory ectatic disorder characterized by bilateral and asymmetrical conical protrusion of the cornea<sup>(2)</sup> with a reported frequency in the general population of approximately 1 in 2000<sup>(3)</sup>. It is notable that keratoconus is a multifactorial disease

caused by several genes disorder, environmental factors and ultrastructural alteration of the collagen matrix<sup>(4)</sup>. According to the keratoconus stage and its progression, different treatments can be used. In the early stages, spectacles or contact lenses can correct this abnormality, whereas in advance cases because of the progressive increase in myopia and corneal irregularity, these optical means cannot resolve the visual blur. Surgical treatments such as intrastromal corneal ring segments (ICRS) and corneal collagen cross-linking (CXL) with riboflavin and ultraviolet A (UVA) can be used in higher stages as less invasive procedures<sup>(5-7)</sup>.

ICRS have been used to correct ectatic corneal disease in order to reduce the corneal steepening, reduce the irregular astigmatism and improve the visual acuity in patients with clear cornea and contact lens intolerance<sup>(5,8,9)</sup>.

The main advantages of ICRS are safety, reversibility, stability, and the fact that surgical process does not affect the central corneal visual axis<sup>(10)</sup>.

The development of a new surgical approach (corneal intrastromal implantation system-CISIS), consisting of a safe and easy to use high precession microkeratome for the creation of the corneal pockets (Pocket Maker Microkeratome, Dioptex GmbH, Austria) and a new kind of full ring implant (MyoRing, Dioptex GmbH, Austria) allows a safe and effective treatment of Myopia, keratoconus and post-LASIK keratoectasia<sup>(11-13)</sup>.

Cross-linking of collagen refers to the ability of collagen fibrils to form strong chemical bonds with adjacent fibrils. By this hypothesis, induction of cross-links in corneal tissue was tested in order to increase the stiffness as a basis for a future conservative treatment of keratectasia<sup>(7)</sup>. Corneal collagen crosslinking (CXL) with riboflavin and ultraviolet A (UVA) is a new technique to strengthen corneal tissue using riboflavin as a photosensitizer and UVA to increase the formation of intrafibrillar and interfibrillar covalent bonds by photosensitized oxidation. This technique stabilizes biomechanics of cornea<sup>(14)</sup>. Studies on CXL have reported stability in progression of the keratoconus, but with minimal improvement in vision quality of patients<sup>(15,16)</sup>. For this reason combined procedures such as intrastromal corneal ring (ICR) implantation have been proposed to maximize the results from CXL<sup>(17,18)</sup>.

Although the combination of MyoRing implantation and CXL have been done before and showed safe and effective treatment<sup>(19,20)</sup>. To the best of our knowledge, this is the first study which is performed to compare combined MyoRing implantation with previously corneal collagen crosslinking (CXL- MyoRing) versus MyoRing implantation in patients with moderate and severe keratoconus.

### ***Patients and methods***

This retrospective, comparative, non-randomized, cohort study included 33 eyes of 33 patients with keratoconus stage II and III according to Amsler-Krumeich keratoconus classification. All surgeries were performed by the same surgeon.

Inclusion criteria for MyoRing implantation was keratoconus grade II and III, contact lens intolerance, corneal thickness at the thinnest point of at least 350  $\mu\text{m}$  and the exclusion criteria included grade I and IV of keratoconus, hydrops, corneal opacity, corneal dystrophy, severe atopy, previous ocular disease or surgery, autoimmune or other systemic disease and pregnancy.

Inclusion criteria in order to realize CXL treatment was progressive keratoconus confirmed by an increase in maximum curvature of at least 1.00 D in the previous 6 months as assessed by corneal topography, no slit lamp evidence of corneal scarring and corneal thickness of at least 400  $\mu\text{m}$ .

Patients were divided into two groups. The group 1 included 22 eyes of 22 patients with no progressive keratoconus in whom only MyoRing implantation was performed. Second group included 11 eyes of 11 patients with progressive keratoconus. In group 2 the patients received crosslinking treatment (CXL) approximately one year before MyoRing implantation at the same place.

In both groups MyoRing implantation was performed between March 2013 and April 2014 for all patients at Bina Eye Hospital, Tehran, Iran. The follow up time after MyoRing implantation in both groups was 12 months.

Inclusion criteria for MyoRing implantation was keratoconus grade II and III, contact lens intolerance, corneal thickness at the thinnest point of at least 350  $\mu\text{m}$  and the exclusion criteria included grade I and IV of keratoconus, hydrops, corneal opacity, corneal dystrophy, severe atopy, previous ocular disease or surgery, autoimmune or other systemic disease and pregnancy.

Inclusion criteria in order to realize CXL treatment was progressive keratoconus confirmed by an increase in maximum curvature of at least 1.00 D in the previous 6 months as assessed by corneal topography, no slit lamp evidence of corneal scarring and corneal thickness of at least 400  $\mu\text{m}$ .

All patients had a complete preoperative and postoperative examination including manifest refraction, corrected distance visual acuity (CDVA), uncorrected distance visual acuity (UDVA) using a standard Snellen chart, Goldman applanation tonometry, pachymetry, corneal topography (Orbscan II, Bausch & Lomb), slit lamp microscopy and fundus examination. Diagnosis of keratoconus was established by the combination of computed videokeratography for anterior and posterior

corneal surface (Orbscan II; Baush&Lomb), keratometry readings, and corneal pachymetry and slit lamp findings.

### ***Surgical technique***

All operations were performed by the same surgeon (KH.J). Corneal crosslinking was performed with a UVA light and full ring intracorneal implantation (MyoRing, DiopTex, GmbH) with PocketMakerMicrokeratome.

### ***Corneal collagen crosslinking (CXL)***

The CXL procedure was performed in an operating room under sterile conditions. Topical anesthetic eye drops were applied. After manual abrasion of the corneal epithelium of at least 7.0 mm, riboflavin 0.1% solution in 20% dextran was applied to the cornea every 2 to 3 minutes during 30 minutes. Saturation of the cornea with riboflavin and its presence in the anterior chamber were monitored closely at the slit lamp before treatment began. Ultraviolet-A (UVA) irradiation was performed using an optical system (Koehler illumination) consisting of an array of 7 UVA diodes with a potentiometer to allow regulation of voltage. Before treatment, the intended surface irradiance of 3 mW/cm<sup>2</sup> (5.4 J/cm<sup>2</sup> surface dose) was calibrated using a UVA meter (LaserMate-Q, Laser 2000) at a working distance of 6 cm. Irradiance was performed for 30 minutes using 3 mW/cm<sup>2</sup>, corresponding to a surface dose of 5.4 J/cm<sup>2</sup>.

During treatment, riboflavin solution was applied every 3 minutes to saturate the cornea with riboflavin and moisten the cornea. After the treatment, topical ciprofloxacin 0.3% (SinaDarou) was applied and a bandage contact lens (Bausch & Lomb PureVision of material balafilcon A) fitted to the corneal surface until re-epithelialization. Bandage lens was removed within 3 to 5 days, pending epithelial healing. Patients were given betamethasone disodium phosphate drops 0.1%, (SinaDarou) 4 times daily, with gradual tapering over the following 2 months.

### ***MyoRing Implantation***

The MyoRing implantation was performed in an operating room under sterile conditions and topical anesthesia (Proparacaine hydrochloride 0.5%). An operation microscope (OMS-800 standard TOPCON Corporation, Japan) was used to mark the central point of intrastromal corneal ring. Additionally, the appropriate MyoRing dimensions

were determined according to the MyoRing nomogram which takes into account the corneal thickness at its thinnest point and the average keratometry (K) - reading.

An intrastromal pocket of 9 mm in diameter and 300  $\mu$ m in depth was created via a small incision of 3 mm using the Pocket Maker Microkeratome as described in detail elsewhere<sup>(11)</sup>. The Microkeratome has a suction ring and a motor-driven blade. First, the suction ring fixes the applanator to the cornea and then the micro-vibrating diamond creates the stromal pocket. Once the pocket is created, the MyoRing is inserted into the pocket using implantation forceps and centration is adjusted using a keratoscope. All procedures were performed with the temporal approach of self-sealing incisions. No intraoperative complications were noted during the surgical procedure in any case. Postoperatively, a silicone bandage contact lens was placed on the cornea and removed 24 hours after the operation. Postoperative treatment included a combination of betamethasone drops (SinaDarou), chloramphenicol drops (SinaDarou), and non-preserved artificial tear (Artelac; Baush & Lomb) 4 times daily. Chloramphenicol was discontinued 1 week postoperatively whereas betamethasone was tapered during 4-6 weeks.

### ***Statistical analysis***

Statistical analysis was performed using SPSS for windows (version 21; SPSS Inc., Chicago, IL, USA). All visual acuity measurements were converted from Snellen notation to logMAR. The normality of data was checked using Kolmogorov-Smirnov (K-S) test. Continuous variables are expressed as mean  $\pm$  SD. The statistical significance of the differences in mean levels of normally distributed variables between pre cxl and post cxl was examined using the paired t-test. A one-way repeated measures ANOVA was conducted to compare the effect of surgery groups; Group 1 (MyoRing implantation) and group 2 (CXL+ MyoRing) on UDVA, CDVA, SE, Sphere, Cylinder, Max K, Min K, and Mean K before and after MyoRing implantation. The threshold of statistical significance was a p value less than 0.05.

### **Results**

Group 1 included 22 eyes of 22 patients, 18 men (81.8%) and 4 women (18.2%), with a mean age of 24.63  $\pm$  3.06 (SD) (range 18 to 28 years)

who had only MyoRing implantation. Of these eyes 15 eyes (68.1 %) and 7 eyes (31.8 %) had stage II keratoconus and stage III keratoconus, respectively. The mean time of follow-up was 12 month. Patients in group 2 received CXL treatment before MyoRing implantation. The mean interval time between CXL and MyoRing implantation was 12 months. This group included 11 eyes of 11 patients, 8 men (72.7 %) and 3 women (27.3 %), with a mean age of  $20.40 \pm 3.58$  (SD) (range 17 to 27 years). There were 7 eyes (63.6%) with stage II keratoconus and 4 eyes (36.3%) with stage III keratoconus (table 1).

In group 2, there was no significant difference

Variables	Group 1 N 22	Group 2 N 11	P value
Age	24.63 ± 3.06	20.40 ± 3.50	0.001
Sex			
Male	18 (81.8 %)	8 (72.7 %)	0.547
Female	4 (18.12 %)	3 (27.3 %)	
KCN stage			
Stage II	15 (68.1 %)	7 (63.6 %)	1
Stage III	7 (31.8 %)	4 (36.3 %)	

**Table 1:** Demographic factors of study population.

Group 1, MyoRing implantation; Group 2 CXL+ MyoRing implantation; KCN, keratoconus

in mean UDVA, CDVA, SE, sphere and manifest cylinder before and after CXL treatment, whereas there was a statistically significant increase in keratometric values after CXL treatment ( $p < 0.001$ ) (table 2).

Table 3 demonstrates that there is no difference between 2 groups over the time for all variables except for CDVA. Additionally, it shows that in group 1 the mean UDVA was improved by 9 lines of logMAR ( $p < 0.001$ ) and the mean CDVA was improved approximately by 4 lines of logMAR ( $p < 0.001$ ). In group 1 the amount of reduction for SE, sphere and cylinder of manifest refraction were 6.08, 4.67 and 3.37 D at 12 months postoperatively, respectively ( $p < 0.001$ ). Also, the maximum k value (K max), minimum k value (k min) and average k-value (k mean) were decreased approximately by 5.54, 2.24 and 4.00 D at 12 months postoperatively, respectively ( $p < 0.001$ ). In group 2, comparing the results after CXL treatment versus post CXL + MyoRing implantation showed a significant difference in all parameters. The mean UDVA improved from  $1.08 \pm 0.30$  to  $0.34 \pm 0.20$  (approximately 8 lines of log MAR) after MyoRing implantation ( $p < 0.001$ ). The mean CDVA improved from  $0.44 \pm$

Parameter	Pre CXL	Post CXL	P value
<b>UDVA (logMAR)</b>			
Mean ± SD	1.15 ± 0.27	1.08 ± 0.30	0.933
Range	0.50 to 1.60	0.70 to 1.60	
<b>CDVA (logMAR)</b>			
Mean ± SD	0.42 ± 0.10	0.44 ± 0.14	0.729
Range	0.30 to 0.60	0.30 to 0.60	
<b>SE (D)</b>			
Mean ± SD	-8.53 ± 3.41	-9.00 ± 4.27	0.150
Range	-15.00 to -4.00	-16.00 to -3.00	
<b>Sphere (D)</b>			
Mean ± SD	-5.70 ± 3.69	-6.86 ± 3.95	0.091
Range	-12.00 to -1.00	-14.00 to 0.00	
<b>Cylinder (D)</b>			
Mean ± SD	-5.65 ± 1.29	-4.97 ± 1.38	0.116
Range	-7.00 to -2.00	-7.00 to -2.50	
<b>Max K (D)</b>			
Mean ± SD	54.52 ± 5.45	55.09 ± 5.33	0.034
Range	45.00 to 61.00	45.20 to 60.16	
<b>Min K (D)</b>			
Mean ± SD	47.75 ± 3.71	48.51 ± 4.12	0.01
Range	42.00 to 53.40	43.40 to 55.00	
<b>Mean K (D)</b>			
Mean ± SD	51.14 ± 4.38	51.80 ± 4.50	0.03
Range	44.00 to 57.00	44.60 to 57.70	

**Table 2:** Comparison of Pre CXL and post CXL outcomes in group 2.

UDVA = uncorrected distance visual acuity; CDVA = corrected distance visual acuity; SE= spherical equivalent; K = Keratometry; Max K = maximum K value; min K= minimum K value; Mean K = average K value; D = diopter.

(approximately 2 lines of log MAR) after MyoRing implantation ( $p = 0.002$ ). In this group, the mean preoperative (post CXL) SE, sphere and cylinder of manifest refraction decreased by 6.40, 5.18 and 2.54 D at the end of follow up respectively and the maximum k value (K max), minimum k value (k min) and average k-value (k mean) decreased approximately by 6.75, 2.96 and 4.85 D at 12 months postoperatively, respectively.

**Discussion**

MyoRing implantation and Corneal Collagen Cross Linking (CXL) are two independent treatment methods for treating Keratoconus.

MyoRing implantation is the technique of

Parameter		Pre- op	Post- op	P Trend	P Interaction
<b>UDVA (log MAR)</b>					
Group 1	Mean ± SD	1.15± 0.27	0.22 ± 0.07	<0.001	0.120
	Range	0.50 to 1.60	0.10 to 0.30		
Group 2	Mean ± SD	1.08 ± 0.30	0.34 ± 0.20	<0.001	
	Range	0.70 to 1.60	0.00 to 0.60		
<b>CDVA (log MAR)</b>					
Group 1	Mean ± SD	0.53 ± 0.20	0.15 ± 0.05	<0.001	0.034
	Range	0.30 to 1.00	0.10 to 0.20		
Group 2	Mean ± SD	0.44 ± 0.14	0.22 ± 0.14	0.002	
	Range	0.30 to 0.60	0.00 to 0.40		
<b>SE(D)</b>					
Group 1	Mean ± SD	-6.35 ± 3.21	-0.27±0.76	<0.001	0.785
	Range	-13.00 to -1.50	-1.50 to +1.00		
Group 2	Mean ± SD	-9.30 ± 4.27	-2.89 ± 2.48	<0.001	
	Range	-16.00 to -3.00	7.50 to 0.50		
<b>Sphere(D)</b>					
Group 1	Mean ± SD	-4.11 ± 3.17	0.56 ± 0.64	<0.001	0.707
	Range	-10.00 to 0.00	-0.75 to +1.00		
Group 2	Mean ± SD	-6.86 ± 3.95	-1.68 ± 2.35	0.002	
	Range	-14.00 to 0.00	-6.00 to 1.00		
<b>Cylinder(D)</b>					
Group 1	Mean ± SD	-5.00 ± 1.07	-1.63 ± 0.76	<0.001	0.094
	Range	-6.50 to -3.25	-3.50 to -0.50		
Group 2	Mean ± SD	-4.97 ± 1.38	-2.43 ± 0.80	<0.001	
	Range	-7.00 to -2.50	-4.00 to -1.50		
<b>Max K(D)</b>					
Group 1	Mean ± SD	52.85 ± 3.09	47.31 ± 1.97	<0.001	0.148
	Range	48.00 to 58.00	44 to 51.80		
Group 2	Mean ± SD	55.09 ± 5.33	48.34 ± 3.01	<0.001	
	Range	45.20 to 60.16	43.40 to 53.80		
<b>Min K(D)</b>					
Group 1	Mean ± SD	47.32 ± 3.09	45.08 ± 2.47	<0.001	0.336
	Range	42.60 to 53.60	41.00 to 49.60		
Group 2	Mean ± SD	48.51 ± 4.12	45.55 ± 2.81	0.007	
	Range	43.40 to 55.00	41.10 to 50.20		
<b>Mean K(D)</b>					
Group 1	Mean ± SD	50.13 ± 2.70	46.14 ± 2.53	<0.001	0.533
	Range	46.20 to 55.60	42.50 to 49.50		
Group 2	Mean ± SD	51.80 ± 4.50	46.95 ± 2.88	<0.001	
	Range	44.60 to 57.70	42.25 to 52.00		

**Table 3:** Results of repeated measures analysis of variance for comparing means for visual and refractive outcomes in two groups of Myoring and CXL + MyoRing implantation.

UDVA, uncorrected distance visual acuity; CDVA, corrected distance visual acuity; SE, spherical equivalent K, keratometry; Max K, maximum k value; Min K, minimum K value; Mean K, average K value; D, diopter; Group 1: MyoRing implantation; Group 2: CXL + MyoRing implantation; Pre- op: before MyoRing implantation; Post- op: after MyoRing implantation

installing the complete intrastromal ring in the developed pocket in cornea. The mechanism of this technique involves adding a volume to the periphery which leads to a new biomechanical equilibrium of the cornea, thereby flattening its center<sup>(11, 12)</sup>. It has been demonstrated that the treatment of keratoconus, post-LASIK ectasia and pellucid marginal degeneration with MyoRing implantation is effective, minimally invasive, and easy to perform<sup>(21-25)</sup>.

The primary indication for the use of CXL is to inhibit the progression of corneal ectasia such as keratoconus<sup>(26-29)</sup>. Healthy cornea contains crosslinks between collagen fibers by which it stays in normal shape. These links are reduced in Keratoconus which in turn results in a bulge with outward orientation. In CXL these crosslinks are reproduced to help cornea regain its standard conditions<sup>(7, 14, 15)</sup>. The present study evaluates the effectiveness of MyoRing implantation independently and MyoRing implantation with previously operated patients using CXL for the first time in patients with Keratoconus.

The results of current study indicated the effectiveness of independent MyoRing implantation. This method reduced spherical and cylindrical component of manifest refraction as well as keratometric values. The mean UDVA and CDVA improved significantly after the independent implantation of MyoRing. Other studies on MyoRing implantation demonstrated the similar results<sup>(21-25)</sup>. Jabbarvand et al.<sup>(23)</sup> evaluated a sample of 98 eyes of 98 patients who underwent MyoRing implantation through which the mean UDVA and CDVA after one year follow up improved by 6 and 3 lines of logMAR, meanwhile, in the current study in group who had only MyoRing implantation, the mean UDVA and CDVA improved by 9 and 4 lines of logMAR, respectively. Jabbarvand's results for refractive parameters such as sphere, cylinder and SE illustrated 5.50, 3.00 and 7.00 D changes respectively. In accordance to Jabbarvand study, these changes were 4.67, 3.37 and 6.08 D in our study. They suggested that this treatment approach is a successful method for Keratoconus treatment.

It has been shown that MyoRing implantation leads to visual rehabilitation in keratoconic patients and it also can stop the progression of the disease by creating a new biomechanical equilibrium<sup>(30)</sup>.

Studies on Keratoconus patients reported various results regarding the effectiveness of CXL<sup>(27-29, 31, 32)</sup>. Raiskup-Wolf et al.<sup>(28)</sup> reported the effectiveness of CXL for keratoconus treatment in a 6- year fol-

low up. Their results showed a significant improvement in CDVA (1 line logMAR). Also according to their results the maximum k value decreased by 1.46 D<sup>(28)</sup>. However, in current study after CXL treatment, maximum k value increased by 0.57 D and we did not observe a significant improvement in mean CDVA, following CXL treatment. Wollensak et al.<sup>(29)</sup> reported that in order to observe the positive outcomes of CXL, a long follow up period is required which was in consistence with some studies<sup>(27, 32)</sup>. Agrawal et al.<sup>(31)</sup> investigated the effect of CXL treatment in 41 Indian patients with progressive keratoconus after 12 months follow-up. Their results showed at least 1 line improvement in CDVA and the maximum keratometry value decreased by 2.47 D. However the results of this study demonstrated that there is no change in visual and refractive outcomes (UDVA, CDVA, SE, sphere and cylinder of manifest refraction) but a slight increase in keratometric values after CXL.

In a systematic review realized by TianChunyu et al.<sup>(33)</sup> of 3 studies with 84 participants, a small regression of corneal topography was found after 18 months post- CXL; K mean value was not significantly different at 18 months post CXL. Likewise based on the result of 5 studies that included 181 participants, the mean UDVA was not improved, only CDVA still showed significant improvement after 18 months post CXL. Our results after CXL procedure were in accordance to these studies which had 18 months follow up.

However, one must not forget that CXL treatment likely only stops or slows down, rather than prevent the progression of keratoconus. A small regression that occurred in our study after CXL treatment may be explained as an effect of the rearrangement of corneal lamellae and the surrounding matrix<sup>(34, 35)</sup>.

Considering the collagen turnover in the cornea over several years, long term studies have yet to determine whether repeated CXL treatment is necessary. Currently no studies have assessed repeated CXL procedures in keratoconus patients because some authors believe that CXL yield good results in long term follow up<sup>(27, 29, 32)</sup>.

While CXL has been shown to halt keratoconus progression, its effect on visual rehabilitation may be insufficient. Intarcornal ring segments (ICRS) produce rapid and substantial improvement in visual parameters but do not halt keratoconus progression<sup>(36)</sup>.

Therefore a logical solution would be to combine the two treatment methods in order to synergize their effect. This way the CXL procedure could be done first in order to stabilize the cornea, followed by ICRS implantation in order to flattening and regularizing the cornea.

Previous studies on ICRS demonstrated the effectiveness of these two treatment together for keratoconus<sup>(17, 18, 37)</sup>, also the combination of full ring implantation (MyoRing) and CXL, can lead to improvement and a long term stability of visual acuity in patients with keratoconus<sup>(12)</sup>. However none of these previous studies evaluated the effect of MyoRing implantation with previously CXL treatment in patients who suffered progressive keratoconus.

The data from examining group who received both treatments (CXL and MyoRing implantation) demonstrated that changes in visual, refractive and keratometry outcomes after MyoRing implantation in comparison with post CXL were statistically significant. The improvement in mean UDVA and CDVA after MyoRing implantation in the group who had CXL prior to MyoRing implantation were approximately 8 and 2 lines of logMAR. It seems that MyoRing implantation is more beneficial than CXL for improving visual and refractive outcomes. MyoRing implantation significantly flattens and regularizes the cornea<sup>(21-25)</sup>.

Coskunseven et al.<sup>(17)</sup> evaluated the effect of combined KeraRing implantation and CXL when applied in two groups with different order of using each method. The study included 48 eyes of 43 patients with keratoconus (Group 1: ICRS first then CXL; Group 2: CXL first then ICRS; mean interval between treatments was approximately 7 months). They evaluated several parameters such as UDVA, CDVA, SE, Cylinder, and Kmean. Their results demonstrated that incorporation of these methods could provide better outcomes, especially when CXL is applied after ICRS implantation. In Coskunseven et al.<sup>(17)</sup> study the group 2 which CXL was applied before ICRS implantation showed approximately 1 line improvement in UDVA and CDVA. The SE and cylinder of manifest refraction decreased by 4.15 and 1.76 D, respectively<sup>(38)</sup>.

In accordance with Coskunseven study, notably the current study showed a greater improvement for CDVA (approximately 2 lines) and UDVA (approximately 8 lines) in group who had CXL treatment prior to MyoRing implantation. It is notable that Kmean reduction on their study

was 4.16 D, whereas in current study was observed a greater reduction (4.85 D).

Chan et al.<sup>(37)</sup> in a retrospective comparative study analyzed 12 eyes of 9 patients who had Intacs implantation without CXL and 13 eyes of 12 patients who had Intacs implantation followed by CXL. The combined surgery group had a significantly greater reduction in cylinder (2.73 versus 1.48 D) and the maximum k value (1.94 versus 0.89 D) than the group having Intacs implantation only. In spite of the study conducted by Chan et al, the current study showed almost no significant differences between parameters of two groups.

A prospective study conducted by Renesto et al. after a 2- year follow up period (39 eyes) showed no difference between patients treated with ICRS implantation alone and patients treated with CXL followed by ICRS implantation 3 months later. Both groups showed similar results in terms of refractive, topographic and pachymetric parameters<sup>(39)</sup>.

A similar retrospective comparative study performed by Legareet al. on 66 eyes showed that 1 year postoperatively, the 34 eyes treated with ICRS had better visual and keratometric results than the 32 eyes treated with a combination of CXL and ICRS<sup>(40)</sup>.

In agreement with Renesto et al. and Legareet al. studies, in current study no significant differences were observed in association with UDVA, SE, sphere, cylinder and keratometric values between two groups (table 2). Only the mean CDVA had a greater improvement (approximately 2 lines of logMAR) in group who had MyoRing implantation alone.

Studený et al.<sup>(20)</sup> described the use of combined MyoRing implantation and CXL in one session in a group of patients with keratoconus. The study included 22 eyes of 22 patients. After 12 months follow up the mean UDVA improved by 6 lines and the mean CDVA improved approximately by 2.50 lines. Our results in group who had CXL approximately 12 months prior to MyoRing implantation were in accordance with Studený et al. study, however we have a greater improvement in mean UDVA.

Also, the mean sphere and cylinder reduced by 2.76 and 1.61 D, respectively in Studený et al. study, whereas in current study sphere and cylinder decreased by 5.18 and 2.54 D in group with both treatment. As it can be seen we obtained more satisfactory results in comparison with Studený et al.

study. Comparing our results to Studeny et al. study leads us to the following hypothesis that more favorable outcomes will be obtained if we apply CXL treatment prior to MyoRing implantation instead of realize combined treatment in one session, because a slight improvement in long term follow up period is a common finding.

Moreover, our results in both groups especially in group who had CXL before MyoRing implantation raise a question if MyoRing can stop the progression of keratoconus?

It has been demonstrated that the progression of keratoconus seems to be associated with selective proteolytic activity which alters the regular orthogonal matrix pattern of the corneal lamellae<sup>(41)</sup>, in the other word the progression of keratoconus is the result of the biomechanical weakness of the diseased cornea. The current study in agreement with previous studies on MyoRing implantation suggests that MyoRing implantation alone may have sufficient power to stop progression of keratoconus without CXL treatment.

Generally, there are two possibilities to strengthen the cornea in order to stop progression: 1st Hardening the corneal tissue on an ultra-structural level by means of corneal collagen crosslinking, 2 nd To support the cornea by adequate mechanical means without changing the itself tissue. Such a support could be the MyoRing implantation. Since MyoRing is a closed, complete ring and located in a pocket that is larger the diameter of the implant and not captured in a tunnel like ICRS, the cornea can find a new biomechanical equilibrium around the implant and resting biomechanically neutral in the postoperative corneal shape<sup>(42)</sup>. However further studies with longer follow up periods are required to clarify this issue in more details.

Although there was no complication in any case during and after surgery, this study had some limitation including the short follow up period, limited number of patients in each group; thus it would be interesting to carry out further long term, prospective study with more participant to evaluate the effect of combined CXL treatment and MyoRing implantation.

Finally we could conclude that MyoRing implantation alone versus MyoRing implantation with previously CXL treatment were both safe and effective methods for moderate and sever keratoconus. Also the group with MyoRing implantation demonstrated more improvement in mean CDVA at

the end of follow up and both groups had the same effect on visual, refractive and keratometric outcomes. It seems that CXL treatment needs longer follow up to show better results and the biomechanical effect of CXL would be present in more longer postoperative period. We also assume that MyoRing implantation could be stop or slow down the progression of keratoconus, however to confirm these findings it is fundamental accomplish further prospective comparative study with longer follow up time for both methods of treatment.

## References

- 1) Tan, D.T. and Y.-M. Por, *Current treatment options for corneal ectasia*. Current opinion in ophthalmology, 2007. 18(4): p. 279-283.
- 2) Rabinowitz, Y.S., *Keratoconus*. Survey of ophthalmology, 1998. 42(4): p. 297-319.
- 3) Kennedy, R.H., W.M. Bourne, and J.A. Dyer, *A 48-year clinical and epidemiologic study of keratoconus*. American journal of ophthalmology, 1986. 101(3): p. 267-273.
- 4) Gordon-Shaag, A., M. Millodot, and E. Shneor, *The epidemiology and etiology of keratoconus*. Epidemiology, 2012. 70: p. 1.
- 5) Colin, J., et al., *INTACS inserts for treating keratoconus: one-year results*. Ophthalmology, 2001. 108(8): p. 1409-1414.
- 6) Siganos, D., et al., *Ferrara intrastromal corneal rings for the correction of keratoconus*. Journal of Cataract & Refractive Surgery, 2002. 28(11): p. 1947-1951.
- 7) Spoerl, E., M. Huhle, and T. Seiler, *Induction of Crosslinks in Corneal Tissue*. Experimental Eye Research, 1998. 66(1): p. 97-103.
- 8) Asbell, P.A. and Ö.Ö. Uçakhan, *Long-term follow-up of Intacs from a single center*. Journal of Cataract & Refractive Surgery, 2001. 27(9): p. 1456-1468.
- 9) Colin, J. and F.J. Malet, *Intacs for the correction of keratoconus: two-year follow-up*. Journal of Cataract & Refractive Surgery, 2007. 33(1): p. 69-74.
- 10) Bakshi, R., et al., *Intra-Stromal Corneal Ring Segments*. The Official Scientific Journal of Delhi Ophthalmological Society, 2013. 24(1): p. 16-22.
- 11) Daxer, A., *Corneal intrastromal implantation surgery for the treatment of moderate and high myopia*. Journal of Cataract & Refractive Surgery, 2008. 34(2): p. 194-198.
- 12) Daxer, A., *Adjustable intracorneal ring in a lamellar pocket for keratoconus*. J Refract Surg, 2010. 26(3): p. 217-221.
- 13) Mahmood, H., R. Venkateswaran, and A. Daxer, *Implantation of a complete corneal ring in an intrastromal pocket for keratoconus*. J Refract Surg, 2011. 27(1): p. 63-68.
- 14) Jankov Ii, M.R., et al., *Corneal Collagen Cross-Linking*. Middle East African Journal of Ophthalmology, 2010. 17(1): p. 21-27.
- 15) Asri, D., et al., *Corneal collagen crosslinking in progressive keratoconus: Multicenter results from the*



- French National Reference Center for Keratoconus. *Journal of Cataract & Refractive Surgery*, 2011. 37(12): p. 2137-2143.
- 16) Raiskup, F., A. Hoyer, and E. Spoerl, *Permanent corneal haze after riboflavin-UVA-induced cross-linking in keratoconus*. *Journal of Refractive Surgery*, 2009. 25(9): p. S824.
  - 17) Coskunseven, E., et al., *Effect of treatment sequence in combined intrastromal corneal rings and corneal collagen crosslinking for keratoconus*. *Journal of Cataract & Refractive Surgery*, 2009. 35(12): p. 2084-2091.
  - 18) Zeraid, F.M., et al., *Visual rehabilitation in low-moderate keratoconus: intracorneal ring segment implantation followed by same-day topography-guided photorefractive keratectomy and collagen cross linking*. *International journal of ophthalmology*, 2014. 7(5): p. 800.
  - 19) Parker, J.S., K. van Dijk, and G.R.J. Melles, *Treatment options for advanced keratoconus: A review*. *Survey of ophthalmology*, 2015. In press.
  - 20) Studeny, P., D. Krizova, and Z. Stranak, *Clinical Outcomes after Complete Intracorneal Ring Implantation and Corneal Collagen Cross-Linking in an Intrastromal Pocket in One Session for Keratoconus*. *Journal of Ophthalmology*, 2014. 2014: p. 5.
  - 21) Alio, J.L., D.P. Piñero, and A. Daxer, *Clinical outcomes after complete ring implantation in corneal ectasia using the femtosecond technology: a pilot study*. *Ophthalmology*, 2011. 118(7): p. 1282-1290.
  - 22) Daxer, A., *MyoRing for central and noncentral keratoconus*. *International Journal of Keratoconus and Ectatic Corneal Diseases*, 2012. 1: p. 117-119.
  - 23) Jabbarvand, M., et al., *Continuous Corneal Intrastromal Ring Implantation for Treatment of Keratoconus in an Iranian Population*. *American journal of ophthalmology*, 2013. 155(5): p. 837-842.e2.
  - 24) Mojaled Nobari, S., C. Villena, and K. Jadidi, *Predictability, Stability and Safety of MyoRing Implantation in Keratoconic Eyes During One Year Follow-Up*. *Iranian Journal of Ophthalmology*, 2014. 26(3): p. 136-143.
  - 25) Mojaled Nobari, S., C. Villena, and K. Jadidi, *Full-Ring Intracorneal Implantation in Corneas With Pellucid Marginal Degeneration*. *Iranian Red Crescent Medical Journal*, 2015. 17(12).
  - 26) Ashwin, P.T. and P.J. McDonnell, *Collagen cross-linkage: a comprehensive review and directions for future research*. *British Journal of Ophthalmology*, 2010. 94(8): p. 965-970.
  - 27) Raiskup, F., et al., *Corneal collagen crosslinking with riboflavin and ultraviolet-A light in progressive keratoconus: Ten-year results*. *Journal of Cataract & Refractive Surgery*, 2008. 41(1): p. 41-46.
  - 28) Raiskup-Wolf, F., et al., *Collagen crosslinking with riboflavin and ultraviolet-A light in keratoconus: Long-term results*. *Journal of Cataract & Refractive Surgery*, 2008. 34(5): p. 796-801.
  - 29) Wollensak, G., E. Spoerl, and T. Seiler, *Riboflavin/ultraviolet a induced collagen crosslinking for the treatment of keratoconus*. *American journal of ophthalmology*, 2003. 135(5): p. 620-627.
  - 30) Daxer, A., *Corneal thickness after MyoRing implantation for keratoconus*. *International Journal of Keratoconus and Ectatic Corneal Diseases*, 2014. 3(1): p. 15.
  - 31) Agrawal, V.B., *Corneal collagen cross-linking with riboflavin and ultraviolet-A light for keratoconus: Results in Indian eyes*. *Indian Journal of Ophthalmology*, 2009. 57(2): p. 111-114.
  - 32) Wittig-Silva, C., et al., *A Randomized, Controlled Trial of Corneal Collagen Cross-Linking in Progressive Keratoconus: Three-Year Results*. *Ophthalmology*, 2014. 121(4): p. 812-821.
  - 33) Chunyu, T., et al., *Corneal collagen cross-linking in keratoconus: A systematic review and meta-analysis*. *Scientific reports*, 2014. 4.
  - 34) Spoerl, E., et al., *Detection of biomechanical changes after corneal cross-linking using Ocular Response Analyzer software*. *Journal of Refractive Surgery*, 2011. 27(6): p. 452-457.
  - 35) Spoerl, E., et al., *Biomechanical condition of the cornea as a new indicator for pathological and structural changes*. *Der Ophthalmologe: Zeitschrift der Deutschen Ophthalmologischen Gesellschaft*, 2009. 106(6): p. 512-520.
  - 36) Pinero, D.P., et al., *Corneal biomechanical changes after intracorneal ring segment implantation in keratoconus*. *Cornea*, 2012. 31(5): p. 491-499.
  - 37) Chan, C.C., M. Sharma, and B.S.B. Wachler, *Effect of inferior-segment Intacs with and without C3-R on keratoconus*. *Journal of Cataract & Refractive Surgery*, 2007. 33(1): p. 75-80.
  - 38) Coskunseven, E., et al., *One-Year Results of Intrastromal Corneal Ring Segment Implantation (KeraRing) using Femtosecond Laser in Patients with Keratoconus*. *American journal of ophthalmology*, 2008. 145(5): p. 775-779.e1.
  - 39) Renesto, A., et al., *Sequential topical riboflavin with or without ultraviolet a radiation with delayed intracorneal ring segment insertion for keratoconus*. *American journal of ophthalmology*, 2012. 153(5): p. 982-993.e3.
  - 40) Legare, M.E., et al., *Intacs with or without same-day corneal collagen cross-linking to treat corneal ectasia*. *Canadian Journal of Ophthalmology/Journal Canadien d'Ophthalmologie*, 2013. 48(3): p. 173-178.
  - 41) Daxer, A. and P. Fratzl, *Collagen fibril orientation in the human corneal stroma and its implication in keratoconus*. *Investigative ophthalmology & visual science*, 1997. 38(1): p. 121-129.

#### Acknowledgements

We would like to acknowledge Ms. Sara Serahati for her precious contribution in statistical analysis.

#### Corresponding author

KHOSROW JADIDI, MD

Ophthalmologist, Associate Professor of Ophthalmology, Bina Eye Hospital Research Center

Between Sayyad-e Shiraz and Imam Ali Highways

Resalat Highway, Tehran

Email: kh.jadidi@gmail.com

(Iran)