Original Research Article

Efficiency evaluation of corneal collagen crosslinking intervention in patients with keratoconus

Miruna Burcel[1*], Catalina Corbu[1,3], Vasile Potop[1,3], Mihaela Constantin[2], Dana Dascalescu[1], Catalina Ionescu[1], Valeria Coviltir[1,3], Marian Burcea[1,3], Radu Ciuluvica[5] and Liliana Voinea[3,4]

[1]Clinical Hospital of Ophthalmologic Emergencies, Piata Alexandru Lahovari1, Bucharest, Romania

[2]Oftaclinic, Bucharest, Romania

[3]Division of Ophthalmology, Faculty of Medicine, "Carol Davila" University of Medicine and Pharmacy, Bulevardul Eroii Sanitari 8, 050474, Bucharest, Romania

[4]Departament of Ophthalmology, University Emergency Hospital, SplaiulIndependetei 169, 050098, Bucharest, Romania

[5]Faculty of Dental Medicine, "Carol Davila" University of Medicine and Pharmacy, Bulevardul Eroii Sanitari 8, 050474, Bucharest, Romania

*Corresponding Author Email: cristea.miruna@yahoo.com Tel.: no. +40767571423

Abstract

The purpose of the paper is to evaluate the safety and efficiency of corneal collagen crosslinking (CXL) intervention in patients with progressive keratoconus. This study included patients having different evaluative stages of keratoconus, showing eligibility criteria for the crosslinking technique. The procedure has been applied to 90 eyes of 72 patients; corrected and uncorrected visual acuity, corneal thickness values and topographic aspects were recorded before and after intervention. Visual acuity improved for the majority of cases. The average decrease of the maximum keratometric values was 1.51±1.85 dioptres. Among the patients who underwent crosslinking, 5 met the criteria for progression and 2 of them underwent redo CXL. Corneal collagen crosslinking is the therapeutic method for increasing corneal biomechanical stability by binding new links between collagen fibrils using ultraviolet light and riboflavin as photo sensibilising agent. A close follow-up is necessary after the procedure. Risk factors associated with progression after primary CXL remain unclear and more studies are needed to clarify it.

Keywords: Corneal collagen crosslinking, Keratoconus, Keratometry, Pachimetry, Topography

INTRODUCTION

Keratoconus, a progressive corneal ectasia, is characterized by thinning and conical protrusion of the corneal inferior zone, which causes myopia and irregular astigmatism. This leads to a decrease of uncorrected visual acuity, best corrected visual acuity and asymmetric inferior steepening on the topography map (Rabinowitz, 1998; Catalina et al., 2016).

The treatment has two objectives: stopping progression and improving visual acuity. Improving visual acuity consists of optical correction with spectacles and all types of contact lens as soft, rigid, hybrid, clera and semiscleral contact lens, intracorneal rings and penetrating keratoplasty in advanced cases. The second objective, stopping the keratoconus progression, is achieved by photo-oxidative collagen crosslinking (Corbu, 2014).

Corneal collagen crosslinking (CXL) was proposed for the first time in 2003 by Wollensak et al as therapeutically method for increasing corneal biomechanical stability by binding new links between collagen fibrils using ultraviolet light and riboflavin as photosensibilizing agent (Wollensak et al., 2003). Since then numerous clinical studies revealed that the procedure has high success rates and provide long term stabilization (Vanissa et al., 2015; Hashemi et al., 2013; Raiskup et al., 2008; Spoerl et al., 2004; Vinciguerra et al., 2009; Caporossi et al., 2010; Kymionis et al., 2014). However, in the current literature, there are a small number of studies that report

failure and progression keratectasia after crosslinking (Kymionis and Karavitaki, 2014; Koller et al., 2009). The purpose of our study is to analyze the efficiency of crosslinking intervention in patients with progressive keratoconus at 6 months, respectively 1 year after it was performed.

MATERIAL AND METHODS

This retrospective study involved 90 eyes of 72 patients with progressive keratoconus who underwent CXL between 2012-2014 in Oftaclinic, Bucharest. Inclusion criteria were progressive keratoconus, no previous ocular surgery, corneal thickness of 400 μm or more. Keratoconus was considered to be progressive if, during a 12 months follow-up, there was an increase in simulated maximum keratometry by at least 1D, based on corneal topography, a deterioration of visual acuity (loss of at least 1 Snellen line) or an increase in astigmatism by at least 1.0D, with subjective deterioration in vision. Exclusion criteria included corneal thickness of less than 400 μm at the thinnest point, central or paracentral corneal opacities, history of herpetic keratitis or recurrent infections, pregnancy, concomitant autoimmune diseases.

All procedures were performed by a single surgeon. All of the patients provided written informed consent before the initiation of crosslinking theraphy. Cases were classified into four stages based on corneal power, astigmatism and corneal thickness according to the classification of Amsler-Krumeich. As parameters we evaluated visual acuity, cornea dioptric powers, as well as pachymetry.

Each patient underwent a complete preoperative ophthalmologic examination including: measurement of uncorrected and of best corrected visual acuity, slit lamp and fundus examination, corneal topography with Topcon CA- 200F Corneal Analyser(Topcon Medical Systems), ultrasound pachymetry (Alcon® OcuScan® RxP Ophthalmic Ultrasound System), corneal biomechanics examination (Ocular Response Analyzer, Reichert, New York).

All patients were treated with UVA-riboflavin CXL in the operating room under sterile conditions and topical anesthesia with oxybuprocaine hydrochloride 0.4% (Benoxi, Unimed Pharma Ltd). Collagen crosslinking was performed according to the classical methodology, with corneal epithelial mechanical debridement in a 9.0 mm diameter area. The epithelial tissue was removed with a blunt spatula to ensure penetration of riboflavin in the corneal stroma. Normoosmolar riboflavin solution 0,1 % was applied to the cornea for 30 min every 3 min. After that, the cornea was exposed to UVA 365 nm light for 30 min at an irradiance of $3.0mW/cm^2$. During the 30 min of irradiation the riboflavin administration was continued every 5 minutes. At the end of surgery, eye drops were instilled in the form of combination of antibiotic (moxifloxacin) and nonsteroidal anti-inflammatory drops (pranoprofen 1mg/ml) and a bandage soft contact lens was applied until corneal epithelium healing was completed. Postoperatively the patients were followed at day one, one week, one month, three months, six months and one year.

RESULTS

Out of 72 patients included with a mean age of 21.53±5.25 (range 10 to 33) years, 46 (63.89%) were males and 26 (36.11%) females. 90 eyes of the 72 patients underwent crosslinking for progressive keratoconus. Patient distribution according to Amsler-Krumeich classification was as follows: stage 1-12eyes (13.33%), stage 2-44 eyes (48.89%), stage 3 -19 eyes (21.11%), stage 4 -15 eyes (16.67%).

Mean Snellen uncorrected visual acuity (UCVA) was 0.28±0.23 (range 0.01-0.9) preoperatively, 0.36±0.28 (range 0.03-1) at 6 months postoperatively and 0.40±0.27 (range 0.011), 1 year postoperatively (Figure 1). Sixmonths postoperatively, 38 (42.22%) eyes maintained their preoperative UCVA; 43 (47.78%) eyes gained at least 1 line and 9 (10%) lost at least 1 line. Furthermore, 1 year postoperatively, 28 eyes (31.11%) maintained their preoperative UCVA, 57 (63.33%) showed a gain of 1 to 3 lines and 5 (5.56%) experienced a loss of visual acuity (Figure 2).

Best corrected visual acuity (BSCVA) ranged both preoperatively and postoperatively between 0,3-1. Visual acuity was corrected in 70cases with rigid gas permeable (RGP) contact lens and ranged between 0.7-1 (2 cases refused wearing the prescribed RGP contact lens). 12 cases used spectacles, visual acuity ranging between 0,3-0,9. After CXL, 8 cases didn't need correction because they obtained a 20/20 visual acuity.

Preoperatively, mean maximum corneal power (Kmax) was 50.67±5.16. Six months postoperative decreased at 50.07±5.12 and 1 year after procedure it was 49.16±4.95.

Before the procedure mean flattest corneal meridian was 46.31±3.78. Postoperatively it reduced at 46.07±3.71 and 1 year after intervention it decreased at 45.67±3.83 (Figure 3).

We observed that after corneal collagen crosslinking, maximum corneal power was constant in 50.00% (45 eyes), decreased in 44.44% (40 eyes) and increased in 5,56% (5 eyes) (Figure 4). The average change of maximum corneal power was (Δkmax) was -0.60±1.67 at six months after the procedure, respectively -1.51±1.85 1 year after.

Mean central corneal thickness (CCT) was 454.13±37.84; 6 months after treatment was 458.91±32.71, and 461.06±32.11 1 year thereafter.

From the total number of eyes enrolled in the study, in 5 eyes of 5 cases was found a progression in the studied
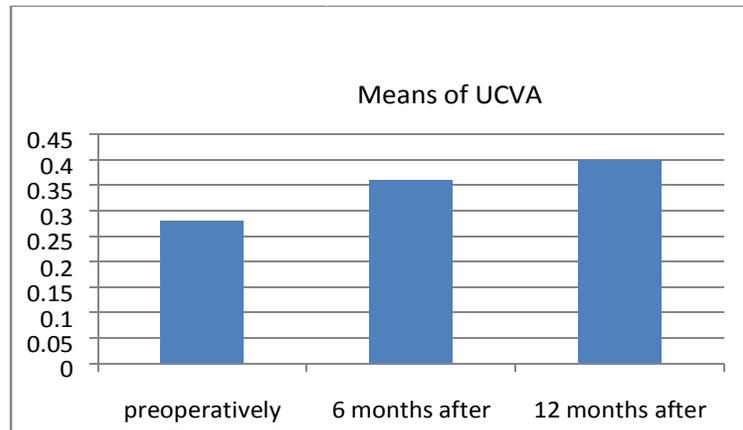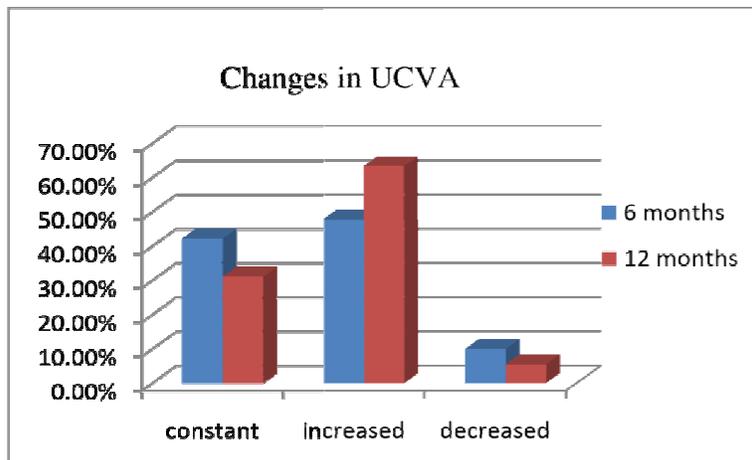
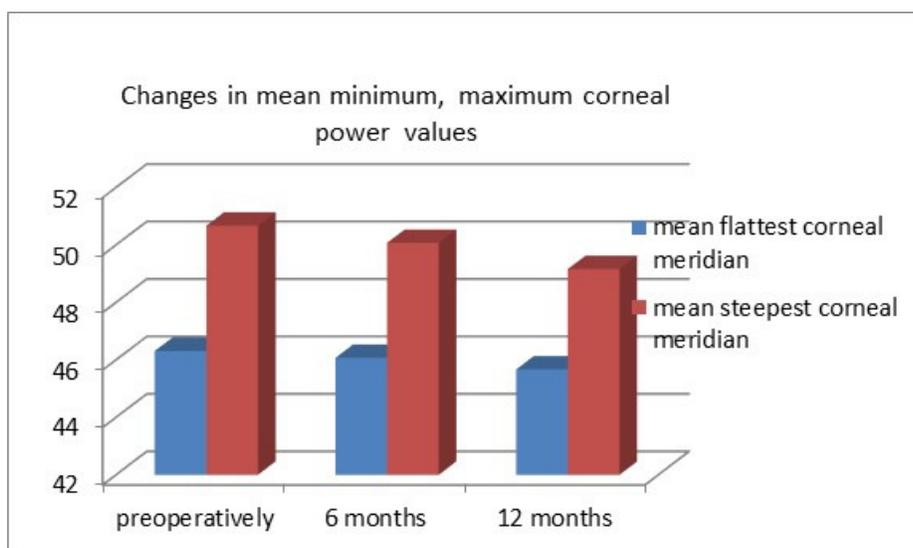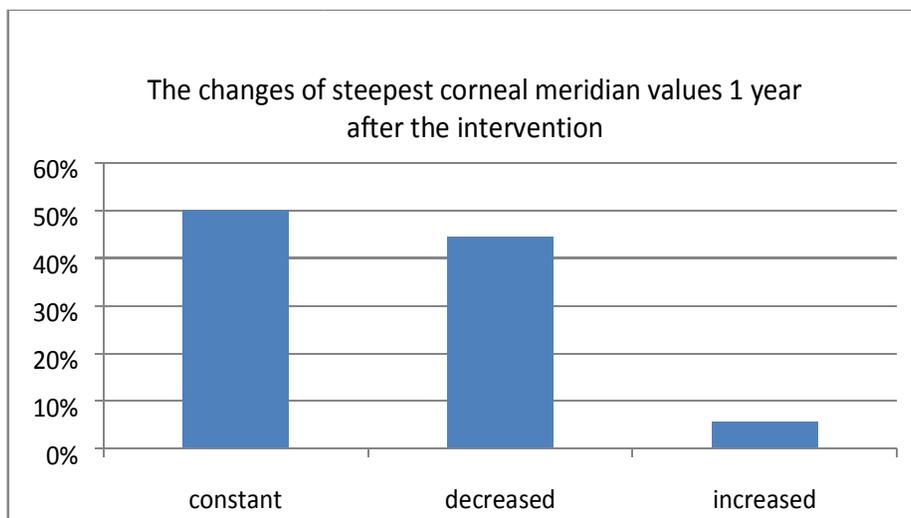**Figure 1.** Mean Snellen uncorrected visual acuity
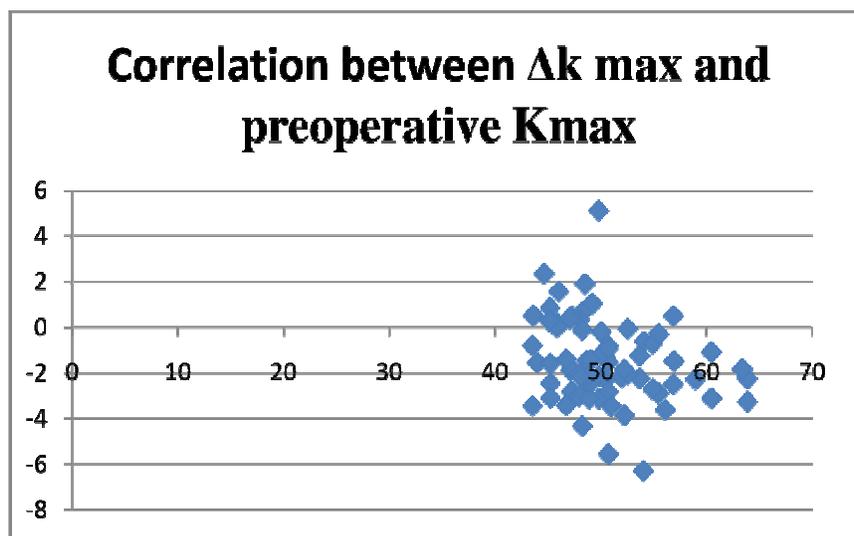

Figure 2. Changes in UCVA

Figure 3. Changes in mean minimum, maximum corneal power values

The changes of steepest corneal meridian values 1 year after the intervention

Figure 4. The changes of maximum corneal power values 1 year after the procedure

Figure 5. Correlation between the average change of Kmax and preoperative Kmax

period. The therapeutic management attitude took in consideration the patient age, the progression rate and whether patient wears or not RGP contact lens. Two patients aged 10 and 15 years old repeated CXL as they increased by 2.5D, respectively 2D. Neither of one was wearing RGP. The three others who had progression, ranged from 1D-1.75D, were followed clinically during those 2 years. All 3 were practicing sport activities regularly and none of them was wearing RGP lens. We decided to temporize them because all three were over 22 years old. Both eyes treated with 2 procedures of CXL were stable 1 year after the second intervention.

Linear regression analyses showed a negative, indirect correlation statistically significant between Δ k max and preoperative steepest corneal meridian ($r = -0.80$, $p=0.0055$) (Figure 5) and between Δ k max and age ($r = -0.28$, $p<0.001$) (Figure 6), 1 year after the procedure. Also the Δk max was negatively correlated with the stage of the disease ($r= -0.43$, $p=0.04$), 1 year after the intervention. A positive correlation was found between preoperative pachimetry and Δk max, 1 year after the procedure ($r= 0.014$, $p=0.006$) (figure 7). These results demonstrate that the greater the preoperative maximum corneal power, the thicker the preoperative pachimetry and the greater the stage of the disease resulted in a larger flattening of the keratoconus using CXL. Also post CXL, younger patients tended to continue to progress more than the older ones.
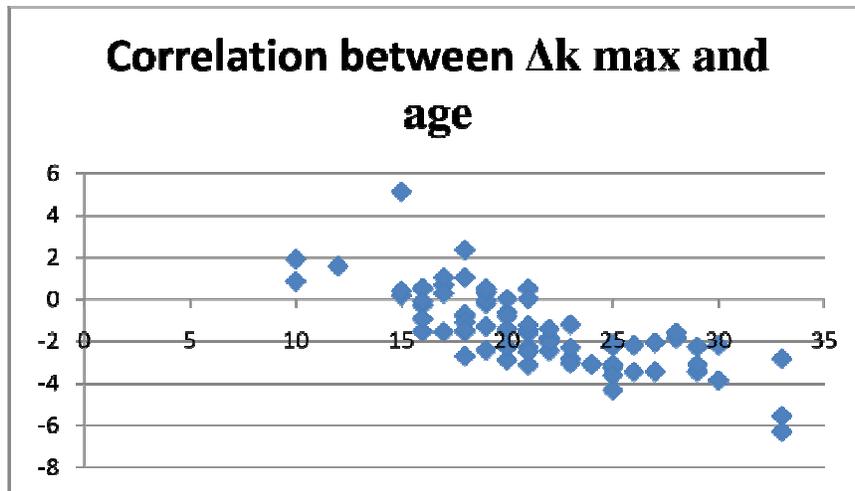
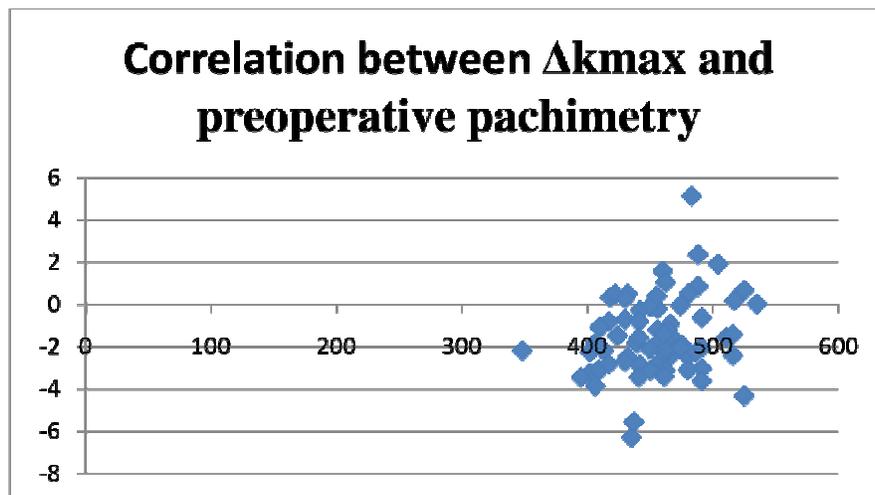**Figure 6.** Correlation between the average change of Kmax and patient's age

Figure 7. Correlation between the average change of Kmax and preoperative pachimetry

DISCUSSIONS

The results of our study showed an increase in vision and a decrease in both steepest and flattest corneal meridians in the majority of cases.

Vision improved in most patients six months after the procedure and continued to improve during the 1 year follow-up. Until now the mechanism by which the vision is improved or altered after corneal collagen crosslinking is not completely understood. A possible explanation for the visual improvement might be the reduced astigmatism resulted from the decrease in corneal curvature. Several studies have revealed that after crosslinking in keratoconus the visual acuity increase (Vinciguerra et al., 2009; Agrawal, 2009; Clark and Peter, 2014).

We observed an improvement of the CCT at 6 months, respectively 1 year after the intervention, but it

was not a significant increase, these findings being conclusive with others studies (Vinciguerra et al., 2009; Greenstein et al., 2011; Mohammad et al., 2015). A possible explanation is that an increase in corneal biomechanical stiffness may change the pattern and distribution of collagen fibers and actually increase CCT.

Topographic results showed, 6 months after the procedure, a mean reduction of 0.60D and 1 year after, a mean reduction of 1.51D. Our results were similar with the findings of other studies (Raiskup et al., 2008; Clark and Peter, 2014; Vinciguerra et al., 2010; Toprak et al., 2014).

Although CXL with riboflavin and UVA light has become an established treatment modality to halt progression in the majority of patients with keratoconus, several studies have been shown that keratoconus progression still may happen after primary CXL

Table 1. Patients characteristics in which reintervention was decided

Patient 1, 10 years old, LE	Refraction	UCVA	BCVA	K max	K min
Before primary CXL	-9.25*158	0.2	0.3	50.41	42.72
6 months after	-0.50<>COUT*157	0.2	0.3	50.79	42.29
12 montl after	-1.50<>COUT*163	0.16	0.3	52.07	42.71
18 montl after	-1.50<>COUT*159	0.1	0.2	53.21	43.63
Reintervention					
6 months after	-1.75<>COUT*159	0.16	0.2	53.84	43.74
12 montl after	-2<>-9*154	0.16	0.2	51.89	43.23
Patient 2, 15 years old, LE					
Before primary CXL	-1.25<>-2*118	0.3	0.7	47.65	44.40
6 months after	-0.50<>-2.25*117	0.3	0.7	47.14	44.76
12 montl after	-3.75<>-3*134	0.16	0.5	49.77	45.46
Reintervention					
6 months after	-3<>-3.25*126	0.16	0.6	48.16	44.85
12 montl after	-2.25<>-2*129	0.1	0.6	48.28	44.82

procedure. In most of the studies the failure rate and the time of progression after CXL varied significantly (Wollensak et al., 2003; Raiskup et al., 2008; Koller et al., 2009; Joelle et al., 2015; Baenninger et al., 2014).

In our study five eyes of five patients presented progression based on the deterioration of visual acuity, on the change in the refraction and on the increase in maximum corneal power between two examinations. We decided to redo the intervention in two cases taking into account the age of those two, being under 18 years old. Both of them had a decrease of visual acuity of at least 1 Snellen line, a change in the refraction and an increase in maximum curvature on the topographic map of 2.42D, respectively 2.12D as can be seen in Table 1.

Risk factors associated with progression after primary CXL are incompletely known. Koller et al reported that female sex and a preoperative maximum K reading of more than 58D were associated with progression, reporting a failure rate of 8% one year after crosslinking in keratoconus (Koller et al., 2009). Despite the Koller's findings in our study the preoperative maximum corneal power associated with progression had variable values. Also the male gender linked with progression. The preoperative Raiskup-Wolf et al found progression in patients with neurodermatitis, which is associated with eye rubbing (Raiskup et al., 2008). In a study among 221

eyes of 130 patients, Joelle Antoun et al found that the only risk factors associated with keratoconus progression after crosslinking were allergic conjunctivitis and eye rubbing (Joelle et al., 2015). In our study, we found the risk factor for the disease progression being the practice of sports activities.

CONCLUSION

In conclusion, corneal collagen crosslinking was developed to halt the progression of keratoconus, change the corneal architecture, in some cases to improve topography characteristics, correlated or not with visual acuity improvement. Monitoring patients with keratoconus under the age of 18 years must be done carefully and more frequently. Practicing sports activities was found to be a risk factor for the disease progression. Wearing RGP lenses, by improving visual acuity and by its biomechanical effect, determines to stop the progression of keratoconus.

Conflict of Interest

The authors declare that there is no conflict of interests

regarding the publication of this paper.

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