

Collagen Cross linkage in Management of Moderate Progressing Keratoconus

Faried. M. Wagdy, Ahmed. A. Elhagaa, Amir.M. Hassan, Moustafa. K. Nassar

Ophthalmology, Faculty of Medicine, Menofia University, Menofia, Egypt
faried.wagdy@hotmail.com

Abstract: Objective: To Evaluate the efficacy of riboflavin ultraviolet (UVA-induced) corneal collagen cross-linking in stabilization of moderate progressive keratoconus. **Patients and Methods:** (20) eyes of (17) patients with moderately progressing keratoconus were treated by corneal cross-linkage and followed up for 6 months. **Results:** there was a statistically significant decrease in the mean keratometric (K value) at the apex between the preoperative values and six months values ($P < 0.05$). The preoperative mean apex K value was ($50.8 \pm 2.07D$) and changed to ($45.54D$) at six months. The K value at the apex decreased by a mean of 5.26 D from preoperative values. Central corneal thickness (CCT) reduced from $441.85 \pm 27.67\mu\text{m}$ pre-operatively to $430.5 \pm 26.4 \mu\text{m}$ at one month that increase gradually to $433.5 \pm 25.4 \mu\text{m}$ but it was statistically insignificant and there was no statistically significant improvement in best corrected visual acuity(BCVA) between the preoperative and 6 months evaluations ($P > 0.05$). **Conclusion:** Cross linkage is an effective and safe procedure in treatment of moderate progressing keratoconus.

[Faried. M. Wagdy, Ahmed. A. Elhagaa, Amir. M. Hassan, Moustafa. K. Nassar. **Collagen Cross linkage in management of moderate progressing Keratoconus.** *J Am Sci* 2013;9(12):35-38]. (ISSN: 1545-1003). <http://www.jofamericanscience.org>, 6

Keywords: cross linkage – moderate- keratoconus.

1.Introduction

Two chief mechanisms for the development of keratoconus have been put forward. One proposes that ectasia is closely associated with tissue degradation or reduced maintenance whereas the other suggests that it is due to slippage between collagen fibrils with no overall tissue loss.¹

Corneal Cross Linking is induced using the photosensitive riboflavin (vit. B2) and UVA. The mechanism works by the action of free radicals and the end result is an increase in the covalent bonding between collagen molecules in the fibrils and also between collagen fibrils.²CXL is the only treatment aiming at slowing the progression of corneal ectasia and thus delay or block corneal ectasia and reducing the demand for penetrating keratoplasty which is a far more invasive procedure.³

2. Patients and Methods

A total of 20 eyes of 17 patients were included in this study (females and males). Those Patients were diagnosed as moderate keratoconus (48–54 D), with history of progression over the previous 12 months. (based on clinical and topographic history), Corneal thickness of at least 400 μm , No slit-lamp evidence of corneal scarring and Age was 15-30 years.Exclusion Criteria were patients with mild and severe keratoconus, Prior corneal surgery, Systemic collagen vascular disease, Patients with slit-lamp evidence of central and paracentral corneal scars both epithelial and stromal, Patients with severe dry eye, Corneal thickness less than 400 μm , Pregnancy and lactation, Use of systemic steroids or Anti-metabolites as it

could affect wound healing and evidence with active ophthalmic inflammation.

Pre -crosslinkage evaluation:

Included Uncorrected (UCVA) and best corrected visual acuity (BCVA, Slit lamp biomicroscopy, corneal topography, keratometry and pachymetry using Pentacam and Dilated fundus examination.

Cross linkage (CXL) procedure:-

Technique (Figure 1)

Peschke meditrade GmbH system was used as a source of UV radiation, the system has the following specifications: Homogenized Radiation System, Wavelength: 370 nm, Illumination Intensity: $< 5 \text{ mW/cm}^2$, Illumination Zone: 7,0 mm / 9,0 mm / 11,0 mm and Power Requirements: 90V – 264V. Prior to first treatment the parameters of the corneal cross-linking system is adjusted as follows: Time: 30 min, Irradiation: 3.0 mw/cm^2 .

Surgical steps:

- Topical anaesthetic is applied.
- Cleaning the eye with betadine diluted 1:10.
- Insertion of a lid speculum.
- Pachymetry (using ultrasonic pachymeter) to check the corneal thickness before removal of corneal epithelium at the central and thinnest points.
- Removal of the corneal epithelium over an area of eight to nine mm diameter measured by the calliper. (Riboflavin molecule is too large to penetrate intact epithelium, thus epithelial removal is essential for effective diffusion of riboflavin.), this is done after

loosening the epithelium by brushing the cornea with a micro sponge soaked with diluted alcohol (20%).

- Instillation of MEDIO CROSS® Riboflavin isotonic solution, (Riboflavin 0.1% in Dextran 20%) one drop every three minutes for 30 minutes. The solution comes in a 3 ml syringe.
- Rechecking of the corneal thickness. If thinnest area is under 400 μ m without epithelium, instillation of Riboflavin hypotonic solution (using a 24 G cannula) to swell cornea. 1 drop every 20 seconds for 5 minutes until minimal corneal thickness is at least 400 μ m.
- UV-illumination treatment: the patient is positioned under illumination device. The corneal cross-linking system is turned on and focused (distance between beam aperture and eye is approximately 50 mm) and the beam diameter to corneal diameter is adjusted (only clear cornea should be irradiated; to protect limbal stem cells).
- Instillation of one drop of riboflavin isotonic solution every five minutes is continued. After 30 minutes of UV-illumination the corneal cross-linking system is switched off automatically.
- Antibiotic eye drops are applied to the cornea then the cornea is covered with a bandage contact lens.
- Post operative topical antibiotics (Gatifloxacin 0.3%) and pain killer (Acular 0.5%).
- The patient is closely followed up until the cornea is reepithelialised

Follow up

Follow-up first done after 3 days for contact lens removal, then after one week to evaluate corneal re-epithelialization then the patients will be followed one and six months for assessment of :

1. BCVA
2. Slit lamp examination.
3. Corneal topography, k readings and corneal thickness measurement using pentacam.

3. Results

Twenty keratoconic eyes of 17 patients were included in the study. All patients followed up to six months. Fourteen (70%) patients were males

and three (15%) were females. The mean age was 24.4 years (range: 17–30 years).

*According to keratometric readings:

Table (1) represents the mean preoperative, one month and sixth months postoperative data according keratometric readings.

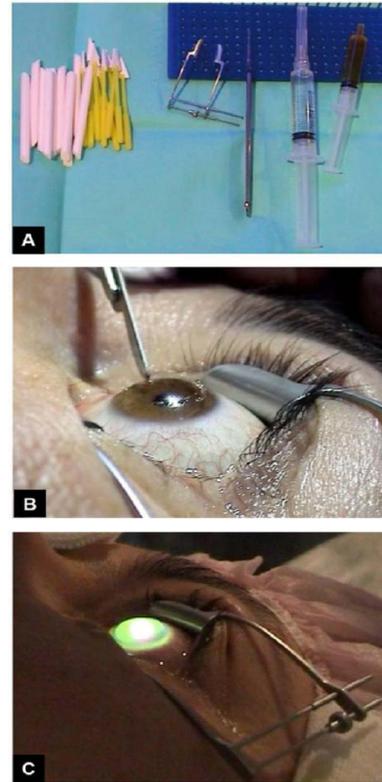


Figure (30): The Cross linkage (CXL) procedure

- A: surgical instruments and riboflavin needed for CXL.
 B: Epithelial removal over an area of 9 mm in diameter.
 C: Fluorescence of the riboflavin-saturated cornea during illumination with UVA.

Table (1): Comparison between preoperative and postoperative mean keratometric reading

Keratometric reading	Mean \pm SD	Range
• Preoperative	50.8 \pm 2.07	48.2 - 55.3
• Post operative		
<i>One month</i>	50.8 \pm 2.07	48.9- 56.1
<i>Six months</i>	45.54 \pm 2.6	39.4 - 49.6
• P-value (ANOVA)	0.38	

From table 1, There was a statistically significant decrease in the mean K value at the apex between the preoperative values and six months values ($P < 0.05$). The preoperative mean apex K value was (50.8 \pm 2.07D) and

changed to (45.54D) at six months. The K value at the apex decreased by a mean of 5.26 D from preoperative values.

*According to central corneal thickness:

Table (2): Comparison between preoperative and postoperative mean central corneal thickness(CCT) follow up

Central corneal thickness(CCT)	Mean \pm SD	Range
• Preoperative	441.85 \pm 27.67	400.5 - 510.2
• Post operative		
<i>One month</i>	430.5 \pm 26.4	390.9- 500.1
<i>Six months</i>	433.5 \pm 25.4	395.4 - 495.6
• P-value (ANOVA)	0.73	

From table 2 , however pachymetry reduced from 441.85 \pm 27.67 μ m pre-operatively to 430.5 \pm 26.4 μ m at one months,six months evaluation showed the pachymetry to increase gradually to 433.5 \pm 25.4 μ m. it was statistically insignificant decrease in the mean K value at the apex between the preoperative values and six months values ($P > 0.05$)

*According to best corrected visual acuity BCVA:

Table (3): Comparison between preoperative and postoperative mean BCVA follow up

BCVA	Mean \pm SD	Range
• Preoperative	0.68 \pm 0.18	0.4- 1.0
• Post operative		
<i>One month</i>	0.67 \pm 0.17	0.5-1.0
<i>Six months</i>	0.76 \pm 0.17	0.5 -1.0
• P-value (ANOVA)	0.34	

From **Table(3)** there was no statistically significant improvement in BCVA between the preoperative and 6 months evaluations. ($P > 0.05$). after 6 months, 7 eyes gained one Snellen line, one eye gained four Snellen lines, one eye gained five Snellen lines, 10 eyes gained one Snellen line of BCVA and only one eye lost one line of BCVA at six months follow up.

*As regarding the postoperative complications, all eyes developed diffuse stromal haze that cleared in 18 eyes (90 %) within 1 month.In only one eye (5 %) the haze cleared within 6 weeks while other sight threatening complications were not recorded in this study.

4.Discussion

In this study, there was a statistically significant decrease in the mean apex K reading between preoperative value (50.8 \pm 2.07 D) and one month value (50.8 \pm 2.07D) and 6 months (45.54 \pm 2.6 D).

Caporossi et al. (2006) recorded topographic mean reduction in dioptric power of 2.1 \pm 0.13 D, and noticed a trend towards a more regular corneal surface accompanied by an increase in the visual acuity after CXL in primary KC.⁴ *Agrawal, (2009)* in another study found similar results among an Indian population of 37 eyes after one year of follow up. K value of the apex decreased by mean of 2.73 D in 66% eyes.⁵ *And also Hersh et al., 2010* stated that the apex K value is a key topographic indicator of the success of CXL because it measures, to some extent, the severity of the keratoconic cone. It was found recently a significant decrease in maximum K value of 1.70 D at 1 year. This statistically significant reduction in K readings revealed that riboflavin-UVA CXL could partially reverse KC.⁶

In contrast to these results, *Arbelaez et al., (2009)* found less reduction in the K value at the apex at the end of one year (by a mean of 1.40 D and 1.63 D, respectively).⁷

As regarding to CCT, there was no statistically significant change in corneal thickness from the preoperative values ($P > 0.05$). The preoperative mean pachymetry was 441.85 \pm 27.67u (range 410-515) and changed to 433.5 \pm 25.4 u (range 400-510).

Findings of *Caporossi et al., (2006)* were similar to those of the present study as they did not find any statistically significant difference in corneal thickness from the preoperative values ($P > 0.05$).⁴

Arbelaez et al., (2009) found a significant reduction in pachymetry using pentacam at the thinnest location and at the apex at 3 months post-operative which increased to reach nearly the preoperative values at the end of one year. Pachymetry at the thinnest location reduced from 452.25 \pm 29.58 μ m pre-operatively to 430.4 \pm 44.38 μ m

m at 3 months. At the apex, there was also a significant decline from $463.96 \pm 27.28 \mu\text{m}$ preoperatively to $439.25 \pm 42.80 \mu\text{m}$ at 3 months. One-year evaluation showed the pachymetry to increase to 455 ± 37.98 at the thinnest location and 463.95 ± 37.36 at the apex⁷. In contrary, *Vinciguerra et al., (2009)* found corneal pachymetry at the thinnest point decreased from baseline values of 451.14 to $436.23 \mu\text{m}$ 1 year after CXL. It increased to recover at $443.04 \mu\text{m}$ 2 years postoperatively.⁹

The reduction in corneal thickness could correspond to the apoptosis that occurs after the treatment (2 to 3 months) and the repopulation that occurs thereafter. Based on this finding, it was suggested that when the CXL treatment is combined with an additional treatment such as Intacs or PRK, a healing interval of approximately 2 to 3 months should be respected to avoid complications caused by the additional damage of the added procedure (*Arbelaez et al., 2009*).⁷

This is similar to the clinical time course of CXL-associated corneal haze, the haze is greatest at one month, plateaus at three months, and decreases significantly after three months postoperatively. Thus, stromal and epithelial healing responses to CXL appear to continue over 6 months, concomitant with the changes in clinical outcomes, which we report here.

Generally, the basic outcomes in our study showed no significant changes in the refractive and topographic outcomes as compared with other studies, and we owe this to the relatively shorter follow up duration and the less number of eyes involved in our study.

In this study, there was no statistically significant improvement in BCVA between the preoperative and 6 months evaluations. ($P > 0.05$).

Similar insignificant BCVA changes obtained by *El-Raggal, (2009)* and *Hersh et al., (2010)*. The cause of BCVA loss in these patients is unclear and did not appear directly related to refractive error or change in corneal topography⁶.

While in contrary, In a study by *Vinciguerra et al. (2009)*, the mean BCVA improved from 0.28 logMAR to 0.14 logMAR twelve months postoperatively⁹.

Also at one year follow-up, *Caporossi et al. (2010)* and *Raiskup-Wolf et al. (2008)* found significant improvements in BCVA (1.34 Snellen lines, and 0.08 logMAR respectively), with continued improvement after one year.^{4,8}

The long term study of *Raiskup-Wolf and colleagues (2008)* included progressive keratoconus

with a maximum follow-up of six years. The BCVA improved significantly ($>$ or $=$ one line) in 53% of eyes in the first year, 57% eyes in the second year, and 58% of eyes in the third year or remained stable (no lines lost) in 20%, 24%, and 29%, respectively.⁹

Sight threatening complications were not encountered in this study denoting the safety of this procedure. All eyes developed diffuse stromal haze that cleared in 18 eyes (90 %) within 1 month. In only one eye (5 %) the haze cleared within 6 weeks. Other sight threatening complications were not recorded in this study.

From above data, Riboflavin-UVA corneal cross-linking is a safe effective treatment to increase stability of the cornea and may arrest or even reverse the progression of moderate keratoconus.

Corresponding author

Faried. M. Wagdy

Ophthalmology, Faculty of Medicine, Menofia University, Menofia, Egypt
faried.wagdy@hotmail.com

References

1. Maurice DM. Some puzzles in the microscopic structure of the stroma. *J Refract Surg*;12:677-83; 1996.
2. Khan Y, Behrens A. Corneal Collagen Cross-Linking for the Treatment of Diseases of the Cornea. *ContempOphth*; 8(8):1-8. 2009.
3. Mazzotta C, Balestrazzi A, Baiocchi S, Tommasi C. Treatment of Progressive Keratoconus by Riboflavin-UVA-Induced Cross-Linking of Corneal Collagen. *Cornea* 2007; 26(4):390-397.
4. Caporossi Aldo, Baiocchi Stefano, Mazzotta Casimo, Traversi Claudio, Caporossi T. Parasurgical therapy for keratoconus by riboflavin-ultraviolet type A rays induced cross-linking of corneal collagen. Preliminary refractive results in an Italian study. *J Cataract Refract Surg*; 32:837-845;2006.
5. Agrawal VB. Corneal collagen cross-linking with riboflavin and ultraviolet – a light for keratoconus: results in Indian eyes. *Indian J Ophthalmol*. 2009; 57(2):111-114.
6. Hersh PS, Greenstein SA, Fry KL, Bhatt J. Natural history of corneal haze after collagen crosslinking for keratoconus and corneal ectasia: Scheimpflug and biomicroscopic analysis. *J Cataract Refract Surg*. 2010; 36(12):2105-2114.
7. Arbelaez M, Sekito M, Vidal C, and Choudhury S. Collagen cross-linking with riboflavin and ultraviolet-A light in keratoconus: One-year results. *Oman J Ophthalmol*. 2009; 2(1): 33-38
8. Raiskup-Wolf F, Hoyer A, Spoerl E, Pillunat LE. Collagen crosslinking with riboflavin and ultraviolet-A light in keratoconus: longterm results. *J Cataract Refract Surg* 34:796-801, 2008.
9. Vinciguerra P, Albe E, Trazza S, Rosetta P, Vinciguerra R, Seiler T, Epstein D. Refractive, topographic, tomographic, and aberrometric analysis of keratoconic eyes undergoing corneal cross-linking. *Ophthalmology* 116:369-378, 2009.