



Changes In The Corneal Topography After Collagen Cross Linking In Patients With Keratoconus

Surbhi Sharma (Assistant Professor, Dr.D.Y.Patil Institute of Optometry & Visual Sciences, Pune)

Dr.Somnath Ghosh (Chief Program Coordinator, department of Allied Health Sciences & Technology, Kazi Nazrul University West Bangal)

Dr.Veshal Vinod Madan (Director, Dr.D.Y.Patil Institute of Optometry & Visual Sciences, Pune)

Susmita Banerjee (Assistant Professor, Dr.D.Y.Patil Institute of Optometry & Visual Sciences, Pune)

INTRODUCTION

Cornea is the most powerful refractive element of the eye which contributes about 43D of refractive power of eye. Since the shape of corneal surface determines its refractive power, even a minor modification of its surface can lead to significant alteration of image formed on retina which can lead to keratoconus.

Keratoconus is a progressive non-inflammatory ectatic condition of the cornea in which the normally round cornea becomes thin and begins to bulge in to a cone like shape. Tiny fibers of the stromal layer are called collagen fiber which helps to hold the shape of cornea in place. When these fibers become weak and cannot hold the shape of the cornea anymore which leads to the cornea becoming bulged and cone shaped. The progressive nature of ectatic condition of keratoconus leads to higher refractive error, thinning of the cornea and scar based on the severity of the disease. [1] The keratoconus are commonly managed with spectacle, contact lenses and surgical intervention based on the severity of the disease. However, contact lenses are the best and successful treatment options for keratoconus. [2]

Tiny fibers of proteins in the eye called **collagens** help hold the cornea in place. When these fibers become weak they cannot hold the shape and the cornea becomes progressively more cone shape. keratoconus is caused by the decrease in the protective **antioxidants** in the cornea. If antioxidant levels are low, the collagen weakens and the cornea bulges out .research suggests the weakening of the corneal tissue that leads

to keratoconus may be due to an imbalance of enzymes within the cornea. This imbalance makes the cornea more susceptible to oxidative damage from compounds called free radicals, causing it to weaken and bulge forward.

Changes in the corneal topography after collagen cross linking in patients with keratoconus

Corneal crosslinking: This procedure, also called corneal collagen cross-linking or CXL, strengthens corneal tissue to halt bulging of the eye's surface in keratoconus.

There are two versions of corneal crosslinking: epithelium-off and epithelium-on. With epithelium-off crosslinking, the outer layer of the cornea (called the epithelium) is removed to allow entry of riboflavin, a type of B vitamin, into the cornea, which then is activated with UV light.

With the epithelium-on method (also called transepithelial crosslinking), the corneal epithelium is left intact during the treatment. The epithelium-on method requires more time for the riboflavin to penetrate into the cornea, but potential advantages include less risk of infection, less discomfort and faster visual recovery.

Corneal CXL with riboflavin is a new technique of corneal tissue strengthening using riboflavin as a photosensitizer and UVA to increase the formation of intra-and interfibrillar covalent bonds by photosensitized oxidants. The major indication for the use of CXL is to inhibit the progression of the corneal ectasias, such as keratoconus and pleucid marginal degenerations. This treatment has also been used to treat infectious corneal ulcers with apparently favorable results. In vitro studies have shown that the cornea absorbs approximately 30% of UVA light while an additional 50% of UVA absorption occurs in the lens.

[2]

It is important to keep in mind that CXL likely “stops” or “reduces” rather than reverses, the progression of the keratoconus. Mild regression that occurs may be explained as an effect of the rearrangement of the corneal lamellae and the surrounding matrix. Due an increased number of cross-linking sites within the collagen molecules after CXL, stiffer fibrils and lamellae are probably generated. This process produces a rearrangement of the corneal lamellae and a relocation of the surrounding matrix, which in turn results in the reduction of the central corneal curvature.

We performed this study because of the small number of studies on the treatment of keratoconic patients with CXL method and the unknown impact of this procedure on the cornea of patients with keratoconus

Corneal collagen cross-linking with riboflavin (CXL), causes new bonds across the adjacent collagen strands in the stromal layer, increases the mechanical strength of the cornea. The purpose of the study was to observe the topographic changes in keratoconic cornea after 6 months of CXL.

Changes in the corneal topography after collagen cross linking in patients with keratoconus

MATERIALS AND METHODOLOGY

It was a prospective study conducted at Wagh Eye Clinic, Gholerod, Pune. Ethically this study was approved by the Institutional ethical committee with Ref No: Opto/16/12/2870A, Dated-16/12/2017. Study population included all the keratoconus patients coming to hospital who were diagnosed with keratoconus. Total 30 eyes of 29 patients were our study subjects. All 29 patients completed the postoperative follow up at 6 months.

Before starting our study patients were informed about the study and the time period. A consent form was signed by all the subjects which stated that they were aware of the study and all the procedures which were about to take place. The keratoconus patients were recruited based on the sets of inclusion and exclusion criteria.

Inclusion criteria included Patients with in the age group of 14-34, patients who underwent collagen cross linking and patients having central corneal thickness more than 400 um were included.

Exclusion criteria included age group below 14 and above 34, Patients who had undergone any intraocular surgery, those with any infectious conditions and patients with ocular or systemic condition that could interfere in the stability of the lacrimal film (i.e., moderate and severe dry eye, eyelid abnormalities,)

Preoperative examination

The assessment of uncorrected visual acuity, manual keratometry, auto kerato-refractometry, objective refraction by means of retinoscopy and best spectacle corrected visual acuity (BSCVA) were recorded. Slit lamp and funduscopy examination was also performed. The corneal topographic values were also measured (CT 1000, Shin-Nippon, Rexam, Japan) before the corneal collagen cross-linking (CXL) treatment. The topography parameters analyzed were: flattest keratometry reading (K1), steepest keratometry reading (K2), average keratometry (Km), topographic astigmatism (dK), and KISA. Pachymetry values were also recorded.

Surgical procedure

CXL was performed using 0.1% riboflavin for 30 min under sterile conditions. The UV-X 1000 machine and the Innocross-R riboflavin isotonic solution (0.1% riboflavin 5-phosphate plus 20% dextran T 500 in 2 mL syringes) were used. Two experienced surgeons performed the procedure. The topical anesthetic 0.5% proxymetacaine hydrochloride (Alcaine; Alcon Laboratories, Inc.) was used for all patients. Epithelial tissue was removed in an 8.0 mm diameter area to allow penetration of riboflavin into the corneal stroma. Thereafter, 0.1% riboflavin was applied (1-2 drops every 5 min) to the cornea for 30 min before irradiation to allow sufficient saturation of the stroma.

Corneal soaking with riboflavin was assessed, and then the cornea (8 mm in size) was exposed to UVA light for 30 min as previously stated. Throughout UVA exposure, riboflavin solution was applied (1-2 drops every 5 min). Upon completion of treatment, the eye was washed with balanced salt solution, and antibiotic eye drops (0.5% moxifloxacin) and steroid eye drops (0.1% dexamethasone) were applied. A bandage contact lens was placed in the eye until complete re-epithelialization.

. Follow-up examination was performed after 1 week, 1 month and 6 months. The topographic values were recorded at 1 and 6 months and analyzed with preoperative data.

Statistical Analysis

The descriptive statistics and paired t-test test were done using SPSS software version 17 (SPSS Inc., Chicago, IL, USA). Results were presented as mean \pm standard deviation or error where applicable. The threshold for statistical significance was set at a *P* value less than 0.05.

Results

All 29 patients completed the postoperative follow up at 6 months. The mean age of the patients was 21.13 ± 6.79 years (range: 14-32 years) out of which 17 were male and 11 females.

The mean simulated keratometry reading for pre and post CXL were 53.63 ± 6.05 D and 53.21 ± 5.73 D, respectively. There was no significant difference ($p=0.511$) observed after CXL in keratoconic cornea [Table 1].

PARAMETERS	VALUE	P VALUE
Pre mean keratometry	53.63 ± 6.05 D	0.5
Post mean keratometry	53.21 ± 5.73 D	

Mean topographic astigmatism (DK) in pre and post CXL were 6.36 ± 3.66 D and 5.60 ± 3.24 D, respectively. The changes in DK were significantly different ($p=0.031$) between pre and post CXL [Table 2].

PARAMETERS	VALUE	P VALUE
Pre mean astigmatism(DK)	6.36 ± 3.66 D	0.03
Post mean astigmatism(DK)	5.60 ± 3.24 D	

Mean keratoconus percentage index (KISA %) in pre and post CXL were $5913.76 \pm 7380.10\%$ and $5201.40 \pm 6927.34\%$, respectively. However, the changes were not significantly different ($p=0.526$) [Table 3].

PARAMETERS	VALUE	P VALUE
Pre mean index (KISA %)	$5913.76 \pm 7380.10\%$	0.52
Post mean index (KISA %)	$5201.40 \pm 6927.34\%$,	

Study has showed no significant changes in topographic values after CXL (The mean simulated keratometry reading for pre and post CXL were 53.63 ± 6.05 D and 53.21 ± 5.73 D, respectively.). However, significant changes were observed in topographic astigmatism after CXL treatment. (Mean topographic astigmatism (DK) in pre and post CXL were 6.36 ± 3.66 D and 5.60 ± 3.24 D, respectively).

Changes in the corneal topography after collagen cross linking in patients with keratoconus

DISCUSSION

Over the last decade, there have been proposed new and improved interventions for KC intended to considerably decrease transplantation rates and arrest disease progression CXL is, at present, the only treatment that can slow down or even stop KC progression. The purpose of CXL is to stabilize the underlying disease process, and corneal topography (Kmax and Km) is considered one of the key outcome measures.

CXL is a new treatment for patients with keratoconus so, response to treatment maybe different among different racial and ethnic groups. In this research, we survey topographic corneal changes six months after CXL in patients with corneal keratoconus .

A study by **Jankov *et al.*** found that progression of keratoconus stopped in all patients who were actively progressing 6 months prior to treatment. After treatment, no eyes lost lines of best spectacle-corrected acuity (BSCVA), 12 maintained BSCVA, one gained one line of BSCVA, five gained two lines of BSCVA and one patient gained three lines of BSCVA.

Mauro C. Tiveron *Jet al.* performed a study on Topographic outcomes after corneal collagen crosslinking in progressive keratoconus, concluded that CXL promoted stabilization or improvement of keratometric values and visual acuity. They found that keratoconus apex stability may be achieved 3 months after the procedure. There was no significant difference in keratometric and refractive values measured between male and female patients.

Wollensaket *al*[5] reported that the riboflavin/UVA treatment leads to a dose-dependent keratocytodamage that can be expected in human corneas down to a depth of $300\mu\text{m}$ using a surface UVA dose of 5.4 J/cm^2 . They concluded that a standard surface UVA dose of 3mW/cm has a toxic effect on the endothelial cells of corneas thinner than $400 \mu\text{m}$.

In 2007, **Chan *et al.*** performed a retrospective, non-randomized, comparative case series of 12 eyes of nine patients who had inferior-segment INTACS placement without CXL and 13 eyes of 12 patients who had inferior-segment INTACS placement followed by CXL The INTACS with CXL group had a significantly greater reduction in cylinder than the INTACS-only group and there was a significantly greater reduction in max K in the INTACS with CXL group Chan *et al.* concluded that the addition of CXL to the INTACS procedure resulted in greater improvements than INTACS insertion alone for keratoconus cases.

A study by **Peter S.Hershet *al.*** in 2017[4] on Corneal Collagen Crosslinking for Treatment of Corneal ectasia after Refractive Surgery reported that the mean maximum K value of the crosslinking treatment group decreased by 0.7 D at 1 year compared with 0.6 D steepening of the control group, a difference of 1.3 D between treatment and control. Thus, crosslinking does appear, generally, to have a beneficial effect on corneal topography in ectasia patients over 1 year.

A study by **Hmed Abdel-KarimEl-Massryet *al.*** in 2017 did a study on corneal collagen cross-linking for keratoconus on the ocular higher-order aberrations concluded that total coma, and spherical aberrations decreased after CXL. Coma has a direct relationship with the improvement of visual function. There was statistically significant improvement in uncorrected visual acuity and best-corrected visual acuity between the preoperative and 6-month evaluations ($P < 0.001$).

CXL has some benefits compared with other methods of keratoconus treatment. There are no cuts in the body of the cornea. It is much safer than a corneal graft which was very successful in the past, and then even a gas-permeable contact lens, and also there is no chance of rejection (some grafts tend to last around 10-15 years). The transplant carries risks such as infection, rejection, cataracts, glaucoma, and astigmatism. At 15 years, there is no difference in the survival rate between penetrating corneal transplants performed for keratoconus and those performed for all other indications. Young keratoconus patients are likely to need one or more repeated grafts during their lifetime. Cross-linking avoids the removal of any corneal structural tissue (only the surface epithelial cells are removed and these grow back mostly within two days).

Our study showed no significant changes in topographic values after CXL. However, significant changes were observed in topographic astigmatism after CXL treatment. All the above studies prove that the collagen cross linking is the best treatment for progressive keratoconus.

Conclusion:

Study has showed significant changes in topographic astigmatism after CXL treatment, however no significant changes were observed in topographic values after CXL. In conclusion, CXL may help in stabilization of keratometric values in keratoconus patients

Footnotes

Source of Support: Wagh Eye Clinic, Ghole road, pune.

Conflict of Interest: None declared.

REFERENCES

1. International Association of Contact Lens Educators IACLE Module 8 2003; Sydney, NSW.
2. American Academy of Ophthalmology (AAO).
3. Agrawal VB. Corneal collagen cross-linking with riboflavin and ultraviolet - A light for keratoconus: Results in Indian eyes. *Indian J Ophthalmol.* 2009;
4. Peter S. Hersh, evaluated the safety and efficacy of corneal collagen crosslinking (CXL) for the treatment of corneal ectasia after laser refractive surgery. *Ophthalmology* 2017 Oct;124(10):1475-1484. doi: 10.1016/j.ophtha.2017.05.036. Epub 2017 Jun 24.
5. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-A-induced collagen cross-linking for the treatment of keratoconus. *Am J Ophthalmol.* 2003;
6. Hersh PS, Greenstein SA, Fry KL. Corneal collagen crosslinking for keratoconus and corelectasia: one-year results. *J Cataract Refract Surg.* 2011 Jan; 37(1):149-60.
7. Greenstein SA, Fry KL, Hersh MJ, Hersh PS. Higher-order aberrations after corneal collagen crosslinking for keratoconus *J Cataract Refract Surg.* 2012;38(2):292–302.
8. Greenstein, S.A., Fry, K.L., and Hersh, P.S. Corneal topography indices after corneal collagen crosslinking for keratoconus and corneal ectasia: one year result. *J Cataract Refract Surg* 2011 Apr;37(4):691-700.
9. Ghanem RC, Santhiago MR, Berti T, Netto MV, Ghanem VC. Topographic, corneal wavefront, and refractive outcomes 2 years after collagen crosslinking for progressive keratoconus. *Cornea*, 2014;33(1):43–48.
10. Hjortdal J. Collagen cross-linking for advanced progressive keratoconus. *Cornea*, 2013;
11. Hafezi F, Kanellopoulos J, Wiltschko R, Seiler T. Corneal collagen crosslinking with riboflavin/UVA for the treatment of induced keratectasia after LASIK. *J Cataract Refract Surg.* 2007;33(12):2035-40. Comment in: *J Cataract Refract Surg.* 2008;34(6):8789; author reply 879.
12. Ivarsen A, Hjortdal J. Collagen cross-linking for advanced progressive keratoconus. *Cornea.* 2013;32(7):903-6.
13. Coskunseven E, Jankov MR, Hafezi F. Comparative study of corneal collagen cross-linking with Riboflavin and UVA irradiation in patients with keratoconus. *J Refract Surg.* 2009;25:371–6.
14. Vinciguerra P, Camesasca FI, Albe E, Trazza S. Corneal collagen cross-linking for ectasia after excimer laser refractive surgery: 1-year results. *J Refract Surg.* 2009;1–12. [Pub Med]
15. Spoerl E, Mrochen M, Sliney D, Trokel S, Seiler T. Safety of UVA – riboflavin cross-linking of the cornea. *Cornea.* 2007;26:385–9. [PubMed: 17457183]
16. Wollensak G. Corneal collagen crosslinking: New horizons. *Expert Review Ophthalmol.* 2010; 5:201–15.
17. Raiskup-Wolf F, Hoyer A, Spoerl E, Pillunat LE. Collagen crosslinking with riboflavin and ultraviolet-A light in keratoconus: Long-term results. *J Cataract Refract Surg.* 2008; 34:796–801 [PubMed: 18471635].
18. Sharma, A., Nottage, J.M., Mirchia, K. et al. Persistent corneal edema after collagen cross-linking for keratoconus. *Am J Ophthalmol* 2012 Dec;154(6):922-926.e1. doi: 10.1016/j.ajo.2012.06.005. Epub 2012 Sep 7.

19. Wisse RPL, Gadiot S, Soeters N, Godefrooij DA, Imhof SM, van der Lelij A. Higher-order aberrations one year after corneal crosslinking for keratoconus and their independent effect on visual acuity. *J Cataract Refract Surg.* 2016;42(7):1046–1052.
20. American Academy of Ophthalmology. Corneal Collagen Crosslinking: Treatment Results InKeratoconus Patients. *Science Daily.* 2008. Nov 9, [Last accessed on 2012 May 25].

