Original Article

Visual and Keratometric Results after Corneal Collagen Cross Linking in Keratoconus

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Purpose: To evaluate the safety and efficacy of riboflavin – ultraviolet type A light rays induced cross-linking of corneal collagen in keratoconus.

Material and Methods: Forty cases of collagen cross-linking were studied retrospectively. Preoperative examination included uncorrected and best-corrected visual acuity, refraction, slit-lamp, fundoscopy and orbscan. Routine cross-linking procedure was performed. Postoperatively, a bandage contact lens was applied which was removed on the 5th day. Subsequent postoperative examinations were performed monthly for six months.

Results: Forty cases completed six months of follow up. There were 21 males and 19 females in the study. The age range was 16-32 years. In the six months study, 13 out of 40 cases showed improvement of un-corrected visual acuity by one line and 15 out of 40 had improvement by 2 or more lines. Only two eyes out of 40 (5%) lost 2 or more lines of uncorrected visual acuity. Keratometric improvement was seen in 22.5%. 65% showed keratometric stability while progression was seen in 12.5%.

Conclusion: Collagen cross – linking is a safe and effective procedure in halting the progression of keratoconus.

Keratoconus is a progressive, non-inflammatory, bilateral (usually asymmetrical) disease of the cornea, characterized by paraxial stromal thinning that leads to corneal surface distortion. The thinning and protrusion in keratoconus induces myopia, irregular astigmatism and scarring, resulting in visual loss and mild to marked impairment of vision. It starts around puberty. Consanguineous marriages and genetic factors have been suggested in the etiology. Asian population is more likely to present with keratoconus compared to whites[1]. It has been said that the transmission is autosomal dominant with incomplete penetrance. Its incidence in the general population is about one in 2000[2].

In keratoconus, central anterior stroma and Bowman's membrane undergo changes in collagen structure and extracellular matrix, apoptosis and necrosis of keratocytes[3,4]. In the early stages of the disease, spectacles and contact lenses are utilized for visual improvement. In cases with stromal opacification, penetrating keratoplasty (PKP) is done. Eventually, 21% of patients require PKP to restore corneal anatomy and eyesight[5]. In cases of advanced disease in younger patients with transparent cornea, lamellar keratoplasty[6,7] and use of Intacs can be employed.

A recent advancement in treating keratoconus is collagen cross-linking (CXL). It Is a method which addresses the underlying pathophysiology of keratoconus[8]. CXL involves photopolymerization of stromal collagen fibres by utilizing riboflavin or vitamin B_2 and UV (ultraviolet) type A radiation[9,10]. There is a dual function of riboflavin. Not only does it act as a photosensitizer for the production of oxygen free radicals (which induce physical cross-linking of

collagen) but also gives a "shielding effect" by absorbing 90% of UV-A radiation thereby preventing damage to the deeper ocular structures. The net result of photopolymerization is increased rigidity of corneal collagen[11], which increases the corneal strength by more than 300%[12]. The process of cross-linking stabilizes the stromal collagen which results in increased biomechanical stability of cornea[13]. A similar mechanism has been seen in corneal aging[14] and young diabetics[15].

The present study was conducted to evaluate the safety and efficacy of CXL in visual improvement and halting the keratometric progression in keratoconus.

MATERIAL AND METHODS

Forty cases that underwent CXL at Amanat Eye Hospital Rawalpindi were studied retrospectively. The time period of study was from Feb. 2008 to Nov. 2010. History of contact lens wear was taken. Soft contact lens was removed for at least 2 weeks and hard contact lens 4 weeks prior to eye examination. Routine eye examination was performed in all the cases. Examination included uncorrected and best spectacle-corrected visual acuity, refraction and keratometry. Orbscan (topography and pachymetry) was performed in all the cases preoperatively. Keratoconus was confirmed by Orbscan findings of increased posterior corneal map differential value of 50 µm or more (with respect to the best fitting sphere), anterior corneal map differential of 25 µm or more, irregular keratometric maps with inferior steepening and central corneal thinning to less than 500 µm.

The inclusion criteria for CXL consisted of patients who fitted diagnostic criteria of keratoconus, evidence of progression on topography and pachymetry, no prior history of ocular surgery, treated eye to have a maximum corneal power of 47-60 D, corneal thickness greater than 450µm and absence of corneal scarring. The cases excluded from the procedure were those with history of prior ocular surgery, average corneal power greater than 60 D, corneal scarring, corneal thickness less than 450 µm, history of herpes simplex keratitis, history of uveitis and pre-existing glaucoma.

After corneal epithelial debridement, riboflavin eye drops were instilled for 30 min. Slitlamp examination was performed to confirm the presence of flare in the anterior chamber. The eye was exposed to UV-A light of 370 nm wavelength at 3mw/cm^2 for a further 30 minutes utilizing the UV-X system. Topical antibiotic was instilled and a bandage contact lens applied. The patient was advised a topical antibiotic/ steroid combination for two weeks. Bandage contact lens was removed on the 5th day. Subsequent postoperative examinations were performed monthly for six months. The data was analyzed on SPSS 17.

RESULTS

40 cases completed six months of follow-up. There were 21 male and 19 female eyes in the study (Fig 1). All had progressive keratoconus. 22 cases (55%) had mild, 13 cases (32.5%) moderate and 5 cases (12.5%) had severe keratoconus. Seven patients underwent bilateral CXL. 12.5% of the cases had been using rigid gas permeable c ontact lenses prior to treatment. The age range was 16 – 32 years. Majority of the cases were in the 16-20 years age group (Table 1).

Table 1: Age range statistics

Age (Years)	Frequency n (%)	Valid Percentage	Cumulative Percentage
16 - 20	24 (60)	60	60
21 - 26	10 (25)	25	85
27 - 32	6 (15)	15	100
Total	40 (100)	100	

Fig 1: Male/female distribution (n=40)

Thirteen out of 40 cases (eyes) showed improvement of un-corrected visual acuity (UCVA) by one line and 15 out of 40 had improvement by 2 or more lines (Fig 2). A total of 28 out of 40 eyes (70%) showed visual improvement. Spearman Correlation

showed the difference to be statistically significant with a p-value of <.05 (confidence limit 95%).

Only two eyes out of 40 (5%) lost 2 or more lines of preoperative UCVA. A mean improvement of 1.2 lines of UCVA was seen by the end of 6 months.

The mean preoperative keratometric reading was 49.14D, which reduced to 49.02D by the end of six months. However, this difference was not statistically significant.

According to keratometric changes, three categories were formed retrospectively; keratometric improvement, stability and progression of original disease groups. A difference of more than 0.50 D between the preoperative and postoperative mean keratometric reading was taken as significant. In the six months study, keratometric improvement was seen in 9 out of 40 cases (22.5%). 26 out of 40 (65%) showed keratometric stability while progression was seen in 12.5% i.e. 5 out of 40 eyes (Fig 3).

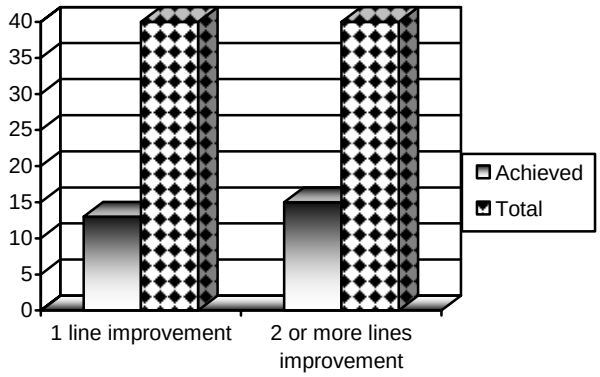

Fig 2: Improvement in UCVA (n=40)

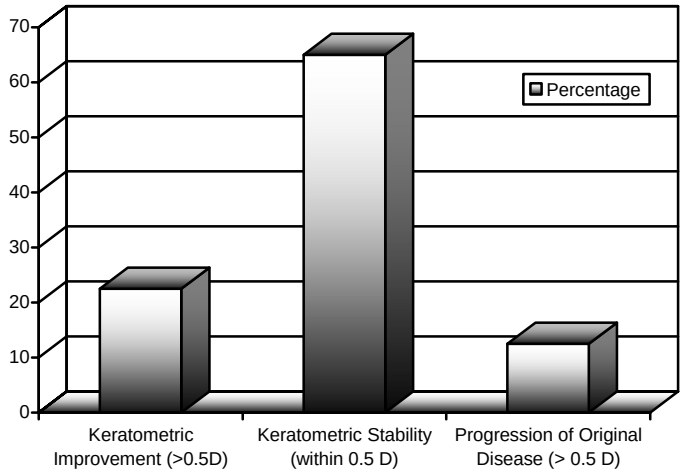

Fig 3: Six months keratometric study (n=4

No ocular complications related to CXL including keratitis or corneal scarring were seen in our cases.

DISCUSSION

Corneal collagen cross linking is a new method for the treatment of keratoconus that acts by increasing the cross links between and within the collagen fibers utilizing UV-A light and riboflavin, both of which act as photomediators[16]. A growing body of recent research has found that not only did CXL stabilize progression of keratoconus, it also resulted in "significant" improvements in visual acuity and reductions in aberrations[8].

Various studies have shown that UV-A light and riboflavin resulted in significant stiffening in the anterior 300μm of cornea which reduced the anterior elevation significantly[17,18].

A study of 117 eyes undergoing CXL published in the Journal of Cataract & Refractive Surgery by Koppen C et al[19] found that one year postoperatively, 2.9% lost two or more Snellen's lines. Our results showed that two eyes (5%) lost 2 or more lines of UCVA after 6 months. In their study, 7.6% of eyes had continued progression. Four of the eyes in their study developed keratitis as compared to none in our study. They concluded that the inclusion criteria of CXL may significantly reduce the complications and failures by including a patient's age of less than 35 years and a preoperative maximum k reading of less than 58.0D. In our study, the age range was 16-32 years.

In study of 153 eyes conducted at Dresden[20], keractoectasia significantly decreased in the first year by 2.29 D, in the second year by 3.27 D and in the third year by 4.34 D. Visual acuity improved in at least one line in 48.9% and remained stable in 23.8% in the first year. Our study showed an improvement of UCVA by one or more lines in 70% of cases in the first six months. Like our study, no serious side effects were noted in their study, while three patients showed continued progression of keratoconus and received re-treatment.

Visual results of Agarwal[21] in Indian eyes showed improvement in best – corrected visual acuity (BCVA) in at least one line in 54% and stability in 28% of eyes after 12 months. In one of the studies conducted in a military hospital in Pakistan,[22] mean preoperative

BCVA improved by at least one line in 61.29%, remained stable in 35.48% and deteriorated in 3.23% of eyes. Preoperative mean of steepest k value was 50.60 ± 5.41 D, which reduced to 48.85 ± 6.11 D. The steepest k value reading improved in 67.74%, remained stable

in 25.81% and deteriorated in 6.45% of cases. 2 eyes (6.45%) developed keratitis leading to scarring.

Dan Reinstein has described that epithelium is thinner in patients with keratoconus, even before keratoconus is evident on corneal topograghy[23]. There are some differences in the results that likely stem from removal of epithelium during standard CXL that results in a thinner corneal pachymetry, at least in the short-term. The k values are said to be steeper when the cornea is measured after epithelium is debrided and supports the notion that epithelium acts as a "masking agent" in very early stage of keratoconus.

In our cases, epithelium was routinely removed before the CXL procedure, which might have caused some keratometric steepening postoperatively. The difference between the preoperative and postoperative mean keratometric readings was not statistically significant. However, the UCVA improved in 70% of cases, which might have been caused by increased tensile strength and a more regular curvature of the cornea. Previous studies have shown that CXL results in stabilization of keratoconus in 90% of cases. However, the disease shows continued progression in about 10%. In our study, 12.5% of eyes had continued progression of keratometric readings. This progression of original disease pattern in our study resembles previous findings.

The limitations of our study are short duration of follow up i.e. six months, lack of control group and postoperative topographic comparison. Hersh, Greenstein and Fry evaluated 71 eyes of 58 patients who underwent CXL. They observed significant increase in keratometry after one month, which was followed by significant decrease between 1 to 3 months and 3 to 6 months. However, no significant change was observed between 6 months to one year.[24] This adds value to our study of 6 months duration. We did not have a control group because it was a retrospective study. Our study was concentrated around keratometric and topographic diagnosis of keratoconus and comparison of preoperative versus postoperative visual and keratometric changes. Regarding keratoconus, Maguire and Lowry observed that refractive changes at the cone apex were a good indicator of progression[25].

We recommend that further studies be carried out with larger treated and control groups for a longer duration and curvature and elevation-guided topographic comparisons be carried out to further ascertain the beneficial effects of CXL.

CONCLUSION

Collagen cross-linking with UV-A light and riboflavin is a safe and effective procedure in improving the visual acuity and halting the progression of keratoconus.

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REFERENCES

1. **Georgiou T, Funnell CL, Cassels – Brown A, et al.** Influence of ethnic origin on the incidence of keratoconus and associated atopic disease in Asians and white patients. Eye 2004; 18: 379-83.
2. **Rabinowitz YS.** Keratoconus. Surv Ophthalmol 1998; 42: 297-319.
3. **Radner W, Zehetmayer M, Skorpik C, et al.** Altered organization of collagen in the apex of keratoconus corneas. Ophthalmic Res. 1998; 30: 327-32.
4. **Kaldawy RM, Wagner J, Ching S, et al.** Evidence of apoptotic cell death in keratoconus. Cornea 2002; 21: 206-9.
5. **Waller SG, Steinert RF, Wagoner MD.** Long-term results of epikeratoplasty for keratoconus. Cornea 1995; 14: 84-8.
6. **Tan BU, Purcell TL, Torres LF, et al.** New surgical approaches to the management of keratoconus and post-lasik ectasia. Trans Am Ophthalmol Soc. 2006; 104: 212-20.
7. **Bilgihan K, Ozdek Sc, Sari A, et al.** Microkeratome assisted lameller keratoplasty for keratoconus: Stromal sandwich. J Cataract Refract Surg. 2003; 29: 1267-72.
8. **Arbelaez MC, Sekito MB, Vidal C,et al.** Collagen cross-linking with riboflavin and ultraviolet-A light in keratoconus: One – year results. Oman Journal of Ophthalmology. 2009; 2: 33-8.

9. **Wollensak G.** Crosslinking treatment of progressive kerato-conus: New hope. Curr Opin Ophthalmol. 2006; 17: 357-60.
10. **Wollensak G, Spoerl E, Seiler T.** Riboflavin/ ultraviolet-A-induced collagen crosslinking for the treatment of keratoconus. Am J Ophthalmol. 2003; 135: 620-7.
11. **Wollensak G, Spoerl E, Seiler T.** Stress-strain measurements of human and porcine corneas after riboflavin-ultraviolet-A-induced cross-linking. J Cataract Refract Surg. 2003; 29: 1780-5.
12. **Hafezi F, Mrochen M, Iseli HP, et al.** Collagen cross-linking with ultraviolet A and hypoosmolar riboflavin solution in thin corneas. J Cataract Refract Surg. 2009; 35: 621-4.
13. **Wollensak G, Spoerl E, Wilsch M, et al.** Endothelial cell damage after riboflavin-ultraviolet-A treatment in the rabbit. J Cataract Refract Surg. 2003; 29: 1786-90.
14. **Daxer A, Misof K, Grabner B, et al.** Collagen fibrils in the human corneal stroma: Structure and aging. Invest Ophthalmol Vis Sci. 1998; 39: 644-8.
15. **Seiler T, Huhle S, Spoerl E, et al.** Manifest diabetes and keratoconus: A retrospective case-control study. Graefe's Archive for Clinical and Experimental Ophthalmology. 2000; 238: 822-5.
16. **Spoerl E, Seiler T.** Techniques for stiffening the cornea. J Refract Surg. 1999; 15: 711-3.
17. **Mazzotta C, Balestrazzi A, Traversi C, et al.** Treatment of progressive keratoconus by riboflavin – UV – A induced cross – linking of corneal collagen: Ultrastructural analysis by Heidelberg Retinal Tomograph II in vivo confocal microscopy in humans. Cornea. 2007; 26: 390-7.
18. **Seiler T, Hafezi F.** Corneal cross – linking – induced stromal demarcation line. Cornea. 2006; 25: 1057-9.
19. **Koppen C, Vryghem JC, Gobin L, et al.** Keratitis and corneal scarring after UVA / riboflavin cross – linking for keratoconus. J Refract Surg. 2009; 25: 819-23.
20. **Hoyer A, Raiskup-Wolf F, Spörl E, et al.** Collagen cross-linking with riboflavin and UVA light in keratoconus. Results from Dresden. Ophthalmologe. 2009; 106: 133-40.
21. **Agarwal VB.** Corneal collagen cross-linking with riboflavin and ultraviolet-A light for keratoconus. Results in Indian eyes. Ind J Ophthalmol. 2009; 57: 111-4.
22. **Khan MD, Ameen SS, Ishtiaq O, et al.** Preliminary results of UV – A riboflavin cross – linking in progressive cases of keratoconus in Pakistani population. Pak J Ophthalmol. 2011; 27: 21-6.
23. **Reinstein DZ, Archer TJ, Gobbe M.** Corneal epithelial thickness profile in the diagnosis of keratoconus. J Refract Surg. 2009; 25: 604-10.
24. **Hersh PS, Greenstein SA, Fry KL.** Corneal collagen cross – linking for keratoconus and corneal ectasia: One – year results. J Cataract Refract Surg. 2011; 37: 149-60.
25. **Maguire IJ, Lowry JC.** Identifying progression of subclinical keratoconus by serial topography analysis. Am J Ophthalmol. 1991; 112: 41-5.