DOI: 10.7860/JCDR/2024/63008.19057

Original Article

Ophthalmology Section

Effect of Corneal Collagen Crosslinking with Riboflavin in Patients of Progressive Keratoconus: A Prospective Cohort Study

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ABSTRACT

Introduction: Keratoconus is a non inflammatory disease characterised by progressive corneal thinning that results in a cone-like ectasia, irregular astigmatism, and decreased vision. Advanced disease can result in corneal scarring and blindness, necessitating penetrating keratoplasty. The only treatment believed to have the ability to stop or decrease the progression of keratoconus is Collagen Cross-Linking (CXL).

Aim: To evaluate the efficacy of corneal collagen cross-linking with riboflavin (C3R) in patients with keratoconus by studying the outcomes in terms of Uncorrected Visual Acuity (UCVA), Best Corrected Visual Acuity (BCVA), manifest refraction, and corneal topography.

Materials and Methods: A hospital-based prospective cohort study was conducted at the Regional Institute of Ophthalmology, Government Medical College, Thiruvananthapuram, Kerala, India from June 2017 to June 2018. Fifteen eyes of 12 patients who underwent corneal collagen cross-linking for progressive keratoconus were included. Routine ophthalmological examinations was done for all patients. Patients under the age of 35 years with progressive keratoconus, an average K value not exceeding 60 D, and who had not undergone any other surgical modalities of treatment were included in the study. Patients with scarred cornea or hydrops, active ocular infection, or pachymetry <400 µm were excluded. Detailed informed consent was obtained from all patients before surgery. Preoperative UCVA, BCVA cylinder, Spherical Equivalent (SE), and topography values were obtained. All patients were followed-up at three and six months postoperative period to look for changes in UCVA, BCVA, manifest refraction, and corneal topography. Data were expressed as the mean±Standard Deviation (SD) pre- and postoperatively and analysed statistically using the paired t-test, with $p<0.05$ considered statistically significant. Analysis was conducted using Statistical Package for Social Sciences (SPSS) version 16.0.

Results: On follow-up at six months post-treatment, UCVA (log MAR) improved from 0.87±0.40 to 0.65±0.35 (p-value=0.001), and BCVA (log MAR) changed from 0.37±0.21 to 0.17±0.22 (p-value=0.001). K max decreased from 54.90±6.05 to 52.67±5.02 (p-value=0.001), and K min decreased from 48.14±4.24 to 45.93±4.07 (p-value=0.001). Astigmatism and SE also showed statistically significant improvement post-procedure (p-value 0.001 and 0.002, respectively). Astigmatism reduced from -3.50±1.58 to -2.90±1.37. SE reduced from -4.93±3.92 to -4.28±3.48. No significant complications were noted in any of the patients.

Conclusion: The CXL is an effective procedure for stabilising the progression of keratoconus, thus reducing the burden of preventable blindness and the need for keratoplasty.

Keywords: Best corrected visual acuity, Corneal ectasia, Corneal topography

INTRODUCTION

Keratoconus is a bilateral, non inflammatory corneal ectasia characterised by progressive corneal thinning and protrusion leading to progressive myopia, irregular astigmatism, and corneal scarring [1]. Several modalities such as hard contact lenses, intracorneal stromal ring implantation, and penetrating keratoplasty are used to treat keratoconus [1]. Spectacles and contact lenses are the usual treatment modalities in the early stages of keratoconus. As the disease advances, severe corneal astigmatism and stromal opacities develop to the point where contact lenses can no longer provide useful vision, and penetrating keratoplasty becomes necessary to restore visual function [2]. Penetrating keratoplasty is the most commonly performed surgical procedure for keratoconus, but is associated with complications, including graft rejection [3], and is also limited by the availability of donor corneas in developing countries. Additionally, all these techniques only correct the refractive error of the cornea with no effect on the progression of keratoconus [4]. The only treatment believed to have the ability to stop or decrease the progression of keratoconus is CXL [5]. CXL changes the biomechanical, thermomechanical, and morphological properties of the cornea [6]. This procedure, utilising riboflavin and ultraviolet-A light, significantly increases the biomechanical strength of the cornea by photochemical cross-linking of individual collagen fibers [4]. Riboflavin (Vitamin B2) has a dual function of acting as a photosensitiser for the production of oxygen free radicals, which induce physical CXL, and it provides a shielding effect by absorbing 90% of the UV-A irradiation, thereby preventing damage to deeper ocular structures. UV-A light of 370 nm wavelength at 3 mW/cm^2 allows approximately 95% of the UV light to be absorbed into the cornea; thus, there is no risk of damage to the lens and retina [2,7]. It increases the stiffness and rigidity of the anterior corneal stroma and enhances corneal resistance to proteolytic enzymes by inducing photochemical cross-linking and covalent bonding between individual collagen fibers [5], thus preventing the progression of corneal ectasia in keratoconus and stabilising the vision. CXL halts the progression of keratoconus with a failure rate of approximately 3% and a complication rate of ≤1% [8]. Since corneal CXL alters the corneal shape and structure, it would be helpful to assess resulting changes in quantitative descriptors of the cornea, which can affect the clinical outcome of this procedure. Studies by Bamdad S et al., and Greenstein SA et al., have shown that CXL improves visual acuity, average keratometry values, and definable measures of corneal topography regularity [9,10].

Though it has been extensively studied in other parts of the world, there are limited studies regarding the same in India. The current study aims to evaluate the efficacy of C3R in preventing the progression of keratoconus and stabilising the vision by studying the outcome in terms of UCVA, BCVA, manifest refraction, and

corneal topography in South Indian patients. The study also had an objective to note the side-effects of CXL, if any.

MATERIALS AND METHODS

This hospital-based prospective cohort study was conducted at the Regional Institute of Ophthalmology, Government Medical College, Thiruvananthapuram, Kerala, India from June 2017 to June 2018. Ethical clearance was obtained from the Institutional Ethics Committee (IEC No.068/HEC/RIOTVPM dated 35/02/2017). Informed consent was obtained from all the patients.

Inclusion criteria: Patients aged <35 years with progressive keratoconus who were not improving with spectacles or contact lenses and with an average k value not exceeding 60D were included in the study.

Exclusion criteria: Patients who had undergone any other surgical modalities of treatment for keratoconus were excluded. Pregnant or lactating women, patients with active ocular inflammation, chronic ocular surface disease, autoimmune diseases, and a past history of herpetic disease were also excluded from the study. Patients with a scarred cornea, central corneal thickness <400 μm, and vision at presentation <2/60 were also excluded from the study.

Sample size: The sample size was calculated from preoperative and postoperative UCVA in the reference study by Arbelaez MC et al., based on the formula [2].

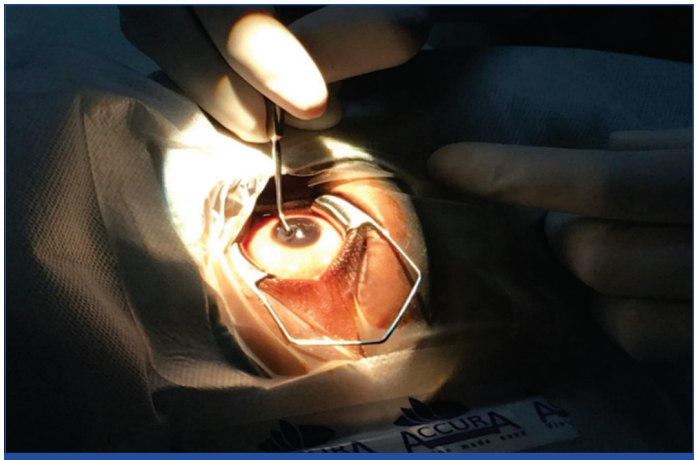
$N=(z_{\alpha/2}+z_{1-\beta})^2 \ (\sigma_1^2+\sigma_2^2)/(\mu1+\mu_2)^2$ Where $(z_{\alpha/2}+z_{1-\beta})^2=7.9$ for $\alpha=0.05$ and $\beta=0.2$

In the reference study, the mean preoperative UCVA was found to be 1.18±0.69 and the mean six months postoperative UCVA was 0.63±0.32. So the calculated sample size was 15.

A history was taken using a proforma, routine ophthalmological examination, and measurement of the following parameters before and after C3R: UCVA, BCVA, cylinder value, and SE. UCVA and BCVA were measured using a log MAR chart. Corneal topography and central corneal thickness were measured with an ultrasonic Pachymeter (Quantel medical- compact touch). Corneal curvature was measured with an auto refractometer/keratometer and corneal topography (Topcon corneal topographer-KR-1W). Refraction was measured with an auto refractometer and subjective refraction. SE was calculated as the spherical refractive error plus 0.5×cylindrical refractive error [11]. For example, if the refraction is +2.50 DS -0.50DC at 90°, the SE is calculated as SE=+2.50+(-0.50/2)=+2.25 DS.

Study Procedure

Initial assessment included history taking using a proforma, and routine ophthalmological examination was done. The procedure was performed in the operating room under sterile conditions. Topical proparacaine hydrochloride (0.5%) eye drops were instilled before the procedure. The central 8 mm corneal epithelium was removed by mechanical debridement to allow better penetration of riboflavin [Table/Fig-1]. This was followed by the application of the photosensitiser riboflavin (0.1% solution) to the de-epithelised cornea every two minutes for a period of approximately 30 minutes. Exposure to UV-A light was initiated after ensuring that adequate penetration of riboflavin had occurred, as indicated by the presence of yellow flare in the anterior chamber [Table/Fig-2]. The cornea was then subjected to UV-A radiation (370 nm) in a dose of 3 mW/cm^2 by an irradiating source placed at a distance of 5 cm from the center of the cornea. To complete photosensitisation and to provide photoprotection by a barrier effect, riboflavin drops were again instilled every two minutes during the irradiation treatment. On completion of the procedure, antibiotic drops were instilled, following which a sterile Bandage contact lens was applied for three days or until there was re-epithelialisation of the cornea. Patients were instructed to use antibiotic and steroid eye drops four times a day for a week following the procedure. The steroid drops were gradually tapered over one month.



[Table/Fig-1]: Mechanical debridement of epithelium in C3R.

[Table/Fig-2]: Exposure to UVA after application of riboflavin.

STATISTICAL ANALYSIS

The data was entered in MS Excel and analysed using SPSS version 16.0. All parameters were analysed pre and postoperatively using the paired t-test for each parameter. The data was expressed as the mean±SD pre and postoperatively. A p-value of <0.05 was considered to be statistically significant.

RESULTS

Fifteen eyes of 12 patients who underwent corneal C3R with riboflavin for progressive keratoconus were studied. Demographic details are shown in [Table/Fig-3].

Patient characteristics	n (%)
Sex	
Males	10 (83.3)
Females	2 (16.7)
Age (years)	
15-20	7 (58.3)
21-26	5 (41.7)
Laterality	
Unilateral	9 (75)
Bilateral	3 (25)

[Table/Fig-3]: Patient characteristics.

Changes in Uncorrected Visual Acuity (UCVA): The mean preoperative UCVA was 0.87±0.40 (log MAR), which improved to 0.75±0.39, three months post-treatment and was found to be statistically significant (p-value=0.001). The UCVA further improved to 0.65±0.35 at six months follow-up (p-value=0.001) [Table/Fig-4].

Changes in Best Corrected Visual Acuity (BCVA): The mean preoperative BCVA was 0.37±0.21 (log MAR), which improved to 0.25±0.27, three months postoperatively, which was found to be statistically significant (p-value=0.001). At six months follow-up,

there was further improvement to 0.17±0.22 (p-value=0.0001) [Table/Fig-5].

Examination time	UCVA (logMAR) Mean±SD	p-value	t value
Preoperative	0.87±0.40	-	-
3 months	0.75±0.39	0.001	4.999
6 months	0.65±0.35	0.001	7.837

[Table/Fig-4]: Mean UCVA before and after surgery.
*analysed with paired t-test, p-value=0.001

Examination time	BCVA (logMAR) SD±mean	p-value	t value
Preoperative	0.37±0.21	-	-
3 months	0.25±0.27	0.001	4.210
6 months	0.17±0.22	0.0001	8.756

[Table/Fig-5]: Mean BCVA before and after surgery.
*analysed with paired t-test, p-value=0.001

Changes in Keratometry

Changes in Kmax

The mean preoperative Kmax was 54.90±6.05. Three months after the procedure, it decreased to 53.67±5.32 and was found to be statistically significant (p-value=0.001). At six months follow-up, it further decreased to 52.67±5.02 (p-value=0.001) [Table/Fig-6].

Examination time	Kmax (dioptres) Mean±SD	p-value	t value
Baseline	54.90±6.05	-	-
3 months	53.67±5.32	0.001	5.212
6 months	52.67±5.02	0.001	5.492

[Table/Fig-6]: Mean kmax before and after C3R.
*analysed with paired t-test, p-value=0.001

Changes in K min

The mean baseline Kmin in dioptres was 48.14±4.24 (mean±SD), which decreased to 46.88±3.89 three months after the procedure (p-value=0.001). At six months follow-up, it further reduced to 45.93±4.07 (p-value=0.001) [Table/Fig-7].

Examination time	Kmin (diopters) Mean±SD	p-value	t-value
Baseline	48.14±4.24	-	-
3 months	46.88±3.89	0.001	4.940
6 months	45.93±4.07	0.001	4.839

[Table/Fig-7]: Mean Kmin before and after C3R.
*analysed with paired t-test, p-value-0.001

Changes in cylinder value: The mean preoperative cylinder value was -3.50±1.58, which decreased to -3.35±1.54 (p-value 0.03) at three months follow-up and -2.90±1.37 at six months follow-up. Both changes were found to be statistically significant (p-value=0.01) [Table/Fig-8].

Examination time	Cylinder value(D) Mean±SD	p-value	t value
Baseline	-3.50±1.58	-	-
3 months	-3.35±1.54	0.03	2.358
6 months	-2.90±1.37	0.001	4.664

[Table/Fig-8]: Mean cylinder value before and after surgery.
*analysed with paired t-test, p-value=0.001

Changes in Spherical Equivalent (SE): The mean preoperative SE was -4.93±3.92, which decreased to -4.69±3.76, three months after the procedure (p-value=0.032). At six-month follow-up, it further decreased to -4.28±3.48 (p-value=0.002) [Table/Fig-9].

In the current study, out of the 15 eyes studied, 14 of the eyes showed improvement in visual acuity, gradual reduction in keratometry values, and gradual flattening of the cornea, reducing the astigmatism post-surgery. Only one patient showed mild worsening of corneal topography and manifest refraction, but he maintained his preoperative UCVA and BCVA with glasses. The patient had chronic allergic conjunctivitis with constant eye rubbing, which probably resulted in further progression of keratoconus.

Examination time	Spherical Equivalent (SE) Mean±SD (dioptres)	p-value	t-value
Baseline	-4.93±3.92	-	-
3 months	-4.69±3.76	0.032	2.377
6 months	-4.28±3.48	0.002	3.912

[Table/Fig-9]: Mean Spherical Equivalent (SE) before and after surgery.
*analysed with paired t-test, p-value=0.002

DISCUSSION

Corneal collagen cross-linking with riboflavin and UVA (CXL) is a new technique of corneal tissue strengthening that combines the use of riboflavin and UVA irradiation. Riboflavin works as a photosensitiser for the induction of cross-links between collagen fibrils and at the same time acts as a shield from the penetration of UVA into the underlying tissues [2]. It was first introduced by Wollensak G et al., as a promising technique to slow or stop the progression of keratoconus. He included 23 eyes with moderate or advanced progressive keratoconus and showed that CXL was effective in halting the progression of keratoconus over a period of four years. In all treated eyes, the progression of keratoconus was at least stopped. In 16 eyes (70%), regression with a reduction of the maximal keratometry readings by 2.01 diopters was noted [4], whereas in the current study, Kmax decreased by 2.23 D.

CXL treatment has an arresting effect on the progression of keratoconus. Due to an increased number of cross-linking sites within the collagen molecule after CXL, stiffer fibrils and lamellae are likely generated. This process produces a rearrangement of corneal lamellae and the consequent relocation of the surrounding matrix, which, in turn, results in the reduction of the central corneal curvature. A small regression occurring may be explained as an effect of the rearrangement of corneal lamellae and the surrounding matrix [12]. Various studies have proved the efficacy of the procedure in reducing the corneal curvature, SE refraction, and astigmatism in keratoconus eyes after the application of CXL [4,9,12-15]. Kymionis GD et al., demonstrated that there was no discrepancy in terms of endothelial cell density between treated and untreated eyes, thus proving the safety of the method [16].

In the present study, 15 eyes of 12 patients with progressive keratoconus who underwent corneal collagen cross-linking were included. In the study done by Nasrollahi K et al., 140 eyes of 110 patients were studied [17]. In a study done by Raiskup-Wolf F et al., 480 eyes of 272 patients were included [18]. Other similar studies with a relatively small sample size include that done by Arbelaez MC et al., where 20 eyes of 19 patients were studied [2]. The minimum age of the patients in the present study was 15, and the maximum age was 26. The mean age of the patients was 19.62±3.52 years. A study done by Fatima T et al., found that in India, keratoconus presents at an early age compared to the Western population [19]. In the study done by Arbelaez MC et al., the mean age of the patients was found to be 24.4 years. Patients ranging from 18-44 years of age were studied by them [2]. Meanwhile, the current study did not include patients aged over 35 years. In a study done by Koller T et al., it was found that restricting patient age to younger than 35 years may reduce the complication rate to 1% [8].

In the study done by Caporossi A et al., patients were divided into three groups based on age: paediatric patients (age ≤18 years), an intermediate group (19-26 years), and adults (≥27 years). The study found that corneal collagen cross-linking was more effective in the paediatric and intermediate age groups on long-term follow-up [20]. The male-to-female ratio in the present study was 5:1. This can be attributed to the fact that the majority of the patients who presented

to the OPD of the institute at the time of the study were males. In a study from North India [21] and one from Western India [22], keratoconus was noted more often in males, while the Central India study found a higher prevalence in women [23].

All the patients were followed-up for a period of six months to look for changes in UCVA, BCVA, corneal topography, and manifest refraction. In the current study, UCVA improved by 0.22 (from 0.87±0.40 to 0.65±0.35) at the final follow-up after six months post-surgery, which was found to be statistically significant (p-value=0.001). In the study done by Arbelaez MC et al., UCVA improved by 0.55 at six months follow-up [2]. In a similar study done by Saffarian L et al., UCVA improved by 0.3D one year after the procedure [14]. BCVA showed an improvement of 0.2 (from 0.37±0.21 to 0.17±0.22) at six months follow-up, which was also found to be statistically significant (p-value=0.001). In the study by Arbelaez MC et al., BCVA improved by 0.16 at six months follow-up [2]. Similar studies done by Bamdad S et al., and Peyman A et al., have found statistically significant improvement in BCVA following the procedure [9,24]. A study done in India on paediatric patients by Arora R et al., has demonstrated statistically significant improvement in both uncorrected and BCVA following the procedure [25]. Thus, most of the studies have demonstrated an improvement in visual acuity following corneal collagen cross-linking irrespective of the population demographic.

In the present study, Kmax and Kmin showed a gradual flattening in comparison with the preoperative values at all postoperative visits in a statistically significant manner. Kmax decreased by 2.23D (from 54.90±6.05 to 52.67±5.02) and Kmin decreased by 2.21D (from 48.14±4.24 to 45.93±4.07) at the final follow-up after six months. Keratometry values showed a reducing trend in all patients except one in the current study. The patient had a history of allergic conjunctivitis with constant eye rubbing, and slight worsening of keratometry values were noted on follow-up.

In the first in-vivo controlled clinical study by Wollensak G et al., which included 23 eyes with moderate or advanced progressive keratoconus, max K decreased by 2.01 D post-procedure [4]. Another study by Jankov II MR et al., found that progression of keratoconus stopped in all patients in which it was actively progressing six months prior to treatment. Max K decreased by more than 2D [12].

Agrawal VB in his study found similar results among an Indian population of 37 eyes after one year of follow-up. The K value of the apex decreased by a mean of 2.73 D in 66% of eyes, and the maximum K value decreased by a mean of 2.47D in 54% of eyes [26]. Wittig-Silva C et al., and Hersh PS et al., observed a reduction in the value of Kmax at the end of their one-year study [13,27]. Kankariya VP et al., noticed transient worsening of the topographic indices in the early postoperative period, but these indices stabilised on subsequent visits without any intervention [28].

The cylinder value decreased by 0.6D at six months in the current study (from -3.50±1.58 to -2.90±1.37). In similar studies done by Bamdad S et al., and Jankov II MR et al., the cylinder value decreased by 0.6D and 0.5 D, respectively [9,12]. In the study done by Saffarian L et al., the mean cylinder value decreased by 0.78D at one-year follow-up [14]. These changes might be indicative of gradual corneal flattening post-corneal collagen cross-linking. In the current study, SE was found to be decreasing in all postoperative visits. It decreased by 0.65 Dioptres at six months follow-up (from -4.93±3.92 to -4.28±3.48). In the study done by Vinciguerra P et al., mean SE refraction showed a significant decrease of 1.57 dioptres 24 months after the procedure [15]. No significant complications were noted in any of the patients post-procedure.

Corneal collagen cross-linking with riboflavin is a promising treatment in arresting the progression of keratoconus. With the patients being diagnosed and treated early, late complications like acute hydrops and corneal scarring can be avoided. It could also reduce the need for keratoplasty. Given the low cost and simplicity of the procedure, it can be widely done in developing countries, compared to other modalities like intracorneal ring segments. Collagen cross-linking is now also being evaluated in the treatment of other conditions like post-LASIK ectasia, keratitis, and corneal oedema [29].

Limitation(s)

Limitations of the present study include a shorter follow-up period. Since the patients were followed-up for only six months, it is not known whether the disease has progressed at a later stage or not.

CONCLUSION(S)

Corneal collagen cross-linking with riboflavin is a safe, simple, and effective procedure for arresting the progression of keratoconus, with the majority of patients obtaining an improvement in visual acuity. It is a simple, safe, and effective procedure that could help to reduce the burden of preventable blindness. Long-term results are necessary to evaluate the duration of the stiffening effect and to exclude long-term side effects.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jul 27, 2023
- Manual Googling: Oct 18, 2023
- iThenticate Software: Dec 09, 2023 (21%)

ETYMOLOGY: Author Origin

EMENDATIONS: 6

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Jul 26, 2023**
Date of Peer Review: **Oct 06, 2023**
Date of Acceptance: **Dec 12, 2023**
Date of Publishing: **Feb 01, 2024**