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Original Research Article

Comparison of Uncorrected Visual Acuity in Patients of Keratoconus Pre and Post Corneal Collagen Cross-Linkage with Riboflavin (C3R)

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Abstract

The present study comprised of 20 eyes of 14 patients with keratoconus presenting at a single centre. The study was conducted to compare the uncorrected visual acuity (UCVA) in patients before and after Corneal Collagen Crosslinking with Riboflavin (C3R). Follow- up period was 6 months. A comprehensive systemic and ocular history was taken and a through slit lamp examination, UCVA, refraction, fundus, intraocular pressure, pachymetry and corneal topography was done. Corneal collagen crosslinking was performed and UCVA was checked at 1 month, 3 months and 6 months. Statistical analysis was performed and it was noted that the mean UCVA improved statistically as compared to the preoperative value. Hence, UCVA is likely to improve in patients who undergo C3R.

Keywords: Uncorrected visual acuity, Keratoconus, Corneal collagen cross-linkage with Riboflavin, Refraction, Topography, Pentacam.

INTRODUCTION

Keratoconus is a progressive non inflammatory ectatic condition of the cornea. It is usually a bilateral condition involving the central two-thirds of the cornea and the apex of the cone is usually centered just below the visual axis [1]. However, there is absence of cellular infiltration and vascularization. Keratoconus was first described in detail by Nottingham in 1854 [2]. Keratoconus occurs at about the age of puberty and has no gender predominance. Its reported frequency is approximately 1 in 2000 in the general population [3]. The course of the disease varies from slight irregular astigmatism to severe visual impairment. The exact cause of keratoconus is uncertain, but it has been associated with detrimental enzymatic activity within cornea. De Bonis *et al.*, in a study did a molecular analysis of five genes in a cohort of 25 sporadic and 77 familial keratoconus and confirmed the possible role of VSXI in the pathogenesis of keratoconus [4]. The majority of reported studies suggested an autosomal dominant mode of inheritance with variable expression.

Risk factors for keratoconus include eye rubbing, family history and connective tissue disorders [3]. Keratoconus is associated with conditions like Down's syndrome [1], Ehlers-Danlos syndrome, osteogenesis imperfecta and joint hypermobility [5, 6], Retinitis pigmentosa [7], Leber's congenital amaurosis [1] and vernal conjunctivitis [7]. Various corneal signs are seen in keratoconus which include: Distortion of corneal reflex, oil droplet reflex in the area of the cone withdilated pupil using a direct ophthalmoscope set on plano also known as "Charleaux's sign" [3], Scissoring effect on retinoscopy, prominent corneal nerves, "Rizzuti's sign" which is focusing of light beam across the cornea in an arrowhead pattern at the nasal limbus when shown from temporal side [8]. In advanced cases deep stromal stress lines known as Vogt striae [8], that clear when pressure is applied to the globe are seen. Bulging of lower lid in down gaze known as "Munson's sign" is also seen. "Fleischer's ring" [9] due to iron deposition in the epithelium at the base of the cone. Hydrops is a manifestation of advanced Keratoconus in which there is a sudden loss of vision usually associated with pain caused by breaks in the Descemet's membrane and acute, marked corneal edema. Based on morphology, keratoconus has been classified into [3]:

- Nipple cone - Cone diameter ≤5mm; round morphology; central or paracentral location. This can be easily corrected with contact-lenses

- Oval cone - Cone diameter ≥5mm; paracentral to peripheral location. Contact lens correction is more difficult,
- Globus cone - Cone located throughout 75% of the cornea. Contact lens correction is very difficult in majority of these cases.

Rabinowitz and Mc Donnel gave a system wherein the central keratometry i.e. K Value > 47.2, inferior minus superior (I-S) asymmetry above 1.2D, Sim K astigmatism > 1.5D and SRAX (skewed radial axes) > 21 degrees [10]. The KISA% index has been developed by Rabinowitz and is helpful for analyzing the suspects [11]. Rabinowitz and Rasheed gave KISA% (keratoconus percentage index) derived from K value, I-S value, SRAX (relative skewing of the steepest radial axes) and AST (keratometric astigmatism) with a cut-off set at 100% for diagnosis of keratoconus.

Scheimpflug photography can be used to provide a more accurate means of measuring corneal thickness and elevation. The Pentacam has a computer program that plots the change in corneal thickness from the thinnest spot moving outward toward the periphery and analyzes the rate of thickness change compared to normative data. A virgin cornea with an isolated island of anterior elevation greater than 11 microns (µm) as detected by the Pentacam, and posterior elevation greater than 20 microns (µm) is suspicious for an ectatic corneal contour. The Topography and Pachymetry of entire anterior and posterior segment of cornea is depicted from limbus to limbus. We used a Scheimpflug device "Pentacam" from (Oculus optikgerate GmbH, Wetzlar) of Germany.

The management of keratoconus begins with correction with spectacle. Once glasses fail to provide adequate visual function, contact lens fittings especially Rigid Gas Permeable (RGP) lenses are required. However, the disadvantage is that RGP lenses may be difficult to wear initially and the patient has to be counseled properly. Besides, contact lenses do not prevent progression of corneal ectasia [1]. Penetrating keratoplasty has traditionally been the surgery of choice for keratoconus but is associated with its own complications like rejection, keratitis and glaucoma. Deep Anterior Lamellar Keratoplasty may be first choice of keratoplasty in most eyes without endothelial abnormalities [12].

All these measures are essentially rehabilitative in nature as none of them address the problem of progression of the disease.

Corneal Collagen Cross-linking with Riboflavin (C3R or CXL) is the most recent addition to the treatment options and has the capability to slow the progression of keratoconus by using a photo-oxidative treatment which increases the rigidity of the corneal stroma [13, 14]. The irradiation of the riboflavin results in chemical reactions that create covalent bonds, which bridge stromal collagen fibrils [15]. C3R decreases both corneal curvature and astigmatism[1]. As long as the cornea treated has a minimum thickness of 400 micron (as recommended), the corneal endothelium will not experience damage, nor will deeper structures such as lens and retina. There have been no reported complications on the endothelial cell count, lens, or retina due to the limitation of UVA transmission through the cornea [16].

A standard CXL procedure begins with the administration of a topical anaesthetic, followed by application of a sterile alcohol swab (70% Isopropyl alcohol) to cornea for 12 seconds, debridement of the central 7 mm to 9 mm of the cornea is done to allow uniform diffusion of the Riboflavin into the stroma. Riboflavin used is of 2 types-Isotonic Riboflavin (0.1%)- This is the standard iso-osmolar Riboflavin. It is used for corneas with a minimal thickness of 400 microns. Hypotonic Riboflavin (0.1%) is used when the minimal corneal thickness is between 350 microns to 400 microns. Riboflavin is allowed to permeate the cornea before UVA irradiation. UVA radiation of 370 nm wavelength and an irradiance of 3 mW/cm2 from the cornea is applied for a period of 30 min, delivering a dose of 5.4 J/cm2 . Antibiotic eye drops are instilled as prophylaxis and a bandage contact lens is inserted, which is then removed at the follow-up visit once epithelial healing is complete.

Collagen cross linking increases the biomechanical strength of human cornea by 300% by the combined action of a photosensitizing substance (Riboflavin) and UV light [17]. Additional chemical bonds are created, inside the anterior corneal stroma by photo polymerization. Alternatively, CXL can be performed transepithelially.

Most published CXL techniques are broadly based on methodology developed by Dresden [13], and this protocol is safe and has been widely accepted internationally.

Wollensak *et al.*, in Germany conducted a prospective study with 23 eyes. The follow-up time was between 3 months and 47 months. In 16 eyes (70%) regression was seen with a reduction of the maximal keratometry readings by 2.01 dioptres and of the refractive error by 1.14 dioptres. Endothelial cell density and intraocular pressure remained. unchanged. Visual acuity improved slightly in 15 eyes (65%) [13].

Fournie *et al.*, conducted a prospective trial in which Kmax decreased by 1.68D ($P < 0.05$); Best corrected visual acuity (BCVA) improved by 0.14($P < 0.05$) [18].

MATERIALS AND METHODS

This Prospective, observational study was carried out on 20 eyes of 14 subjects with Keratoconus enrolled from the outpatient department of a single centre who underwent corneal collagen cross linking with Riboflavin. Of the 20 eyes, there were 11 right and 9 left eyes. 15 eyes were of male subjects and 5 eyes were of female subjects. Results were compared at the end of the study and data analyzed statistically.

INCLUSION CRITERIA

Diagnosed cases of Keratoconus- Confirmed by clinical evaluation and on topography, Disease progression- Proven and documented by Topography, serial refractions or Keratometry, Central Corneal Thickness (CCT) greater than 400 microns for C3R with Isotonic Riboflavin and 350 microns for C3R with Hypotonic Riboflavin.

EXCLUSION CRITERIA

Minimum Corneal Thickness of less than 350 microns on Ultrasonic Pachymetry or Pentacam or Anterior Optical Coherence Tomography (OCT), Previous Ocular surgery**,** Central corneal opacities, Abnormality in Lens or Retina on biomicroscopic examination, Patients too young or not cooperative enough to perform C3R, Patients who were pregnant or breast feeding. Informed consent was taken from all patients.

EXAMINATION AND PROCEDURE

After entering demographic data (name, age and sex) and clinical history, each patient underwent a complete ophthalmic examination, including Visual acuity, Refraction slit lamp examination dilated fundoscopy Intraocular pressure, Tear film examination, Pachymetry Corneal topography by a Scheimpflug device "Pentacam" from (Oculus optikgerate GmbH, Wetzlar) of Germany.

SURGICAL TECHNIQUE

Topical anesthesia of proparacaine hydrochloride 0.5% was instilled. A sterile alcohol swab (70% Isopropyl alcohol) was applied to the cornea. The epithelium was debrided using a blunt spatula in a 8.0 mm diameter corneal area. As a photosensitizer Riboflavin 0.1% was applied. Isotonic Riboflavin (0.1%) was used for corneas with a minimal thickness of 400 micron and Hypotonic Riboflavin (0.1%) was used when the minimal corneal thickness was between 350 microns to 400 microns. Riboflavin is applied every 2 minutes for 30 minutes. The cornea is then irradiated with ultraviolet A (UVA) light at 370 nm for the next 30 minutes using a UV-X™ IROC (Zurich, Switzerland). UV-X™ is a UVA generating device. Cornea should swell up to 400 microns on Ultrasound pachymetry. At the end of the procedure a Bandage Contact lens (BCL) is applied. The BCL is removed after corneal epithelialization is complete. This takes 3-5 days and is usually removed on the 4th day. Post -operatively patients were given Moxifloxacin (0.5%)e/d Carboxymethylcellulose (0.5%) Prednisolone (1%) e/d. Uncorrected visual acuity (UCVA), BCVA, Tear film and Intraocular pressure were checked on 1 week, 1 month, 3 months and 6 months post operatively. Refraction and Topography were done at the 1 month, 3 months and 6 months visits.

Statistical analysis was performed using the SPSS (version 17.0). Categorical variables are presented as frequency and percentage. Continuous variables at different time points, are presented as mean ± SD and were analysed using repeated measures and further paired comparison (from baseline) was done at 1month, 3 months and 6 months using paired t test. $P < 0.05$ was considered statistically significant.

RESULT AND DISCUSSION

In our study, the number of patients less than 15 years of age was one, between 16 and 20 years were nine, between 21 and 25 years was one, and between 26 and 30 years were three.

Age-Wise Distribution

Age Group	Frequency	%
<=15 yrs	1	7.1%
16 - 20 yrs	9	64.3%
21 - 25 yrs	1	7.1%
26 - 30 yrs	3	21.4%
Total	14	100%
Mean ± SD	20.85 ± 4.86	

Sex Distribution

Sex	Frequency	%
Female	3	21.4%
Male	11	78.6%
Total	14	100%

In the study group of 14 eyes, three (21.4%) subjects were females and 11 (78.6%) were males.

Trend of Mean UCVA in Logmar

UCVA (Logmar)	Mean ± SD	Min – Max (Range)	P Value
Baseline (Pre-operative)	0.935 ± 0.30	0.45 - 1.40	<0.001
1st wk	0.946 ± 0.27	0.45 - 1.40	
4th wk	0.869 ± 0.30	0.45 - 1.30	
3 months	0.692 ± 0.24	0.30 - 1.30	
6 months	0.612 ± 0.21	0.30 - 1.00	

The mean logMAR UCVA prior to C3R was 0.935 logMAR (SD ± 0.30), which changed to 0.946 logMAR (SD ± 0.27) at first week, 0.869 logMAR (SD ± 0.30) at first month, 0.692 logMAR (SD ± 0.24) at third month, 0.612 logMAR(SD ± 0.21) at sixth month. There is an overall decreasing trend of mean logMAR UCVA from baseline to six months ($p < 0.001$), which implies a trend of improving UCVA.

Comparison of Mean Baseline Ucva to Post-Op Visits

UCVA (Logmar)		Mean Difference (Preoperative- Postoperative)	Std. Error	P Value
Baseline (Pre operative)	1st wk	-.011	.028	1.000
	4th wk	.066	.051	1.000
	3 months	.243	.047	.001
	6 months	.323	.050	<0.001

Changes compared to baseline were statistically significant at third and sixth months ($p = 0.001$ and $p < 0.001$, respectively).

Outcomes In Terms of Stabilisation/Improvement/Deterioration of UCVA As Compared To As Compared To Baseline at Each Visit:

	1st wk	4th wk	3 months	6 months
Improvement	2 (10%)	9 (45%)	14 (70%)	17 (85%)
Stable	15 (75%)	8 (40%)	6 (30%)	3 (15%)
Deterioration	3 (15%)	3 (15%)	0 (%)	0 (%)

- At first week post-op visit, UCVA in 15 (75%) eyes showed stability, three (15%) eyes deteriorated and two (10%) eyes improved as compared to baseline.
- At first month post-op visit, UCVA in eight (40%) eyes showed stability, three (15%) eye deteriorated and nine (45%) eyes improved as compared to baseline.
- At third months post-op, UCVA in six (30%) eyes showed stability, 14 (70%) eyes improved as compared to baseline.
- At sixth months post-op visit, UCVA in three (15%) eyes showed stability, 17 (85%) eyes improved as compared to baseline.

Outcomes In Terms of Change in Snellen's Lines for UCVA

	UCVA			
	1 week	4 week	3 months	6 months
0	15	8	6	3
1+	2	6	4	4
1-	1	2		
2+		1	5	6
2-	1			
3+	1	1	1	2
3-				
4+		1	3	3
4-		1		
5+			1	1
5-				
6+				1
6-				
7+				
7-				

At first week post-op, one eye improved by one line, one eye improved by three lines, two eyes worsened by one line, one eye worsened by two lines and 15 eyes showed stability.

At first month post-op, six eyes improved by one line and one eye improved by two lines and one eye improved by three lines and one eye improved by four lines, two eyes worsened by one line and one eye worsened by four lines, eight eyes showed stability. One patient had a drop of vision by 4 lines. This patient had developed allergic keratoconjunctivitis with corneal erosions which subsequently resolved after treatment.

At third month post-op, four eyes improved by one line and five eyes improved by two lines and one eye improved by three lines and three eyes improved by four lines and one eyes improved by five lines, none worsened and six eyes showed stability.

At sixth month post-op, four eyes improved by one line and six eyes improved by two lines and two eyes improved by three lines and three eyes improved by four lines and one eye improved by five lines and one eye improved by six lines, none worsened and three eyes showed stability.

Overall, there was an improvement of at least one Snellen's line at the end of sixth month in 17 eyes (85%).

The mean logMAR UCVA prior to C3R was 0.935 logMAR (SD = 0.30) which changed to 0.946 logMAR (SD = 0.27) at first week, 0.869 logMAR (SD = 0.30) at first month, 0.692 logMAR (SD = 0.24) at third month, 0.612 logMAR (SD = 0.21) at sixth month. Changes compared to baseline were statistically significant at third and sixth months ($p = 0.001$ and $p < 0.001$, respectively). At first week follow-up, UCVA remained unchanged in 15 (75%) eyes, improved in two (10%) eyes and deteriorated in three (15%) eyes. At first month follow-up, UCVA remained unchanged as compared to baseline-in eight (40%) eyes, improved in nine eyes (45%), and worsened in three (15%) eyes. At three months, 14 (70%) eyes showed improvement from baseline and six (30%) eyes were stable. By sixth months, 17 (85%) eyes showed improvement from baseline, three (15%) eyes showed stability, and none of the eyes deteriorated. Out of 20 eyes, improvement of one line was seen in four eyes, two lines in six eyes, three lines in two eyes, four lines in three eyes, five lines in one eye and six lines in one eye at the end of six months as compared to baseline. At the end of six months, a mean improvement of 0.323 logMAR was seen that corresponds to an improvement of three Snellen's lines from baseline and this change was statistically significant ($p < 0.001$).There was an improvement in the mean UVCA by 3 Snellen lines over the preoperative value in the study.

CONCLUSION

The mean UCVA improved statistically as compared to the preoperative value. The mean logMAR UCVA improved from 0.935 preoperatively to 0.612 at final follow up.

In our study, an improvement of approximately three Snellen's lines from baseline in mean UCVA was seen at the end of 6 months. Hence, our study showed that C3R was effective in significant improvement in the UCVA at the end of 6 months.

The limitations of this study are single centre research, small sample size and lack of long term follow up. Hence multi-centeric study with larger number of patients and longer follow-ups are required to corroborate our findings.

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