AN ANALYTICAL STUDY OF EFFICACY OF CORNEAL COLLAGEN CROSSLINKING C3R PROCEDURE IN PROGRESSIVE KERATOCONUS PATIENTS

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ABSTRACT

BACKGROUND

Keratoconus affects a significant number of the general population with conical weakened protruded area from the cornea due to weakening of the corneal stroma by a genetically premeditated preponderance. We see keratoconus as a standalone disease or accompanying other syndrome manifestations in patients. Mainly, the inferotemporal cornea is affected and the conical protrusion causes profound high irregular myopic astigmatism as a refractive error, which is very difficult to correct in progressed advanced stages. Especially in economically productive age group patients, the poor vision becomes very difficult to live with. Corneal collagen crosslinking procedure is a novel tool in the armamentarium of treatment procedures against this malady.

MATERIALS AND METHODS

This analytical study was conducted at cornea services, Regional Institute of Ophthalmology and Government Ophthalmic Hospital, Chennai, for a period of 14 months. Forty five eyes of forty patients with early progressive keratoconus who presented to cornea services were subjected to riboflavin UVA collagen crosslinking procedures using a standard protocol after getting an informed consent. Further response to treatment were assessed in the follow up period.

RESULTS

Out of 40 patients in our series, 23 were males and 17 were females. The maximum patients in our series were in the age group between 10 to 25 yrs. Epi-off procedure was done in 31 eyes and epi-on procedure was done in 14 eyes. The patients with pachymetry 400-450 microns underwent epi-on procedure and more than 450 microns underwent epi-off C3R procedure. The K values in our series were between 49D to maximum 63D. The topographic flattening was seen in 52% in epi-on and epi-off procedures. Vision improvement in our series was 57% following epi-on and 65% following epi-off procedures.

CONCLUSION

C3R is a very promising therapeutic modality that may halt the progression of ectatic process. It is a less invasive mode of treatment, which gives better outcome. This treatment is now being offered to patients with documented progression of keratoconus, but we are sure that with more experience, refinement in the process will allow it to be done in all stages of the disease and be a very important treatment process in this progressive disease.

KEYWORDS

Keratoconus, Corneal Collagen Crosslinking, Corneal Topography, Riboflavin.

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BACKGROUND

Cornea is the main refractive interface of the eye with approximately 40 dioptres of refractive power. It has five layers whose structural and functional integrity is very essential for maintaining the transparency of the cornea. It is like a watch glass with a prolate quality in majority of the population. The main function of the cornea is optical. It forms the principle refractive surface accounting for 70% of the total refractive power.[1]

Cornea has five layers, of which keratoconus predominantly affects stromal layer. The stroma consists of regularly arranged lamella of collagen fibres. They lie in a proteoglycan ground substance (chondroitin sulphate and keratan sulphate) with interspersed modified keratocytes. Corneal stroma scatters less than 10% of the normal incident light.[2] Maintenance of the regular arrangement and spacing of collagen is crucial for optical clarity. The stroma cannot regenerate following damage. The repair of the stroma after injuries involve keratocyte activation, migration and fibroblast transformation and formation of scar tissue.

Light emitted from a source and travelling through a media has a wave motion and the frequency of vibration maybe constant, but velocity and wavelength vary according

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to the density of media it travels.[3] The transparency of cornea is due to the regular arrangement of lattice stromal fibres.

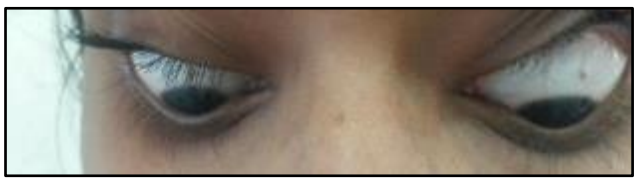

Figure 1. Munson Sign

Keratoconus is a degenerative noninflammatory disorder of the cornea characterised by stromal thinning and resultant conical ectasia with associated irregular astigmatism and visual loss.[4] Keratoconus often arises in one eye before arising in the fellow eye. Keratoconus may remain latent at a subclinical state or be completely uninvolved in the fellow eye for upto 6% of cases.[5] The characteristic stromal thinning and loss of Bowman's layer found in keratoconic cornea are associated with increased degenerative enzyme activities and decline in the enzyme inhibitors. Increased levels of lysosomal enzymes like acid esterases, acid phosphatases, acidic lipase, cathepsins and matrix metalloproteinases-2. Correspondingly, inhibitors of these enzymes such as alpha-1 proteinase inhibitor, alpha-2 macroglobulin, tissue inhibitor of metalloproteinase-1 and -3 are decreased. Immunohistochemical studies showed that keratoconic corneas have decreased fibronectin, laminin, entactin, type IV and XII collagen and elevated levels of type III collagen, Tenascin-C, fibrillin-1 and keratocan.

The diagnosis of keratoconus is based on slit-lamp examination. The area of maximal thinning corresponds to the area of maximal ectasia. Fleisher's iron ring is a sign of keratoconus and it partially or completely encircles the base of the cone.[6] Abnormal topography in the presence of normal slit-lamp examination is keratoconus suspect also called forme fruste keratoconus.

Figure 2. Slit Lamp Showing Corneal Thinning

Figure 3. Rizzuti Sign

Corneal hydrops is a manifestation of advanced keratoconus where there is sudden loss of vision associated with pain caused by breaks in Descemet's. A marked corneal oedema with fluid clefts in stroma. It resolves over weeks resulting in scarring and flattening with or without corneal neovascularisation.

Figure 4. Corneal Hydrops

Significant scarring with reticular pattern may develop in advanced keratoconus.

Corneal Topography- Corneal curvature is defined as either prolate or oblate. To study this curvature traditionally, a placido disc having concentric circles is projected onto the cornea and the reflection pattern with distortions are studied. Modern days, this is done by equipments called corneal topography. Orbscan and Pentacam are two widely used machines. Overtime, we have defined the parameters in such a way that we understand they have predictive value and form a part of the indices studied.

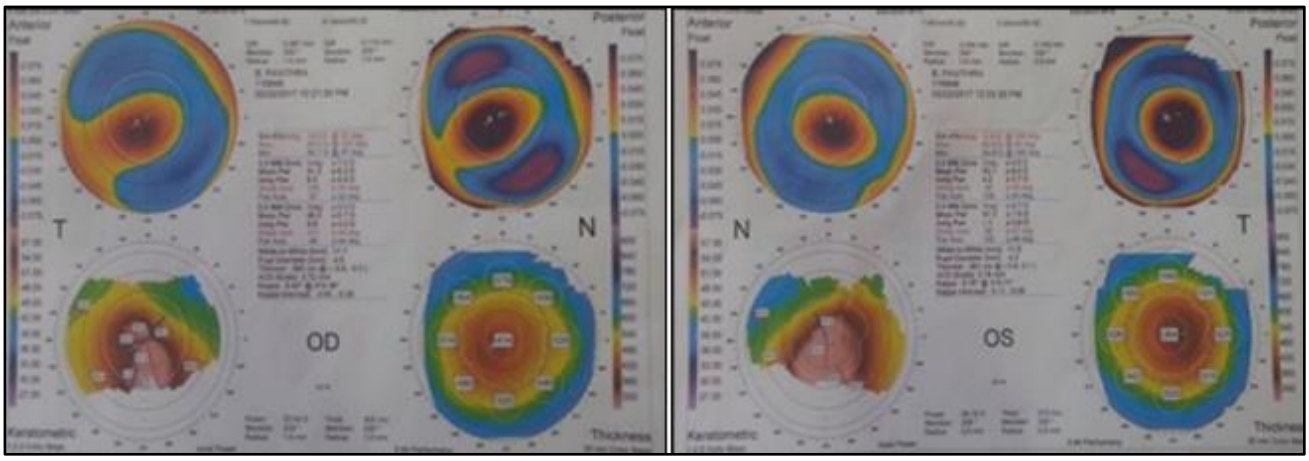

Figure 5. Orbscan of Both Eyes

Keratoconus Prediction Indices	KISA Index
1. Simk1. 2. Simk2. 3. SAI. 4. Differential Sector Index (DSI). 5. Opposite Sector Index (OSI). 6. Centre Surround Index (CSI). 7. Irregular Astigmatism Index (IAI). 8. Analysed Area (AA).	1. Quantifies the topographic features in patients with clinical keratoconus. K value, an expression of central corneal steepening. 2. KISA % = K x I-Sx AST x SRAX x 100/300 I-S value, inferior superior dioptric asymmetry. 3. AST indices, regular corneal astigmatism (simk1-simk2). 4. SRAX index-irregular astigmatism in keratoconus.

Table 1. Keratoconus Indices

The Orbscan is a hybrid system, which combines a projectile slit scanning device with a reflective placido technique. The Pentacam uses rotating Scheimpflug imaging technology to generate a complex image of the anterior segment of the eye within 2 secs.

Management- As the cornea is irregularly shaped in keratoconus, each cornea needs to be individually treated. Patients may benefit.

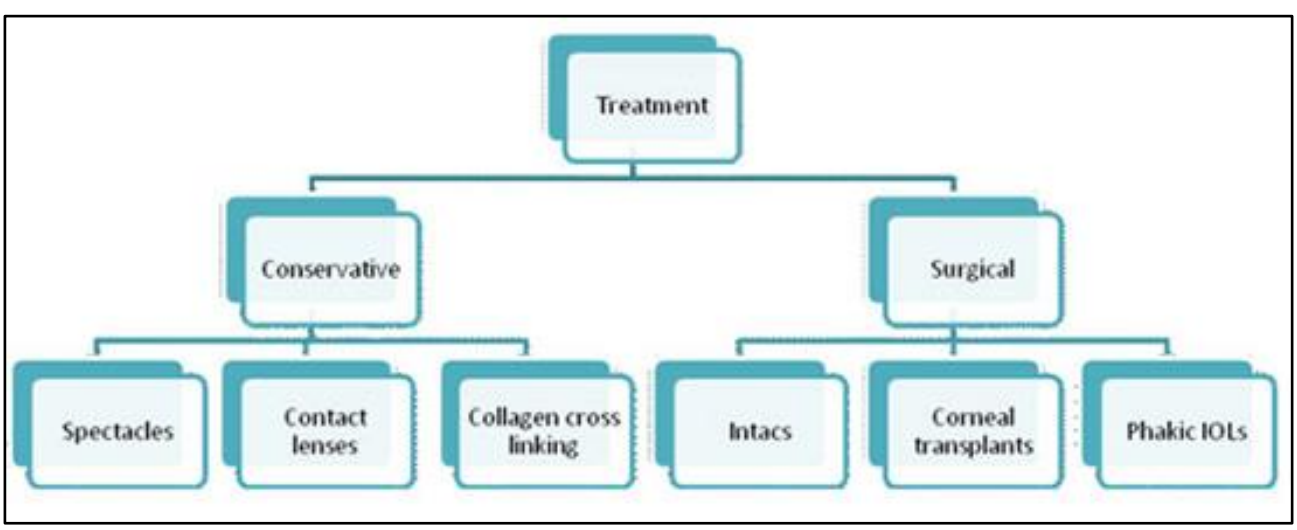

Figure 6. Management of Keratoconus

Corneal Collagen Crosslinking Procedure- Crosslinking of human collagen is a physiological process, which is found to be defective in keratoconus patients inducing corneal collagen crosslinking, also known as C3R/CCL/CXL is a new approach to increase the mechanical and chemical stability of corneal tissue. The primary aim of the treatment is to create additional chemical bonds inside the corneal stroma by means of highly localised photopolymerisation, while minimising exposure to the surrounding structure of the eye.[7]

Patient's cornea is anaesthetised with topical proparacaine. The epithelium over the central 8 mm is scrapped with a trephine in Epi-off procedures. Then, riboflavin is dropped over the cornea, which is simultaneously exposed to UVA 370 nm light. The combination creates a lot of ROS reactive oxygen species and to a minimal extent superoxide anion radicals. This ROS

reacts with collagen and induces crosslinking, which strengthens the cornea. 370 nm is used, because at this wavelength, the riboflavin absorbs maximum.

Figure 7, 8, 9, 10. Showing Corneal Collagen Crosslinking Procedures

Visual impairment because of scarring and contact lens failure are indications of surgical intervention to restore corneal anatomy. Penetrating keratoplasty is a safe and effective management of keratoconus.

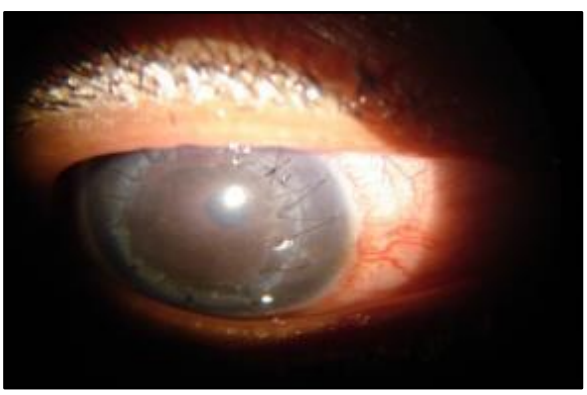

Figure 11. Surgical Management

Aim- To study the efficiency of corneal collagen crosslinking procedure in patients with progressive keratoconus. To analyse the results of Epi-on and Epi-off procedures.

MATERIALS AND METHODS

Forty five eyes of forty patients with early progressive keratoconus who presented to cornea services RIOGOH, Egmore, for a period of 14 months were analysed. Evaluation of the patients included uncorrected visual acuity, best corrected visual acuity, thorough slit-lamp examination, corneal topography and pachymetry. All the selected patients were subjected to corneal collagen crosslinking procedure with UVA exposure. Patients with pachymetry more than 450 microns underwent Epi-on C3R. The results of Epi-on and Epi-off C3R were compared.

Inclusion Criteria

Patients with following criteria were included in study-

1. Progressive loss of vision.
2. Patient not improving with spectacles or contact lenses.
3. Keratoconus values should be progressive.
4. Thinnest cornea should be more than 400 microns.
5. No central scarring.
6. Max corneal curvature should be less than 63D.

Exclusion Criteria

1. Pachymetry less than 400 microns.
2. Patients with hydrops.
3. Vision at presentation less than 2/60 were not included in the study.

RESULTS

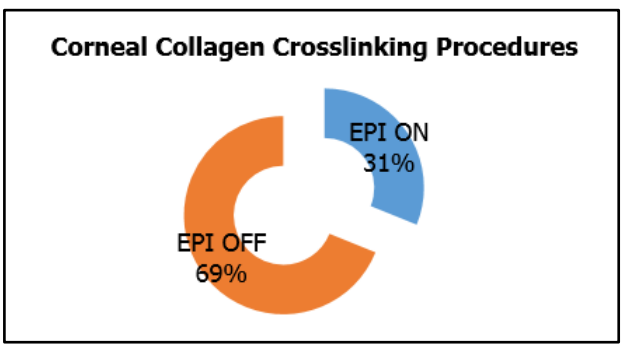

Chart 1. Chart Showing Collagen Crosslinking Procedure

31 (69%) eyes had pachymetry more than 450 microns and underwent Epi-off C3R procedure. 14 (31%) eyes underwent Epi-on C3R.

Sl. No.	Age	Total pts. (40)	Epi-off (27)	Epi-on (13)
1.	10-15 yrs.	10 (25%)	6 (22.2%)	4 (30.7%)
2.	16-20 yrs.	7 (17.5%)	4 (14.8%)	3 (23.1%)
3.	21-25 yrs.	11 (27.5%)	8 (29.6%)	3 (23.1%)
4.	26-30 yrs.	8 (20%)	6 (22.2%)	2 (15.4%)
5.	More than 30 yrs.	4 (10%)	3 (11.1%)	1 (7.7%)

Table 2. Age Distribution

Chi-sq = 1.04; p = 0.9.

Most of them belong to the age group of 21-25 (28%) followed by age group of 10-15 (25%). Identification is high in this age group seeking refraction for defective vision 10% belong to age group more than 30 yrs.

Sl. No.	Sex	Total (40)	Epi-off (27)	Epi-on (13)
1.	Male	23 (57.5%)	17 (63%)	6 (46.2%)
2.	Female	17 (42.5%)	10 (37%)	7 (53.8%)

Table 3. Sex Distribution

Chi-sq = 1.01; p = 0.3.

Majority were males (57%) compared to females (42%). In Epi-off, C3R (63%) had male predominance. In Epi-off, C3R (46%) were males.

Sl. No.	Laterality	Total (45) Eyes	EPI-off (31)	EPI-on (14)
1.	Right eye	14	10	4
2.	Left eye	21	13	8
3.	Both eyes	5 patients	4	1

Table 4. Laterality

Chi-sq = 0.75; p = 0.6.

Laterality was more common to left side in 5 patients corneal collagen crosslinking procedure was done in both eyes.

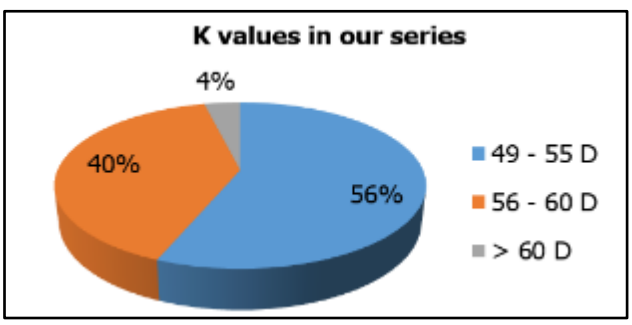

Chart 2. Chart Showing K Values in Our Series

56% belong to K value of 49-55 D followed by 40% belonging to 56-60D.

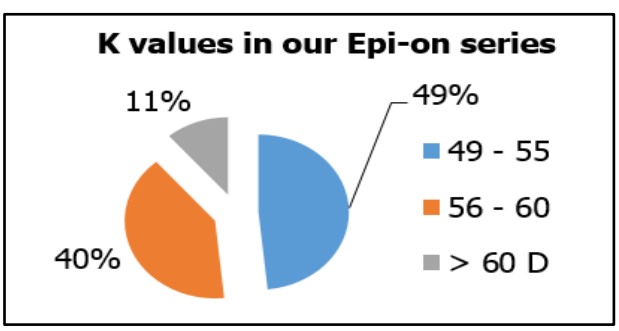

Chart 3. Chart Showing K Values in Our Epi-On Series

49% belong to K value of 49-55 D followed by 40% belonging to 56-60D.

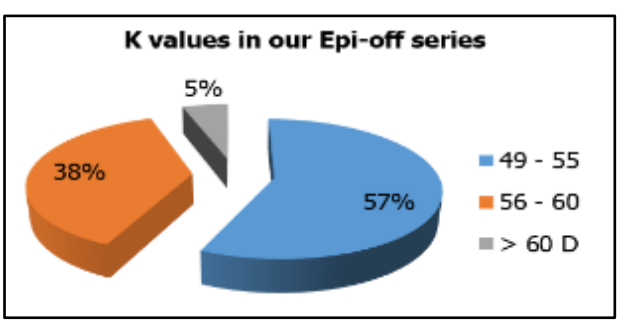

Chart 4. Chart Showing K Values in Our Epi-Off Series

57% belong to 49-55D followed by 38% belonging to 56-60D.

Sl. No.	Pachymetry	Epi-off (31)	Epi-on (14)
1.	400-420 microns		3 (21%)
2.	421-440 microns		6 (43%)
3.	441-450 microns		5 (36%)
4.	450-480 microns	15 (48%)	
5.	481-520 microns	10 (32%)	
6.	More than 520 microns	6 (20%)	

Table 5. Pachymetry Readings

Pachymetry values were the clear indicators of Epi-off or Epi-on C3R procedures. The minimum patchy value was 405 and maximum 552 microns. The maximum distribution was seen between 450-520 microns (56%).

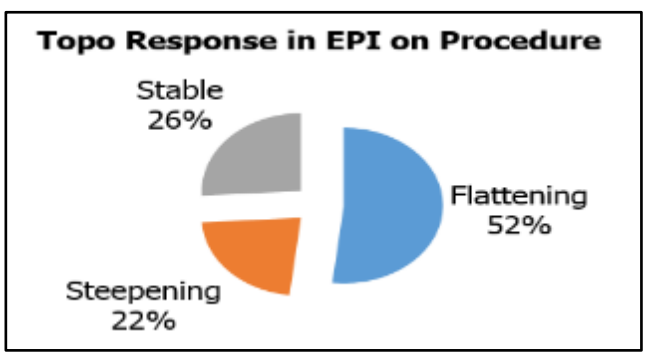

Chart 5. Chart Showing Topo Response in Epi-On Procedure

11 eyes out of 14 showed good therapeutic response, flattening was seen in 52% and stability in 29%. 3 cases showed steepening in K values. Out of which, 2 patients were in the age group 10-15 yrs. showing progressive nature of the disease.

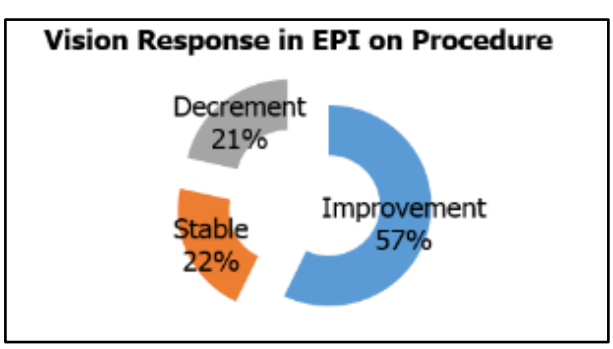

Chart 6. Chart Showing Vision Response in Epi-On Procedure

Majority had visual improvement (57%) in Epi-On C3R procedure. The maximum of three line improvement is seen in 2 eyes out of 14 eyes.

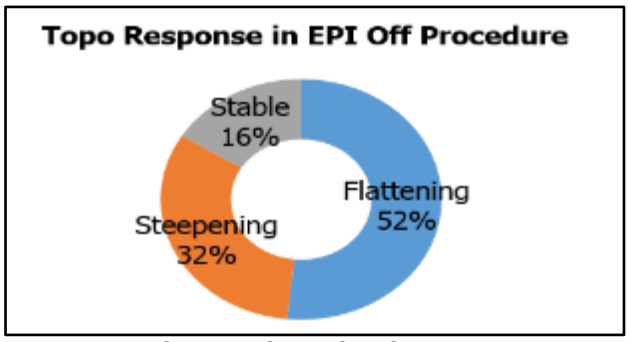

Chart 7. Chart Showing Topo Response in Epi-Off Procedure

Majority (52%) had flattening topo response following Epi-off procedure followed by steepening (32%). Stable topo seen in (16%).

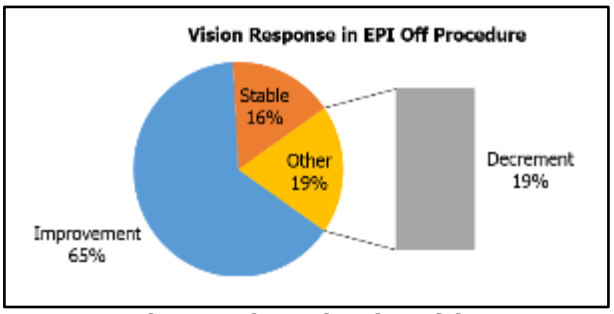

Chart 8. Chart Showing Vision Response in Epi-Off Procedure

Majority (65%) had visual improvement in epi-off procedure followed by decrement in 19%.

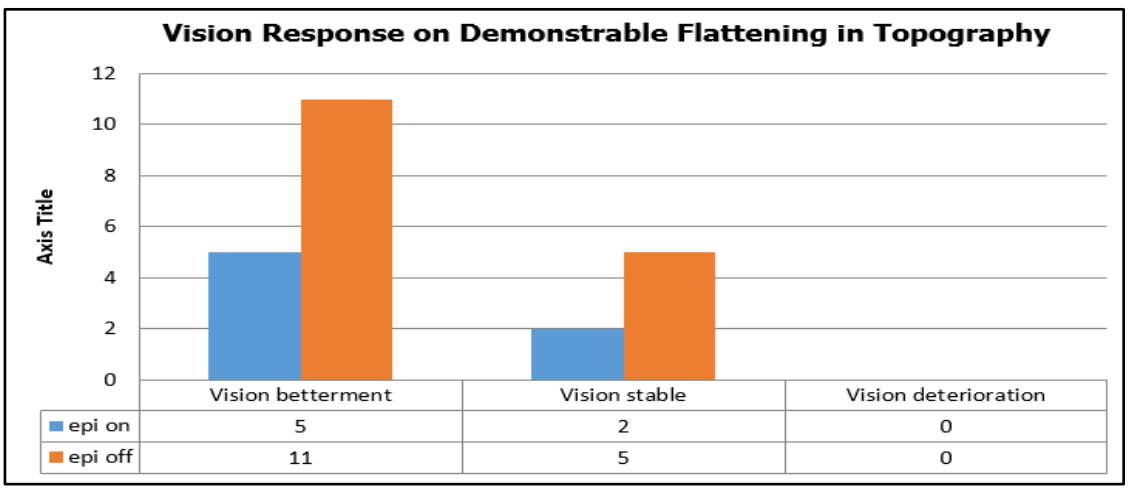

Chart 9. Vision Response on Demonstrable Flattening in Topography

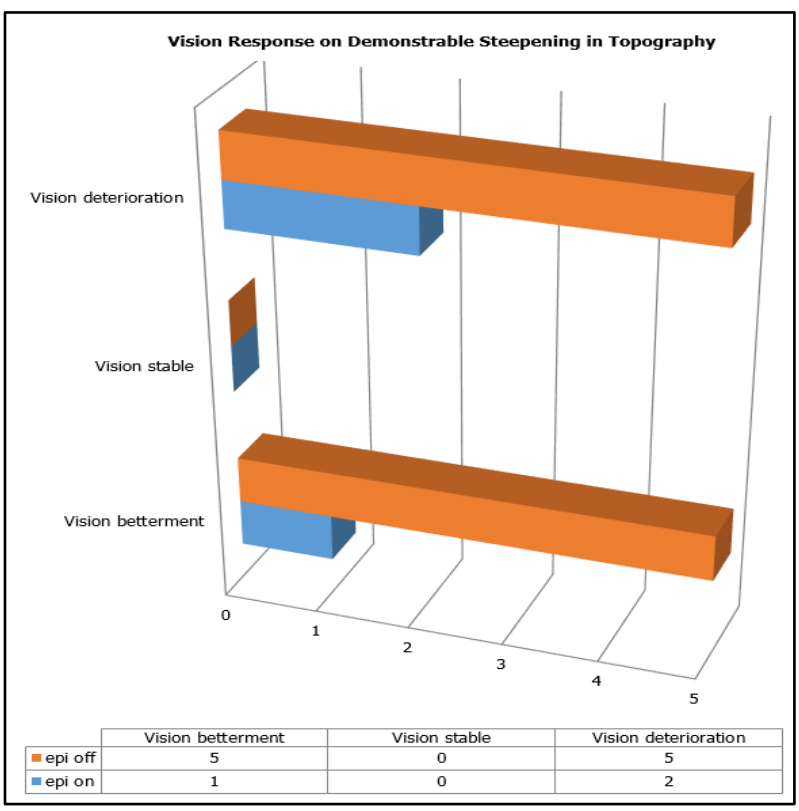

Chart 10. Vision Response in Demonstrable Steepening in Topography

Sl. No.	C3R	OKP
1.	Epi-off	3 out of 31 eyes (10%)
2.	Epi-on	1 out of 14 eyes (8%)

Table 6. OKP Following C3R

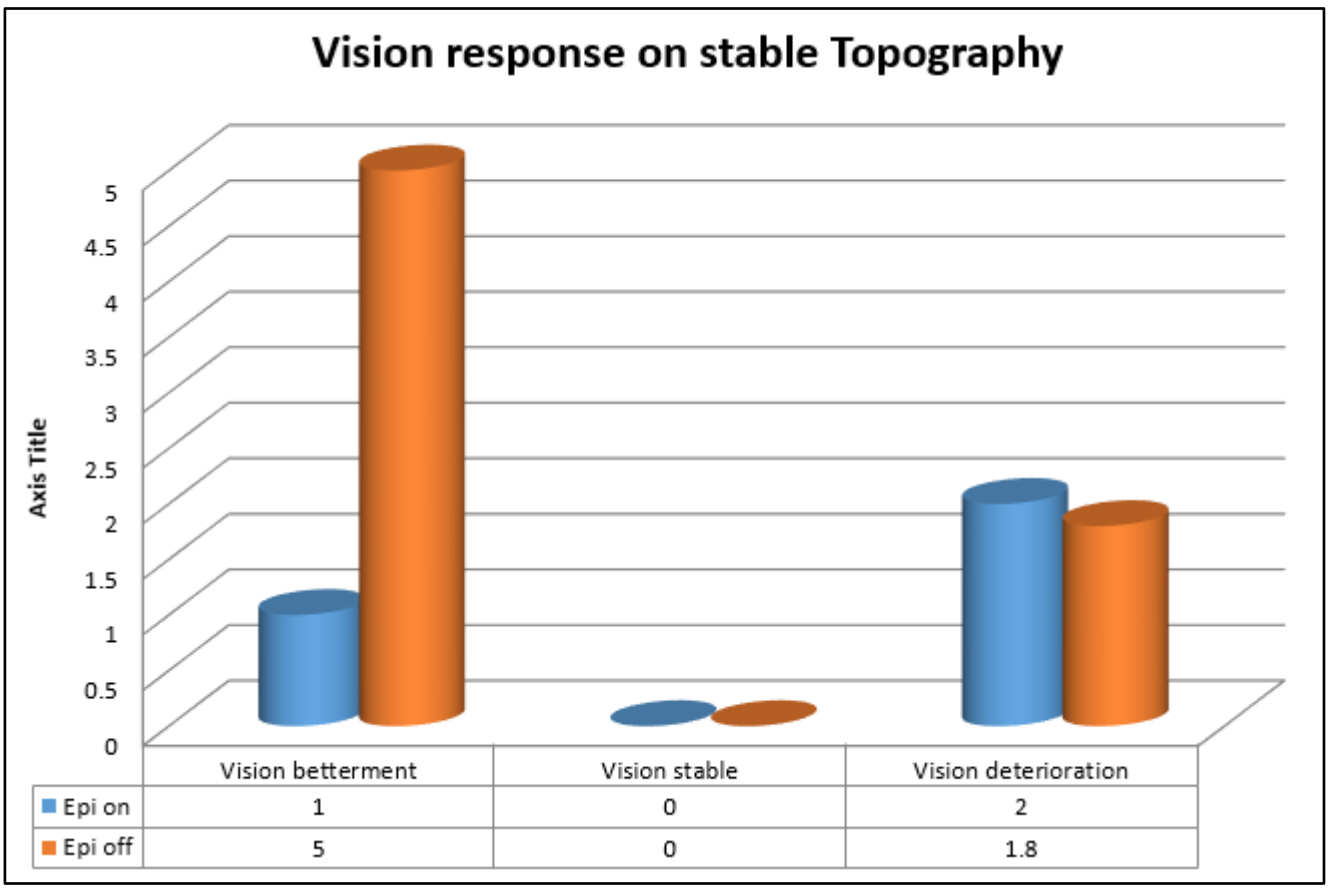

Chart 11. Vision Response on Stable Topography

Patient No 1. 27/M Demonstrating Flattening in Topo Values Following C3R

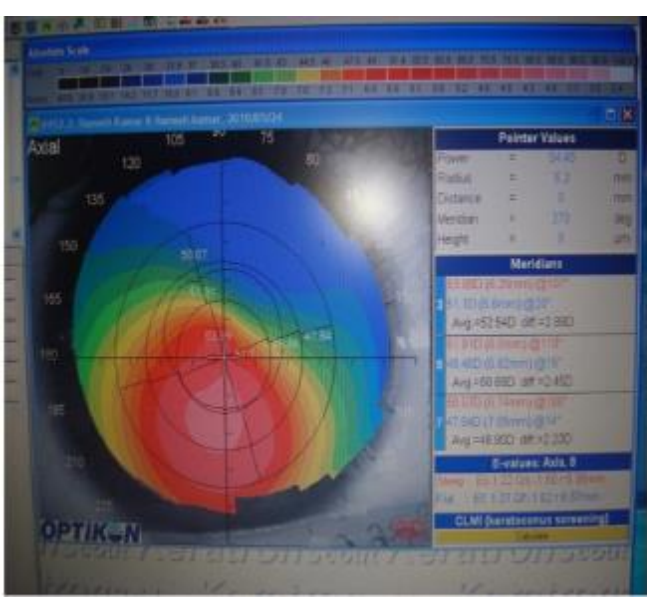

Figure 12. Pre C3R

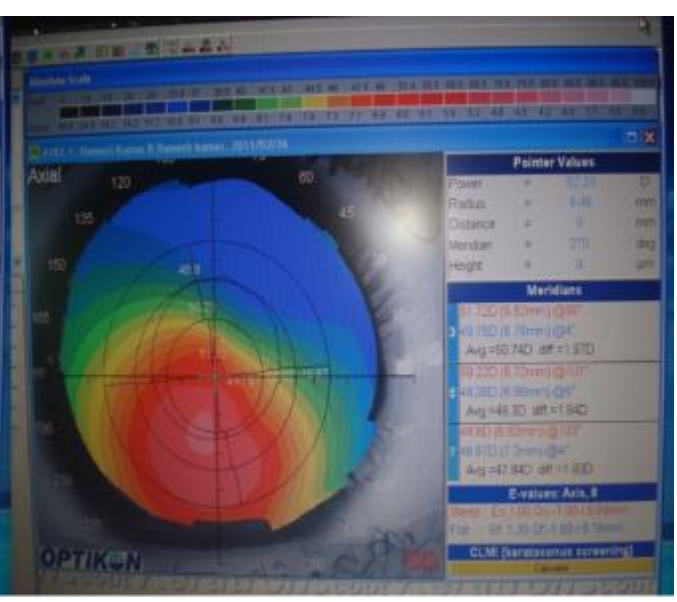

Figure 13. Post C3R

Patient No. 2. 22/M Demonstrating Irregular Bowtie Pattern in Topography

Figure 14. Pre C3R

Figure 15. Post C3R

Patient No. 3. 23/M Symmetrical Bowtie Pattern Responding Well to C3R with Flattening

Figure 16. Pre C3R

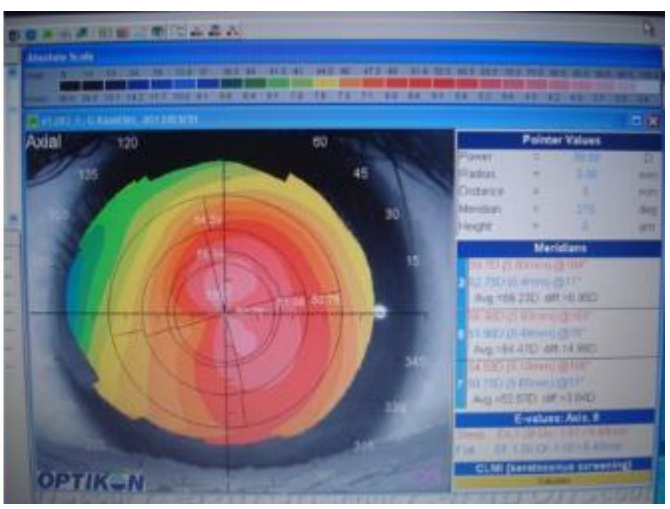

Figure 17. Post C3R

Patient No. 4. 20/F flattening of Topo Values Following Epi-on Procedure in C3R

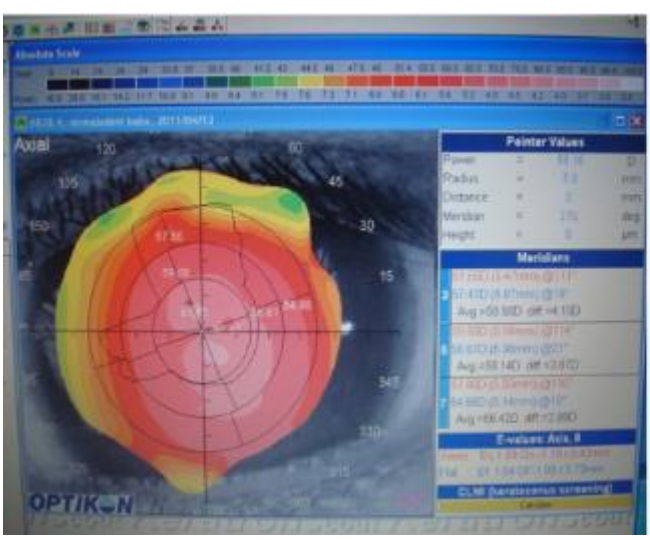

Figure 18. Pre C3R

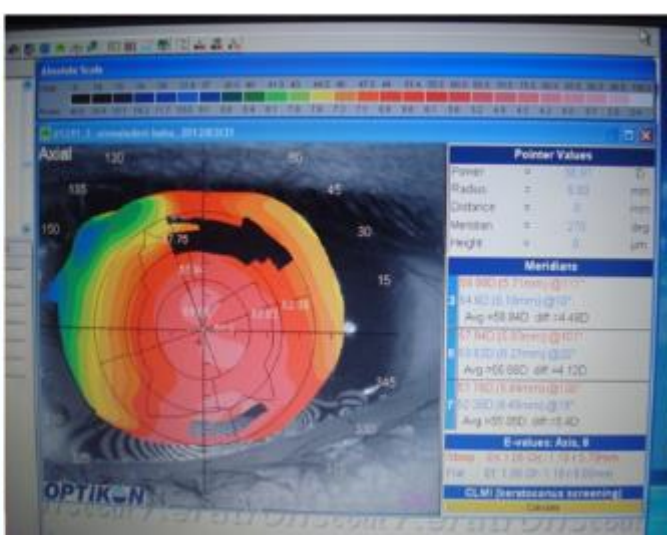

Figure 19 Post C3R

Patient No. 5. 27/F RE Demonstrating Irregular Bowtie with Skewed Deviation with Stable

Figure 20. Pre C3R

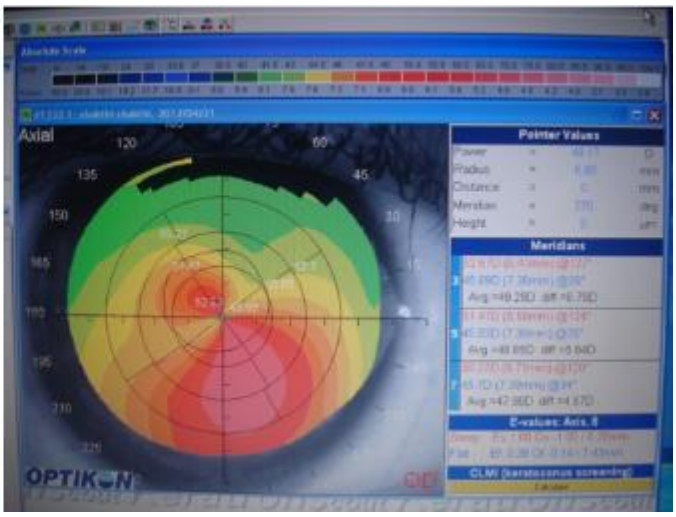

Figure 21. Post C3R

DISCUSSION

Out of 40 patients in our series, 23 were males and 17 were females. Epi-off procedure was done in 31 eyes and epi-on procedure in 14 eyes.

Age distribution- We had a range of 11-35 years and the maximum sample in the age group 10-15 yrs. and 21-35 yrs. Case identification is high in 10-15 yrs. children seeking refraction for defective vision and similarly 21-25 yrs. as patient need for refractive procedures is high in this age group.

Laterality in our series was right eye in 14 patients and left eye 21 patients and both eyes in 5 patients.

This is compared to a study done by Wollensak et al, which showed that corneal crosslinking was able to stop progressive keratoconus. The patient ranged in age from 13-58 yrs. with average age 34.7 ± 11.9 yrs. with the youngest age 13 yrs. A reduction in steep keratometry values of 2.01 D seen in 70% eyes and with a refractive correction of 1.14 D.[8]

The topographic flattening is seen in 52% in epi-on and epi-off procedures. In epi-on treatment, 11 eyes out of 14 showed good therapeutic response. Topographic response was stable in 29% of eyes with epi-on and 60% of eyes with epi-off procedures.

This is compared to a study done by Wittig-Silva C et al, which showed in a series of 66 eyes, there was progressive flattening of steepest simulated keratometry value over a period of 12 months.[9]

Vision improvement in our series was almost equal in both epi-on and epi-off procedures.

This is compared with Robert Pinelli who reported his 6 months results and found equivalent results of epi-on C3R in terms of changes in keratometry and vision compared to epi-off C3R.[10] Safety and effectiveness was the same between two groups. Patient satisfaction was high on epi-on C3R. Few patients who have undergone epi-off treatment presented with pain and haziness in the area of epithelial removal.

Corneal C3R mediated by riboflavin and UVA appears to be a safe and efficacious procedure in halting the progression of keratoconus. CXL reduces the corneal curvature, spherical equivalent refraction and refractive cylinder in eyes with progressive keratoconus. Riboflavin is the key component of the treatment as it increases the corneal absorption of UV rays to approximately 95%[11] and thereby protects the deeper structure especially endothelium from UVA cleavage.

After 30 minutes of C3R, fluorescein was diffusely observed with intact epithelium, which is consistent with a same clinical outcome achieved with epithelial removal.[12]

There has been individual case reports of increase in BCVA without changes in topography. These maybe explained by the optical regularisation of cornea resulting from crosslinking.[7]

Few patients showed progression in spite of C3R. These include patients with initial K reading of more than 58D, patient with low BCVA at presentation, patient with high initial cylinder values and central corneal thickness less than 420 microns. Corneal transplantation is the standard treatment for keratoconus patients who have decreased visual acuity due to corneal scarring or who are contact lens intolerant.[13]

CONCLUSION

C3R may represent one of the most important advances in ophthalmology in the recent past. It is a safe, effective and elegant treatment for a disease, which commonly causes significant morbidity and reduction of vision throughout the world. Corneal Collagen Crosslinking especially in early keratoconus patients works by improving the collagen tissue integrity and thereby preventing worsening of corneal curvature as demonstrated by stable K values. This mechanism of action is very physiological and hence yields results with no adverse tissue events.

In the future, C3R will have an even greater impact at saving newly-diagnosed patients from vision loss and problems that accompany that losses. Improved management of this disease may lessen the burden for patients and improve not only their vision, but also their quality of life.

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