LONG-TERM OUTCOME OF PATIENTS WITH KERATOCONUS WHO HAVE UNDERGONE CORNEAL COLLAGEN CROSS LINKING IN ONE EYE AND THE STATUS OF THE FELLOW EYE

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CONTENTS

INTRODUCTION

Corneal ectasias are disorders that affect the corneal shape. These include conditions such as keratoconus, keratoglobus and pellucid marginal degeneration, and other causes, such as progressive post-laser assisted keratomileusis (LASIK) keratectasia (PPLK). In these conditions there is progressive corneal thinning, leading to bulging of the cornea. This may, in turn, lead to progressive astigmatism, which reduces visual acuity in the affected individual.

Ectatic conditions are most commonly bilateral, asymmetric and progressive in nature, which leads to irregular corneal steepening. The incidence of ectatic conditions in the general population is estimated to be 1 in 2000. These conditions most commonly affect individuals in their early teens (Rabinowitz *et al.*, 1998)[1]. In these conditions, corneal thinning is more common in the inferior part, which leads to an off-centered apex, resulting in irregular astigmatism.[1]

Histopathological examination of a keratoconus lesion shows stromal thinning, a break in Bowman's membrane and iron deposition within the epithelium.

Management of keratoconus includes the use of various modalities, including spectacles for refractive correction, contact lenses; intra-stromal

corneal ring segments (INTACS) and, in advanced cases surgical interventions such as lamellar or penetrating keratoplasty.

Corneal collagen cross-linking (C3R) is a newer procedure which is used to arrest the progression of ectasia in keratoconus (Wollensak *et al.*, 2003)[2]. This procedure was first described by Spoerl (Spoerl *et al.*, 1998)[3] and Wollensak *et al.*[2] at the University of Dresden, Germany.

C3R acts by creating additional covalent bonds in the corneal stroma by means of a photopolymerization reaction (Wollensak *et al.*, 2006).[4]

This technique involves the sequential use of riboflavin (vitamin B2) and ultraviolet light (UV-A) to induce collagen cross-linking. It increases the mechanical and chemical stability of the corneal tissue by creating additional chemical bonds in the corneal stroma. This leads to arrest of progression of ectasia[2,4]; in the long-term, this treatment eliminates the need for corneal transplantation.

In vitro studies have shown that the cornea absorbs approximately 30% of UV-A while the lens absorbs 50% UV-A. (1). Corneal UV- A absorption can be considerably increased by using a with photo-sensitizer, such as riboflavin. With irradiance of 3mW/cm^2 of UV-A and 1% riboflavin, as much as 95% of UV-A will be absorbed by the cornea. This results in a 20- fold reduction of irradiance down to 0.15 mW/cm^2 (at the endothelial level), which is well below 0.36 mW/cm^2, the threshold considered

cytotoxic for the corneal endothelium [(2)] The UV-A wavelength used for this procedure is 370 nm.

Riboflavin, on exposure to UV-A, is excited and it is converted into a triple state. This causes production of reactive oxygen species (ROS). These ROS react with the covalent bonds within the cornea, bridging the amino acid group's, collagen fibrils in type II photochemical reaction[4]. This procedure increases corneal rigidity by 328.9 % (Wollensak *et al.*, 2003)[5]. This is because of the increase in diameter of the collagen fibrils, mainly due to inter-fibrillar and intra-fibrillar covalent bond formation, finally resulting in a more compact and strong cornea which is resistant to deformation and ectasia.

C3R is indicated for progressive keratoconus, pellucid marginal degeneration and iatrogenic post- LASIK ectasia. This procedure can be done for corneas more than 400 µm thick to prevent damage to the corneal endothelium (Spoerl *et al.*, 2007).[6]

C3R has the advantage of halting the progression of the disease[2,4]; there is also a shorter rehabilitation period, when compared with that of other therapeutic modalities. It is also devoid of the complications associated with other procedures, such as keratoplasty.

A major drawback of this procedure is that it cannot be used in thin corneas (less than 400 µm thick) and in scarred corneas, unlike keratoplasty.

Hafezi F *et al.* (2009) described a technique wherein hypotonic riboflavin is used for thin corneas, leading to swelling of the corneal stroma; if the corneal thickness reaches 400 µm, as revealed by pachymetry, then C3R is performed.[7]

Various modification of the basic procedure have been described; these include the original Seiler method[2,4,] Caporossi's technique[8], Kanellopolus intralase technique[9], Sanchez Leon modified method in post-LASIK ectasia, phototherapeutic keratectomy (PTK) cross-linking and also simultaneous topography- guided photo refractive keratectomy (PRK) and cross-linking.

A possible complication have been associated with this technique is the which includes occurrence of infection due to epithelial scraping or use of contaminated riboflavin or bandage contact lens (BCL)-induced infection. To avoid infection, a new "no touch technique" is used, wherein epithelial debridement is done using excimer laser, instead of manual scrapping of the epithelium. Corneal endothelial toxicity is caused by use of high frequency of UV-A or a high concentration of riboflavin, which is most commonly noted with thinner corneas; this can be prevented by proper calibration of UV-A intensity. Riboflavin solution also prevents absorption of UV-A beyond 300 µm, and thereby reduces endothelial toxicity. Adequate saturation of the riboflavin solution can be seen (under a blue filter) as a yellow flare in the anterior chamber.

A part from the indications mentioned above C3R in recent times has been used in combination with INTACS for management of severe keratoconus. C3R can also be done prior PRK to delay corneal transplantation.

Other research trials have evaluated the efficacy of the C3R procedure to manage pseudophakic bullous keratopathy, corneal melting and persistent, non-healing corneal ulceration. The use of C3R for these conditions carries the risk of corneal perforation, hence is not used frequently.

C3R is a safe and effective technique in arresting the progression of corneal ectasia in which the benefits outweigh the drawbacks.

In recent times C3R has been used to treat keratoconus (Wollensak *et al.*, Caporossie et al.)[2,8]. However these studies were done on a variable number of patients and the duration and outcome measured were variable.

In this current study, an attempt has been made to study the efficacy of corneal collagen cross-linking (C3R) in patients with progressive keratoconus in an Indian population; the Clinical status of the fellow eye was also studied simultaneously.

AIM OF THE STUDY

A. To determine the long-term efficacy and safety of corneal collagen cross-linking to halt the progression of keratoconus by studying the outcomes achieved in terms of uncorrected and best corrected visual acuity, cylinder value and corneal topography

B. To review on the status of the fellow eye since keratoconus is most commonly a bilateral condition

REVIEW OF LITERATURE

Keratoconus is a clinical term used to describe a condition in which the cornea assumes a conical shape due to thinning and protrusion. It is usually a progressive bilateral and non-inflammatory corneal ectasia which causes mild to marked impairment of the quality of vision (Krachmer JH *et al.*, 1984)[8].

Patients with keratoconus usually present in their teenage years with complaints of visual disturbance secondary to a refractive error, usually myopia or high astigmatism. Photophobia and glare are other presenting complaints (Espander *et al.*, 2010).

It is difficult to detect corneal ectasia in the very early stages; in such cases, pachymetry is useful for detection of keratoconus, since it shows the relative thickness of various parts of the cornea, and also it provides useful and accurate information with regard to the position of the ectasia; it is also helpful in detecting the progression of the disease. A corneal topography is considered the diagnostic tool for identification of corneal ectasia.

Corneal topography provides useful and accurate information with regard to the position of ectasia; it is also helpful in detecting the progression of the disease. On topography, keratoconus can present either as a central symmetric, but lopsided or ‘lazy eight’, bow-tie with a skewed radial axis,

or as an asymmetric bow tie with or without skewing (Rabinowitz and Rasheed., 1999)[9]. 'Forme frusta' keratoconus (FFK) is a cornea that has no abnormal finding by both slit-lamp examination and placido-based topography, with the fellow eye suffering from clinical keratoconus

The Rabinowitz criteria for diagnosis of keratoconus consist of two topography - derived indices, with a keratometry value exceeding 47.50D, steepening of the inferior cornea (compared with that of the superior cornea) of more than 1.4 D, and skewing of the radial axis (Rabinowitz YS *et al.*, 1995)[10].

The progression of keratoconus is uneven between the two eyes. In case of familial keratoconus, a 'J' pattern or 'inverted J' pattern may be noted.[11]

However Maeda *et al.*, (1997) demonstrated a method of classifying corneal maps; and this method was found to be more sensitive and specific to detect early corneal ectatic changes than looking for elevated Sim-K readings and infero-superior asymmetry (I-S) values.[12]

Many instruments are used for corneal ectasia, both as diagnostic and prognostic tools; each one of which may vary in their working principles.

The Magellan Mapper ™ (Nidek, Gamagori, Japan) uses the neural network application (Klyce SD *et al.*, 2005)[13]. The Orbscan™ corneal

topography uses the principle of “placido disc” to determine the curvature of the cornea. In this method, 40 slit-images of the cornea are taken, based on which various parameters are analyzed; this is able to suggest a risk for ectasia if there is a variance in astigmatism of more than 1. 00D between the two eyes, or by detecting irregularity of the central cornea at 3mm to 5mm. Ectatic risk is also suggested when the posterior surface float is greater than 0.05mm, or if the thinnest area is 20 µm thinner than the thickness of corneal edema; 2 abnormal maps may indicate early ectasia (Karpecki *et al.*, 2006).[14]

The Pentacam ™ (Oculus, Wetzlar, Germany) has a higher depth of focus; this system uses a rotating Scheimpflug camera. This is a multifunctional imaging device is a ‘comprehensive eye scanner for the anterior eye segment’. It mainly measures the central corneal thickness, Anterior chamber depth and corneal curvature, both anterior and posterior. A total of 25 images are captured within 2 seconds, with each being composed of 25, 000 elevation points that include 500 true elevation points. An anterior elevation difference less than +12 µm is considered normal, an anterior elevation difference greater than +15 µm is indicative of keratoconus and anterior elevation difference between +12 and +15 µm is considered suspicious (Maus M *et al.*, 2006).[15]

The Galilie ™ (Ziemer Ophthalmic System AG, Port Switzerland) combines technology, such as placid topography, dual-Scheimpflug tomography and optical biometry (Klyce D *et al.*, 2009). [16]

The Reichert Ocular Response Analyzer™ measures corneal hysteresis (CH) and the corneal resistance factor (CRF). **Corneal hysteresis** provides an indication of the biomechanical properties of the cornea, which differ from thickness and topography, which are geometrical attributes. Corneal hysteresis and the corneal resistance factor may serve as may be a diagnostic tools to determine the risk of post-refractive ectasia (Kirwan *et al.*, 2008)[17]; (Ortiz D *et al.*, 2007). [18]

Wavefront aberrometers can also be used to detect early corneal ectasia. An increase in total higher order aberration is noted in keratoconus, and is attributed to corneal shape. Maeda *et al.* (2002) reported that eyes with keratoconus showed a coma in a wave front aberrometers.[19]

Therapeutic options for keratoconus include spectacles in the early stages for refractive error correction; other modalities include specialized contact lenses, intra-stromal corneal ring segments (INTACS) and lamellar or penetrating keratoplasty. Corneal collagen cross-linking is used to arrest the progression of the ecstatic condition.

The management of keratoconus depends on the stage and the rate of progression of the disease. In the early stages, spectacles are an option for refractive error correction if the vision improvement is good; however, as the disease advances, the patient may require contact lenses to reduce the image distortion and to provide better vision. Rigid gas-permeable (RGP) lenses, ranging in size from 8 to 10mm, are used in small central cones, or in mild keratoconus. Advantages of RGP-lenses are that they provide a smooth regular surface that masks the underlying corneal irregularity; they also permit a good tear exchange. Disadvantages of these lenses include possible decenteration and difficulty in adaptation for the patient.

Soft contact lenses and soft toric lenses are indicated in the early stages and also in cases of de-centered keratoconus. These lenses fit centered over the cornea and are most commonly used in patients who have trouble with RGP-lenses.

The ‘piggyback lens’ involves fitting a soft contact lenses beneath a corneal gas permeable (GP) lens. This modality is usually indicated when there is poor comfort or significant epithelial disruption when using GP lenses; occurrence of apical epithelial nodules, or accompanying epithelial basement membrane dystrophy, are also indications for the piggyback lens. Improved GP and soft contact lenses provide better oxygen permeability and prevent corneal edema and hypoxia. The base curve of a soft lens can be

modified to alter the fitting relationship of a GP lens; a plus-powered soft lens is used to flatten the GP fit, while a minus-powered soft lens is used to steepen the GP fit. Disadvantages of the 'piggyback lens' are the inconvenience and need for multiple lens care systems.[20]

Hybrid contact lenses have a GP-centered a soft skirt. These lenses include SynergEyes A™, which is designed for use in early to moderate keratoconus, and SynergEye KC™, which is used in advanced keratoconus. These lenses provide a good centration and high oxygen permeability. One disadvantage is late-term lens tightening, which occurs months after the initial fitting; it may also be difficult to evaluate proper fitting.[20]

When the cone is a central nipple, then Rose K™ lenses can be selected. These are multicurve lenses with a small optical zone which fits the cone, to impart the so-called 'feather touch' to the cornea. The success rate of fitting the Rose K™ lens in keratoconus is more than 90%. Once an optimal fit is obtained, the final power should be calculated after performing a spherical over refraction with trial lenses.

Rose K2™ contact lenses are shown to improve visual acuity and comfort; they can also avoid the need for piggy back lenses in management of an irregular cornea.

Scleral contact lenses rest on the sclera and do not touch the cornea or limbus, leaving a clear area between the contact lens and the cornea. These lenses are indicated when all other contact lenses fail to improve the vision because or because of inability to get an optimal fit with rigid GP lenses, rigid GP lens intolerance, vascularisation following use of piggyback lenses, advanced keratoconus or scarring of cornea. Disadvantages to the use of scleral contact lenses include the specific care regimen required for the scleral lenses, different insertion and removal technique using plungers, and the frequent change of saline bottles. The fenestrated lenses are removed using plungers at the center. With non-fenestrated lenses, the plunger is applied at the junction of the vault and haptic, and the lenses are then removed. The advantage of scleral lenses, apart from the provision of improved comfort and stable visual acuity, is that they delay the need for keratoplasty.[33 - 35]

Corneal collagen cross-linking (C3R) is a technique which is currently very commonly used to arrest the progression of the disease. This method was basically used to harden materials in polymer industries and also to stabilize tissues in bioengineering. In the cornea, this cross-linking technique is done using UV-A at 370nm to convert riboflavin to its triplet stage, which leads to production of reactive oxygen species (ROS); this induces development of inter- and intra- fibrillar covalent bonds in the

corneal stroma, therein strengthening it [4.] Trials in animal trials have shown that this method increases the corneal rigidity by 70%[5]. In humans also, this procedure has shown significant results in halting the progression of the ectasia condition. These effects of C3R provide a major advantage tothis procedure vis-á-vis the other methods to treat corneal ectasia.

The corneal tensile strength is found to be decreased in ecstatic corneas. The effect of this procedure is maximal in the anterior 300 µm of the cornea[5].

Wollensak *et al.* (2004)[21], after performing C3R in experimental rabbit eyes, noted that the diameter of corneal collagen fibers was increased by 12.2% in the anterior stroma and by 4.6% in the posterior stroma. These investigators hypothesized that these effects were possibly due to the pushing of existing collagen peptide bonds by the induced cross-links, resulting in increase in intermolecular spacing; they also noted that this type of increasing collagen fiber diameter and corneal rigidity due to C3R, also occurs in diabetes mellitus and ageing.

In porcine eyes, the cross-linking procedure results in increased resistance against digestion by collagenases, with the effect being stronger in the anterior part of the cornea. This resistance possibly plays a role in ameliorating keratoconus, since the tear samples in keratoconus patients

show a 2.5 times higher collagenase metabolite when compared to those in normal eyes (Spoerl *et al.*, 2004)[22].

In the hydrothermal shrinkage theory, in cross-linked corneas, a higher shrinkage temperature was observed in the anterior part of the stroma (75^0) compared to the posterior stroma (70^0), suggesting a higher degree of cross-linking in the anterior stroma. This anterior or localization of the cross-linking effect is advantageous for the endothelium and for preservation of the anterior corneal curvature (Spoerl E *et al.*, 2004). [23]

When cross-linked porcine eyes were examined by biomicroscopy and light microscopy, a lower degree of edema was noted in the anterior stroma, confirming the previous findings that the cross-linking effect is stronger in the anterior stroma. But, this effect did not induce any change in optical coherence tomography (OCT), suggesting that OCT is not a suitable method to study the cross-linking effect (Wollensak *et al.*, 2007). [24]

In a study by Mazotta *et al.* (2007)Heidelberg Retinal Tomography II Rostock Corneal Module (HRT II-RCM*) in vivo* confocal microscopy showed rarefaction of keratocytes in the anterior and intermediate stroma, associated with stromal edema, immediately after the C3R procedure At 3 months after the procedure, repopulation by keratocytes was noted in the central treated area, while edema had disappeared; at 6 months after the procedure, the keratocyte repopulation was complete, accompanied by

increased density of stromal fibers. No endothelial damage was observed at any time. (Mazotta *et al.*, 2007)[25]

Wollensak *et al.*, (2003)[2] are credited with the first clinical study that showed that the C3R procedure was able to arrest the progression of keratoconus in 23 eyes of 22 patients. In these patients, the steep keratometry values reduced from 2.01 diopters in 70% of eyes, with correction of 1.14 diopters over a follow-up of 23 months. No scarring, lenticular opacities or endothelial cell loss were seen after the procedure.

Caporossi *et al.*, (2006)[26], in a prospective study on10 eyes with bilateral keratoconus in Italy, reported improvement in visual acuity following C3R; this was accompanied by a reduction in the mean keratometry reading, confirmed by corneal topography. These investigators also conducted a long-term study, known as The Siena Eye cross study, on 363 eyes with progressive keratoconus with a mean follow-up of 52.4 months; in this study also, long-term improvement in the visual acuity was observed (Caporosso *et al.*, 2010). [27]

Wolf *et al.* (2008)[28] performed another long-term follow-up study, in Germany on 480 eyes with progressive keratoconus which had undergone the C3R procedure; based on the results obtained, these investigators concluded that long-term stabilization of the disease progression, as well as better visual acuity outcomes, were achieved after C3R procedure.

Goldich *et al.* (2012)[29] performed a prospective study on 14 patients, in Israel, who had undergone C3R. Results similar to those of earlier studies were noted. In addition, at the end of this study, it was observed that there was no change in the corneal thickness or the endothelial density, suggesting that this procedure was safe.

Cifariello F *et al.* (2018)[30], in a study performed in Italy, compared 2 different techniques of the C3R procedure, namely, the 'Epi-on' versus the ' Epi-off'; the study included 40 eyes. Based on the results obtained, it was concluded that both procedures are able to slow down the progression of the disease. Interestingly, the C3R 'Epi–on' technique is mostly preferred, since this technique preserves the corneal thickness and also reduces post-procedure ocular discomfort.

Choi M *et al.* (2017)[31], in a study, compared the effectiveness of an accelerated protocol with higher intensity UV-A versus that of the conventional Dresden protocol. The study included 28 eyes in 2 groups. It was observed that despite the higher UV dose, only a smaller topographic flattening effect was achieved with the accelerated protocol, when compared with the effect achieved when the conventional Dresden protocol was used.

In recent years, C3R is being combined with intrastromal corneal ring segments (INTACS) in an attempt to flatten the cornea. However, this does

not solve the problem of weakening of collagen. INTACS acts only as an additive measure to flatten out the corneal surface.

The C3R procedure has also been tried in pseudophakic bullous keratopathy. In these cases, the cornea has to be initially de-swelled using glycerol till the corneal thickness at the thinnest point is 400 µm. [36] in corneal melting; C3R can be tried with a lower surface irradiation in order to compensate the thinness of the cornea.

Recent studies have also shown the efficacy of photoactivated riboflavin in C3R for treatment of refractory infectious keratitis. The result of one such study showed a cessation in corneal melting in all treated cases (Panda et al 2013).[32]

Despite the many advantages of the C3R procedure, a few complications have also been reported. Wasilewski D et al. (2013), in a study conducted in Brazil, reported that the corneal cross-linking procedure done performed in 36 eyes induced a decrease in corneal sensitivity; this decrease in sensitivity was more intense in the first few weeks after the procedure, with a progressive recovery over a period of 6 months. [37]

A case of pseudomonal keratitis in a 19year old who underwent the C3R procedure was reported by Sharma *et al.* (2010); this was attributed to the use of a bandage contact lens in the early post-operative period.[38]

The various papers cited above show that a significant amount of research as well as clinical practice has been performed globally with reference to the C3R procedure. It is interesting to note, however, that there has been a relatively smaller quantum of work in India itself. Moreover, there are few studies that have also taken into account the clinical status of the fellow eye.

Hence, in this current study, an attempt has been made to study the efficacy of C3R in patients with progressive keratoconus in an Indian population; the clinical status of the fellow eye also been studied simultaneously.

MATERIALS AND METHODS

1. Nature and duration of the study

The current study was a prospective observational study on patients suffering from keratoconus who presented to the Cornea Clinic, Joseph Eye Hospital, Tiruchirapalli, Tamil nadu, over an15 month period (June 2018 to August 2019) and who underwent corneal collagen cross-linking (C3R) to prevent the progression of their condition. This study was approved by the Institutional Ethics Committee. This study was done to assess the efficacy of C3R in keratoconus and its role in preventing the progression of the condition.

2. Sample size

Since this was a prospective study, an attempt was made to calculate a sample Size. For sample size estimation, an online calculator at www. raosoft. com was used Population size was found to be 24 cases in 18 months.

Response distribution = 90%

Margin of error = 5%

Confidence level = 95%

Based on these variables, a sample size of 24 eyes was calculated.

3. Inclusion Criteria

Patients were considered for inclusion in the study if they fulfilled the following criteria:

a) Presented with unilateral or bilateral progressive keratoconus;
b) Were Aged between 15 to 40 years;
c) The affected eye had keratoconus with an average K value not exceeding 60 Diopter;
d) The affected eye had a central corneal thickness of more than 400µm at the thinnest point; and
e) The affected eye had keratoconus which was not found to be associated with any sub-epithelial or stromal scarring on slit lamp examination.

4. Exclusion Criteria

Patients were not considered for the study (exclusion criteria) if any of the following was present:

a) Patient was more than 40 years of age;
b) The affected eye had a Central corneal thickness less than 400µm at the thinnest point;
c) The patient was pregnancy and lactating mothers;
d) Stationary keratoconus, a scarred cornea or acute hydrops was present;

e) The patient suffered from an active ocular infection;

f) The patient was suffering from any autoimmune disease or diabetes mellitus;

g) The patient declined to participate in the study or to provide written informed consent for the procedure.

5. Clinical examination of the patient and investigations done

All patients included in this study underwent clinical examination before and after the procedure

A diagnosis of keratoconus was made if any of the following clinical signs were noted:

a) Munson's sign (protrusion of lower lid on downward gaze); or

b) Rizzuti's sign (conical reflection of nasal cornea when light was shone temporally)

A diagnosis of keratoconus was made if slit-lamp examination of these patients showed any of the following signs; inferior paracentral corneal thinning, presence of an ecstatic cone, inferior corneal steepening, vertical stress lines in the posterior stroma (Vogt's striae), iron deposition in the basal epithelium (Fleischer ring), or a linear scar as a result of a break in the Bowman's layer.

The following clinical parameters were analyzed before and after the surgery

1. Uncorrected visual acuity (decimals)
2. Best corrected visual acuity (decimals)
3. Spherical equivalent (diopters)
4. Cylinder value (diopters)
5. All patients also underwent corneal topography (Zeiss Atlas 9000); changes in the keratometry value in the steeper meridian (K1), the flatter meridian (K2) and the average keratometry value (K avg) were determined before and after surgery.

6. Procedure

All patients undergoing C3R were well-informed about the procedure and all possible outcomes, including post-operative complications, were explained. A written informed consent was obtained from each individual before performing the procedure. All the procedures were performed by a single surgeon under aseptic conditions.

Topical proparacaine hydrochloride (0. 5%) was instilled prior to the procedure. The central 9mm of the corneal epithelium was debrided mechanically using a blunt hockey knife (to permit better penetration of riboflavin). A drop of 0.1% solution of riboflavin (X Linker riboflavin ophthalmic solution (isotonic)) was applied every 2 minutes up to 30

minutes. After adequate penetration of riboflavin had occurred (as assessed using a blue filter by presence of yellow flare in the anterior chamber), the cornea was then exposed to calibrated UV-A, with a radiation frequency of 370 nm, in a dose of 3mW/cm^2. The UV-A source was placed at distance of 5 cms away from the cornea. Irradiation was done for 30 minutes, along with topical instillation of riboflavin drops every 2 minutes, to ensure adequate photosensitization and photoprotection by the barrier effect. After the process was complete, a drop each of ofloxacin 0.3% and flurbiprofen 0.03% eye drops was instilled, and a sterile eye patch was applied to help re-epithelisation of the cornea.

7. Post-operative care

Post-operatively, the patient was prescribed with topical ofloxacin eye drops (4 times a day) along with flurbiprofen eye drops (4 times a day) for three days until the epithelium had healed completely. Following this topical steroid eye drops were applied 4 times daily to start with, and then gradually tapered over a month. Topical lubricating eye drops (Refresh liquigel 0.5 fl oz) were also applied 4 times daily for upto 6 months after the surgery.

8. Measures of outcome

The main outcomes measured in this study were uncorrected visual acuity, Best corrected visual acuity, Spherical equivalent, Cylinder value

and keratometry readings (K1, K2 and Average K) corneal topography before and after C3R procedure.

9. Statistical analysis

The statistical significance of differences by means of best corrected vision in data was evaluated by Chi square test. The statistical significance of differences in continuous (quantitative) data was evaluated by unpaired ‘t’ test. Statistical analysis was done using one-way analysis of variance (ANOVA) and post hoc testing was applied to compare the differences in various parameters at different time points of examination. A probability value < 0.05 was considered statistically significant

RESULTS

The present investigation was a prospective, interventional study on patients who presented with various grades of keratoconus at the Cornea Clinic, Joseph Eye Hospital, Trichy, over a period of 15 months. (June 2018 to August 2019). Patients who underwent corneal collagen cross linking procedure between June 2018 and August 2019 were enrolled and, follow-up was over a period of 12 months, and data were analyzed subsequently.

A total of 33 individuals with features of keratoconus who underwent corneal collagen cross linking procedure were seen during the enrolment period. Of these, nine individuals had at least one exclusion criterion or declined to participate in the study. Finally, 21 patients (42 eyes) who satisfied the inclusion criteria and who consented to undergo corneal collagen cross-linking with riboflavin (C3R) were enrolled in the study.

These 21 patients were divided into 3 groups based on the laterality of the disease process and procedure done. Accordingly, Group A had 4 patients who had unilateral keratoconus and underwent the C3R procedure in the affected eye (4 operated eyes and 4 unoperated fellow eyes) while group B had 10 patients who had bilateral keratoconus but underwent C3R procedure in one eye only (progressive keratoconus) with the fellow eye being stable (10 operated eyes and 10 unoperated fellow eyes). Group C had

seven patients who presented with progressive keratoconus in both eyes. The C3R procedure was done in both eyes, with the severe eye operated first followed by the fellow eye within an interval of a week (a total of 14 operated eyes in this group). Both eyes were followed simultaneously during each follow- up visit.

Different parameters, such as uncorrected visual acuity (UCVA), Best corrected visual acuity (BCVA), cylinder value, spherical equivalent (SE), axis, K-reading (K1 or steep K, K2 or flat K and Average K) were analyzed at baseline (pre-operative) and _at 1 month, 6months and 1 year post-operatively to determine whether the C3R procedure halted the progression of keratoconus and stabilized the various parameters studied.

1) DEMOGRAPHIC ASPECTS

1.1) Gender and Age Distribution:

Forty two eyes of 21 patients were included in this study. There were nine males (42.85%) and 12 females (57.14%). The mean age of the patients was 21.09±3.9 years (range 15 to 40 years). There were 11 (52.38%) patients aged between 15 to 20 years, eight (38.09%) between 21-25 years and two (9.5%) between above 25 years. (Figures 1 and 2).

1.2) Laterality of the eye undergoing corneal collagen cross-linking with riboflavin:

Of the total 21 patients, 14 (66.66%) patients underwent the C3R procedure in one eye and these patients were included in Groups A and B. Seven (33.33%) of the 21 patients had bilateral progressive keratoconus; these 7 patients underwent the procedure in both eyes within the study period and were included in Group C.

Among the 14 patients who underwent the C3R procedure in one eye only (Group A and B), seven (50%) patients underwent the procedure in the right eye and seven (50%) in the left eye (Fig.3)

Group C comprised seven patients who presented with bilateral progressive keratoconus and underwent the C3R procedure in both eyes, with the most affected eye operated first and the other eye operated within an interval of 1 week in all patients. In this group, both the eyes were followed up simultaneously at every follow up visit for upto 1 year.

2. Clinical features of patients enrolled in the current study

2.1 Preoperative mean uncorrected visual acuity (UCVA)

2.1.1 GROUP A (4 patients, unilateral keratoconus; study eye operated; fellow eye not operated)

The preoperative mean UCVA (decimals) was 0.212±0.075 (Table 1; Figs.4.1.1 and 4.1.2) in the (operated) study eye and 0.19±0.11in the (unoperated) fellow eye; the difference between the two groups in preoperative mean UCVA was not statistically significant.

2.1.2 GROUP B (10 patients, bilateral keratoconus; study eye keratoconic, operated; fellow eye keratoconic, not operated)

The pre-operative mean UCVA (decimals) was 0.23±1.8 in the study (operated) eye and 0.27±0.20 in the fellow (unoperated) eye; this difference was not statistically significant (Unpaired 't' test [degree of freedom {df}=18]; t= 0.45; P=0.66) (Table 2; Figs.4.2.1 and 4.2.2).

2.1.3 GROUP C (7 patients, bilateral keratoconus; study eye = worse eye, operated first; fellow eye = better eye, operated after one week)

The pre-operative mean UCVA (decimals) was 0.17±0.06 in the (worse, first operated) study eye and 0.18±0.09 in the (better, second operated) fellow eye; this difference was not statistically significant (Unpaired' t ' test, [df=12]; t= 0.42; P=0.68) (Table 3; Figs.4.3.1 and 4.3.2).

2.2. Preoperative mean best corrected visual acuity (BCVA)

2.2.1 GROUP A (4 patients, unilateral keratoconus; study eye operated; fellow eye not operated)

The pre-operative mean BCVA (decimals) in the study eye was 0.71±0.20 and in fellow eye was 0.83±0.19; this difference was not statistically significant (unpaired' t' test [df=6]; t = 1.08; P=0.32) (Table 4; Figs.5.1.1 and 5.1.2).

2.2.2 GROUP B (10 patients, bilateral keratoconus; study eye keratoconic operated; fellow eye keratoconic, not operated)

The pre-operative mean BCVA (decimals) in the study eye was 0.45±0.25 and in fellow eye was 0.54±0.26; this difference was not statistically significant (unpaired 't' test [df=18]; t= 0.70; P=0.50) (Table 5; Figs.5.2.1 and 5.2.2).

2.2.3 GROUP C. (7 patients, bilateral keratoconus; study eye = worse eye, operated first; fellow eye = better eye, operated after one week)

Pre-operative mean BCVA (decimals) in the study eye was 0.52±0.26 and in fellow eye, it was 0.54±0.16; the difference between the two groups in preoperative mean BCVA was not statistically significant (unpaired 't' test [df=12]; t = 0.26; P=0.8 (Table 6; Figs.5.3.1 and5.3.2).

2.3. Preoperative mean Cylinder value (Dcyl)

2.3.1 GROUP A (4 patients, unilateral keratoconus; study eye operated; fellow eye not operated)

The pre operative mean Dcyl (Diopters) value in study eye was 1.75±1.7 and in fellow eye it was 1.8±1.3; the difference between the two groups in preoperative mean Dcyl value was not statistically significant (unpaired ‘t’ test [df=6]; t=0.12; P=0.91) (Table 7; Figs.6.1.1 and 6.1.2)

2.3.2 GROUP B (10 patients, bilateral keratoconus; study eye keratoconic operated; fellow eye keratoconic, not operated)

The pre operative mean Dcyl value (dioptres) in the study eye was 3.45±2.8 and in fellow eye it was 2.7±2.08; this difference was not statistically significant (unpaired ‘t’ test [df=18]; t = 0.75; P=0.46) (Table 8; Figs.6.2.1 and 6.2.2).

2.3.3 GROUP C. (7 patients, bilateral keratoconus; study eye = worse eye, operated first; fellow eye = better eye, operated after one week)

The pre operative mean Dcyl value (dioptres) in the study eye was 2.85±1.3 and in fellow eye it was 2.71±1.6; this difference was not statistically significant (unpaired ‘t’ test [df=12]; t =0.19; P=0.85) (Table 9; Figs.6.3.1 and 6.3.2).

2.4. Preoperative mean Spherical equivalent value (SE)

2.4.1 GROUP A (4 patients, unilateral keratoconus; study eye operated; fellow eye not operated)

The pre operative mean SE (Diopters) in the study eye was 3.3±0.75 and in fellow eye was 2.02±0.93; **the difference between the two groups in preoperative mean SE approached statistical significance** (unpaired 't' test [df=6]; t = 2.24; P=0.07) (Table 10; Figs.7.1.1 and 7.1.2)

2.4.2 GROUP B (10 patients, bilateral keratoconus; study eye keratoconic, operated; fellow eye keratoconic, not operated)

The pre operative mean SE (dioptres) was 3.3±2.5 in the study eye and 2.21±1.9 in the fellow eye; this difference was not statistically significant (unpaired 't' test [df=18]; t = 1.14; P=0.27) (Table 11 ; Figs.7.2.1 and 7.2.2).

2.4.3. GROUP C. (7 patients, bilateral keratoconus; study eye = worse eye, operated first; fellow eye = better eye, operated after one week)

The pre operative mean SE (dioptres) was 4.21±2.17 in the study eye and 3.97±1.6 in the fellow eye; this difference between the two groups in preoperative mean SE was not statistically significant (unpaired 't' test [df=12]; t= 0.22; P=0.83) (Table 12; Figs.7.3.1 and 7.3.2)

2.5 Preoperative mean K1 value (steep K)

2.5.1 GROUP A (4 patients, unilateral keratoconus; study eye operated; fellow eye not operated)

The pre operative mean K1 (Diopters) was 50.76±2.2 in the study eye and 45.83±2 in the fellow eye; this difference **was statistically significant (**unpaired 't' [df=6]; t = 3.29; **P=0.02)** (Table 13; Figs.8.1.1 and 8.1.2)

2.5.2 GROUP B (10 patients, bilateral keratoconus; study eye keratoconic, operated; fellow eye keratoconic, not operated)

The pre operative mean K1 (dioptres) was 52.34±4.4 in the study eye and 47.26±1.8 in the fellow eye; this difference **was statistically significant** (unpaired 't' test [df=18]; t = 3.33; **P=0.004)** (Table 14; Figs.8.2.1 and 8.2.2)

2.5.3 GROUP C (7 patients, bilateral keratoconus; study eye = worse eye, operated first; fellow eye = better eye, operated after one week)

The pre operative mean K1 was 51.64±4.5 in the study eye and 50.43±4.3 in the fellow eye; the difference between the two groups in preoperative mean K1 value was not statistically significant (unpaired 't' test [df=12]; t = 0.51; P=0.62) (Table 15; Figs.8.3.1 and 8.3.2)

2.6 Preoperative mean K2 value (Flat K)

2.6.1 GROUP A (4 patients, unilateral keratoconus; study eye operated; fellow eye not operated)

The preoperative mean K2 (Diopters) in the study eye was 45.77±3.02 and in the fellow eye it was 43.4±1.7; there was no statistically significant difference between the study eyes and fellow eyes in this parameter (unpaired 't' test [df=6]; t = 1.32; P=0.24) (Table 16; Figs.9.1.1 and 9.1.2.)

2.6.2 GROUP B (10 patients, bilateral keratoconus; study eye keratoconic, operated; fellow eye keratoconic, not operated)

The preoperative mean K2 (dioptres) in the study eye was 46.39±3.3 and in the fellow eye it was 43.39±1.4; there was a **statistically significant difference** noted between the study eyes and fellow eyes in this parameter (unpaired't' test [df=18]; t = 2.58; **P=0.02**) (Table 17; Figs.9.2.1.and 9.2.2.).

2.6.3 GROUP C (7 patients, bilateral keratoconus; study eye = worse eye, operated first; fellow eye = better eye, operated after one week)

The preoperative mean K2 (dioptres) among the study eyes was 45.64±1.9 and that of the fellow eyes was 45.13±2.4; , there was no statistically significant difference noted between the two groups (Unpaired' t' test [df=12]; 't' = 0.42; P=0.68) (Table 18; Figs.9.3.1.and 9.3.2)

2.7. Preoperative mean Average K

2.7.1 GROUP A (4 patients, unilateral keratoconus; study eye operated; fellow eye not operated)

The preoperative mean Average k value was 48.26±2.5 in the study eye and 44.64±1.7 in fellow eye; **this difference was statistically significant** (unpaired 't' test [df=6]; t = 2.32; **P=0.05**) (Table 19; Figs.10.1.1 and 10.1.2).

2.7.2 GROUP B (10 patients, bilateral keratoconus; study eye keratoconic, operated; fellow eye keratoconic, not operated)

The mean pre operative Average K value in the study eye was 49.37±3.6 and in the fellow eye it was 45.42±1.4; **this difference was statistically significant (**unpaired 't' test [df=18]; t = 3.17**; P=0.005)** (Table 20; Fig.10.2.1 and 10.2.2).

2.7.3 GROUP C (7 patients, bilateral keratoconus; study eye = worse eye, operated first; fellow eye = better eye, operated after one week)

The mean pre operative average K in the study eye was 48.64±2.7 and 47.78±3.1 in the fellow eye; , there was no statistically significant difference noted between the study eyes and fellow eyes in this parameter in this group (unpaired 't' test [df=12]; t = 0.50; P=0.67) (Table 21 and 22; Figs.10.3.1 and 10.3.2)

3.3. Postoperative mean values

3.3.1. Postoperative mean Uncorrected visual acuity (UCVA)

3.3.1.1 GROUP A (4 patients, unilateral keratoconus; study eye operated; fellow eye not operated)

The mean UCVA (Decimals) in study eyes at one month follow up post operatively was 0.27±0.04, in the fellow eye the mean UCVA in one month follow up was 0.28±0.2 6 (Table 1; Figs.4.1.1.and 4.1.2.)

The mean UCVA in study eye at 6 months post operative follow up was 0.29±0.04 and in fellow eye it was stable with mean of 0.28±0.26 (table 1 Figs.4.1.1.and 4.1.2.)

The mean UCVA in the study eye by end of one year was 0.33±0.01 and in fellow eye it was stable (0.28±0.26). (Table 1 Figure 4 Figs.4.1.1.and 4.1.2.)

In all the three post operative visits, there was no statistical significance noted between the mean UCVA values in the study eyes and fellow eyes in Group A.

3.3.1.2 GROUP B (10 patients, bilateral keratoconus; study eye keratoconic, operated; fellow eye keratoconic, not operated)

The mean UCVA in study eye post C3R procedure by one month was 0.27±0.18 and the fellow eye at one month was 0.29±0.19 (Table 2 Figure 4, Figs.4.2.1.and 4.2.2.))

6 months mean at follow up of study eye showed increase in UCVA of 0.34±0.26 while the fellow eye the mean was stable (0.295 ±0.19) (Table 2, Figure 4, 4.2.1.and 4.2.2.)

At subsequent follow up of one year the mean UCVA in study eye increased to 0.42±0.25 while in the fellow eye the value reduced to 0.27±0.21 (table 2 Figure 4, 4.2.1.and 4.2.2.)

3.3.1.3 GROUP C (7 patients, bilateral keratoconus; study eye = worse eye, operated first; fellow eye = better eye, operated after one week)

The mean UCVA at one month in study eye post C3R procedure increased to 0.19±0.08 and fellow eye also showed increase in mean UCVA of 0.23±0.14. (Table 3 Figure 4, Figs.4.31.and 4.3.2.)

There was aN increase Of mean UCVA in both study eye and in fellow eye by 6 month 0.26±0.12 and 0.35±0.19 respectively (table 3, Figure 4 Figs.4.31.and 4.3.2.)

In one year follow up the study eye mean UCVA was increased to 0.39±0.19 and fellow eye also increased to 0.52±0.29 (table 3, Figure 4 Figs.4.31.and 4.3.2.)

3.3.2 Postoperative mean Best corrected visual acuity (BCVA)

3.3.2.1 GROUP A (4 patients, unilateral keratoconus; study eye operated; fellow eye not operated)

In study eye there was a reduced mean BCVA (decimals) at one month follow up post C3R procedure to 0.60±0.31 while the fellow eye the mean BCVA was stable by one month 0.831±0.19; . There was no statistical difference noted between the mean BCVA values (unpaired t test (df =6); t= 0.56 P = 0.6 (Table 4; Figure 5, Figs.5.1.1 and 5.1.2)

At 6 months follow-up the mean BCVA in study increased post operatively to 0.71±0.20 and in fellow eye reduced to 0.79±0.24. The difference was not statistically significant (unpaired t test df (6)=0.49, P = 0.64) (Table 4, Figure 5, Figs.5.1.1 and 5.1.2)

At 1 year post operatively the mean BCVA in study eye was 0.83±0.19 and in fellow eye it was 0.66±0.23; this difference was not statistically significant (unpaired t test; df =6; t=1.08 P = 0.32) (Table 4; Fig5, Figs.5.1.1 and 5.1.2)

3.3.2.2 GROUP B (10 patients, bilateral keratoconus; study eye keratoconic, operated; fellow eye keratoconic, not operated)

The mean BCVA (decimals) at one month post operative follow up in study eye was 0.52±0.21 and in fellow eye it was 0.56±0.24. There was no significant difference between the mean values (unpaired t df =`18; t=0.33 P= 0.74 (Table 5; Figure 5; Figs.5.2.1.and 5.2.2)

The mean BCVA by 6 months post procedure in study eye was increased to 0.66±0.22 and in fellow eye it was 0.52±0.24. There was no statistical difference between the mean values (unpaired t =1.26 (df=18) P = 0.22) (Table 5, Figure 5, Figs.5.2.1.and 5.2.2)

At one year follow up the mean postoperative BCVA in study eye was increased to 0.75±0.17 and in fellow eye the mean was 0.49±0.39; **this difference approached statistical significance (unpaired t test [df18]; t =1.87; P= 0.08) (**Table 5, Figure 5, Figs.5.2.1.and 5.2.2)

3.3.2.3 GROUP C (7 patients, bilateral keratoconus; study eye = worse eye, operated first; fellow eye = better eye, operated after one week)

The mean BCVA (decimals) in post- operative follow up at one month was 0.56±0.22 and fellow eye was 0.64±0.17. There was no statistical difference between these mean values (Unpaired' t' test df [12], t =0.72; P = 0.48) (Table 6 Figure 5; 5.3.1 and 5.3.2)

The mean BCVA in post operative 6 month follow up in study group increased to 0.60±0.24 and the fellow eye was 0.69±0.22. This difference was not statistically significant (Unpaired ‘t’ test [df =12]; t= 0.64; P = 0.54) (Table 6; Figure 5; Figs.5.3.1 and 5.3.2)

The mean BCVA post operatively in one year follow up in study eye was0.64±0.28, and the fellow eye also increased postoperatively to 0.81±0.24. This difference was not statistically significant (unpaired ‘t’ test [df=12]; t= 1.22; P= 0.25) (Table 6 Figure 5: Figs.5.3.1 and 5.3.2)

3.3.3 Postoperative mean cylinder value (Dcyl)

3.3.3.1 GROUP A (4 patients, unilateral keratoconus; study eye operated; fellow eye not operated)

At one month, the Dcyl value (dioptres) postoperatively in the study eye was 2.12±1.15 and the fellow eye was 2±1.4; this difference was not statistically significant (unpaired ‘t’ [df=6]; t= 0.09; P= 0.93) (Table 7; Figure 6; Figs.6.1.1 and 6.1.2)

At 6 month follow up, the mean Dcyl value in study eye post operatively was 1.75±1.2 and in fellow eye it was 1.75±1.2; this difference was not statistically significant (unpaired ‘t’ [df=6]; t= 0.00; P= 1.0) (Table 7; Figure 6; Figs.6.1.1 and 6.1.2)

At one year follow up the mean Dcyl value was reduced to 1.5±1 in study eye and increased to 2.00±0.21 in fellow eye. This difference was not statistically significant (unpaired ‘t’ [df=6]; t= 0.77; P= 0.47) (Table 7; Figure 6; Figs.6.1.1 and 6.1.2).

3.3.3.2 GROUP B (10 patients, bilateral keratoconus; study eye keratoconic, operated; fellow eye keratoconic, not operated)

At one month follow up, the mean Dcyl value (dioptres) post procedure in study eye was 3.3±2.00 and fellow eye was 2.7±1.9; this difference was not statistically significant (unpaired ‘t’ [df=18]; t= 0.57; P= 0.57) (Table 8; Figure 6; Figs.6.2.1 and 6.2.2)

At 6 month follow up there was reduction in mean Dcyl value post-procedure in study eye (2.9±2.2), while the mean Dcyl in fellow eye was 2.85±2.00. This difference was not statistically significant (unpaired ‘t’ [df=18]; t= 0.22; P= 0.83) (Table 8; Figure 6; Figs.6.2.1 and 6.2.2)

At 1year post procedure the mean Dcyl in study eye was 2.65±1.8 and fellow eye was stable with mean 2.85±2.00. This difference was not statistically significant (unpaired ‘t’ [df=18]; t= 0.23; P= 0.82) (Table 8; Figure 6; Figs.6.2.1 and 6.2.2)

3.3.3.3 GROUP C (7 patients, bilateral keratoconus; study eye = worse eye, operated first; fellow eye = better eye, operated after one week)

One month post C3R procedure, the mean Dcyl value (dioptres) in study eye was 2.71±1.7 and in fellow eye it was 2.5±1.6. The difference was not statistically significant (unpaired t test; df [12] t= 0.23; P = 0.82) (Table 9; Figure 6; Figs.6.3.1.and 6.3.2)

At 6 month follow up there was reduction in the mean Dcyl value in study group 2.25±1.16 and fellow eye was 2.28±1.3. The difference was not statistically significant (unpaired t test [df=12]; t= 0.16; P= 0.87) (Table 9 Figure 6; Figs.6.3.1 and 6.3.2)

At one year follow up post operatively, the mean Dcyl value in study eye was 2.07±1.9 and fellow eye was 1.8±1.21; the difference was not statistically significant (unpaired t test [df=12]; t= 0.24; P = 0.81) (Table 9; Figure 6; Figs.6.3.1 and 6.3.2)

3.3.4. Postoperative mean Spherical equivalent (SE)

3.3.4.1 GROUP A (4 patients, unilateral keratoconus; study eye operated; fellow eye not operated)

One month post operative mean SE (dioptres) in study eye was 3.31±0.55 and the fellow eye was 2.25±1.19. The difference was not statistically significant (Unpaired t test [df=6]; t= 1.6; P= 0.16) (Table 10; Figure 7; Figs.7.1.1 and 7.1.2)

By 6 month follow up the mean SE in study eye post procedure was reduced to 1.8±1.4 and the fellow eye was 2.10±1.3; the difference was not statistically significant (unpaired' t' test [df=6]; t=0.50; P= 0.63) (Table 10 Figure 7 Figs.7.1.1 and 7.1.2)

At one year the mean SE post procedure in study eye was 1.5±1 and fellow eye was 2.5±1.5. There was no statistically significant difference by unpaired t test (t= 1.07 [df=6]; P= 0.33) (Table 10 Figure 7; Figs.7.1.1 and 7.1.2)

3.3.4.2 GROUP B (10 patients, bilateral keratoconus; study eye keratoconic operated; fellow eye keratoconic, not operated)

One month post operative mean SE (dioptres) in study group was 3.45±2.9 and in fellow eye mean was 2.4±1.6. There was no statistically significant difference between these mean values (unpaired t test; t= 0.95 [df=18]; P= 0.36). (Table 11; Figure 7; Figs.7.2.1 and 7.2.2).

Six month follow up post operative mean SE in study eye was 2.7±2.3 and the fellow eye was 2.5±1.2. There was no statistically significant difference between these mean values (unpaired t test; t= 0.21 [df=18]; P = 0.84) (Table 11; Figure 7; Figs.7.2.1 and 7.2.2)

At one year Post procedure follow up, the mean SE was reduced to 2.1±1.7 in study eye and 2.82±1.3 in the fellow eye. No statistically

significant difference was noted (unpaired t test, t= 1.07 [df=18]; P =0.30 (Table 11; Figure 7; Figs.7.2.1 and 7.2.2)

3.3.4.3 GROUP C (7 patients, bilateral keratoconus; study eye = worse eye, operated first; fellow eye = better eye, operated after one week)

One month follow up mean SE (dioptres) in study eye was 3.8±2.1 and fellow eye was 3.4±1.6; there was no statistically significant difference (unpaired t test; t= 0.36 [df=12]; P = 0.73) (Table 12 Figure 7; Figs.7.3.1 and 7.3.2)

At 6 months, the mean SE in the post procedure study eye was 3.44±1.79 and fellow eye was 3.28±1.25; no statistically significant difference was noted (unpaired t test; t= 0.28 [df=12], P=0.79) (Table12, Figure 7; Figs.7.3.1 and 7.3.2)

By end of one year follow up, the mean SE reduced in the study group to 3.17±2.2 and in fellow eye it was 2.67±1.24. No statistically significant difference was noted (unpaired t test; t= 0.51 [df=12]; P= 0.62) (Table 12 Figure 7; Figs.7.3.1 and 7.3.2)

3.3.5 Postoperative mean K1 (Steep K)

3.3.5.1 GROUP A (4 patients, unilateral keratoconus; study eye operated; fellow eye not operated)

One month follow up mean K1 (dioptres) in post procedure study eye was 50.25±2.00 and in fellow eye was 46.09±1.7; **this difference was statistically significant** (**unpaired 't' test [df=6]; t= 3.70; P = 0.01)** (Table 13 Figure 8; Figs.8.1.1 and 8.1.2)

At 6 months follow up, the mean K1 of post operative study eye was 49.75±2.4 and that of the fellow eye was 46.02±1.9. T**his difference was statistically significant** (**unpaired 't' test; t=2.38 [df=6]; P= 0.05)** (Table 13 Figure 8; Figs.8.1.1 and 8.1.2)

By the end of one year follow up, the mean K1 in study eye was 49.24±2.1 and in fellow eye it was 45.66±2.11. T**his difference was statistically significant** (**unpaired t test; t= 2.38 [df=6]; P= 0.05) (**Table 13 Figure 8; Figs.8.1.1 and 8.1.2)

3.3.5.2 GROUP B (10 patients, bilateral keratoconus; study eye keratoconic, operated; fellow eye keratoconic, not operated)

By one month follow up post C3R procedure, the mean K1 (dioptres) of study eye was 51.97±4.2 and fellow eye was 47.31±1.9. T**his difference was highly statistically significant (unpaired t test; t = 3.18 [df18]; P = 0.005)** (Table 14; Figure 8; Figs.8.2.1 and 8.2.2)

The mean K1 by 6 months in the study eye was 50.46±4.5 and in the fellow eye it was 47.31±1.9; this difference **approached statistical significance** (unpaired t test; t= 1.98 [df=18]; **P= 0.06)** (Table 14 Figure 8; Figs.8.2.1 and 8.2.2)

The mean K1 by one year follow up was 49.97±4.4 in the study eye and 48.3±3.2 in fellow eye. No statistically significant difference was noted (unpaired t test; t= 0.93 [df=18]; P= 0.37 (Table 14 Figure 8; Figs.8.2.1 and 8.2.2)

3.3.5.3 GROUP C (7 patients, bilateral keratoconus; study eye = worse eye, operated first; fellow eye = better eye, operated after one week)

One month post procedure mean K1 (dioptres) in study eye was 51.36±4.7 in the fellow eye it was 50.28±4.3. No statistically significant difference was noted (unpaired t test; t=0.44 [df=12]; P= 0.67) (Table 15 Figure 8; Figs.8.3.1 and 8.3.2)

At 6 months the mean K1 reduced to 51.06±4.7 in the study eye and 49.87±4.6 in the fellow eye. No statistically significant difference was noted (unpaired t test; t=0.46 [df=12]; P =0.65) (Table 15 Figure 8; Figs.8.3.1 and 8.3.2)

One year follow up showed mean K1 in study eyes was 50.74±4.7 and fellow eye was 49.63±4.4. No statistically significant difference was noted

(unpaired t test ; t= 0.45 [df=12]; P= 0.66) (Table 15 Figure 8; Figs.8.3.1 and 8.3.2)

3.3.6 Postoperative mean K2 (Flat K)

3.3.6.1 GROUP A (4 patients, unilateral keratoconus; study eye operated; fellow eye not operated)

The mean K2 (dioptres) post operatively of the study eye was 45.38±3.3 and that of the fellow eye was 44.01±1.4.in one month follow up. No statistically significant difference was noted (unpaired t test; t= 0.76 [df=6]; P 0.48) (Table 16; Figure 9; Figs.9.1.1 and 9.1.2)

At 6 months follow up, the post operative mean K2 value in study eyes was 45.24±3.3 and in fellow eye it was 43.91±1.4. No statistically significant difference was noted (unpaired t test; t= 0.72 [df=6]; P= 0.50) (Table 16; Figure 9 Figs.9.1.1 and 9.1.2).

At one year post operative the mean K2 in study eye was 45.17±3.3 and in fellow eye the mean K2 was 43.91±1.44. No statistically significant difference was noted (unpaired t test; t= 0.70 [df=6]; P= 0.51) (Table 16; Figure 9; Figs.9.1.1 and 9.1.2)

3.3.6.2 GROUP B (10 patients, bilateral keratoconus; study eye keratoconic, operated; fellow eye keratoconic, not operated)

The mean K2 (dioptres) at one month follow up in study eye was 46.32±3.7 post operatively and the fellow eye was 43.81±1.7. **This difference approached statistical significance (unpaired t test; t= 1.92 [df= 18]; P= 0.07) (**Table 17; Figure 9; Figs.9.2.1 and 9.2.2)

The mean K2 at 6 months follow up was 45.91±3.8 in study eye and 44.09±1.6 in the fellow eye. No statistically significant difference was noted (unpaired t test; t= 1.38 [df=18]; P= 1.8) (Table 17; Figure 9; Figs.9.2.1 and 9.2.2)

One year follow up showed a reduction in the mean K2 in study eyes 45.75±3.8 and in fellow eye it was 44.54±1.6. No statistically significant difference was noted (unpaired' t' test; t= 0.9 [df=18]; P= 0.38) (Table 17; Figure 9; Figs.9.2.1 and 9.2.2)

3.3.6.3 GROUP C (7 patients, bilateral keratoconus; study eye = worse eye, operated first; fellow eye = better eye, operated after one week)

At one month post procedure, the mean K2 (dioptres) in study eye was 45.37±1.6 and in fellow eye it was 44.71±2.7. No statistically significant difference was noted (unpaired t test; t= 0.42 [df=12]; P= 0.68) (Table 18; Figure 9; Figs.9.3.1 and 9.3.2)

In 6 months post operative, the mean K2 in study eye and fellow eye was 45.26±2.0 and 44.36±2.6, respectively. There was no statistically significant difference (unpaired t test; t= 0.72 [df=12]; P= 0.49) (Table 18; Figure 9; Figs.9.3.1 and 9.3.2)

In one year follow up, the mean study eye and fellow eye mean K2 was 44.98±2.06 and 44.39±3.4, respectively. No statistically significant difference was noted (unpaired' t' test; t= 0.44 [df=12]; P= 0.67) (Table 18; Figure 9 Figs.9.3.1 and 9.3.2)

3.3.7 Postoperative mean Average K (Avrg k)

3.3.7.1 GROUP A (4 patients, unilateral keratoconus; study eye operated; fellow eye not operated)

At one month post operative, the mean Kavrg was 47.81±2.6 in the study eye and 45.05±1.5 in the fellow eye. **This difference approached statistical significance (unpaired t test; t= 1.98 [df=6]; P= 0.09) (**Table 19; Figure 10; Figs.10.1.1 and 10.1.2)

In 6 month follow up, the mean average Kavrg was 47.49±2.9 in study eye and 44.79±1.77 in fellow eye. No statistically significant difference was observed (unpaired t test; t= 1.58 [df=6]; P= 0.16) (Table 19; Figure 10; Figs.10.1.1 and 10.1.2)

At one year follow up, the mean average K was stable with 47.20±2.7 in study eye and 44.78±1.77 in fellow eye. No statistically significant difference was apparent (unpaired t test; t = 1.49 [df=6]; P = 0.19 (Table 19; Figure 10; Figs.10.1.1 and 10.1.2)

3.3.7.2 GROUP B (10 patients, bilateral keratoconus; study eye keratoconic, operated; fellow eye keratoconic, not operated)

At one month post- operative, the mean average K in the study eye was 49.11±3.6 and in the fellow eye it was 45.55±1.5; **this difference was statistically significant (unpaired t test; t= 2.85 [df=18]; P= 0.01)** (Table 20; Figure 10; Figs.10.2.1 and 10.2.2)

At 6 month follow up, the mean average K was 48.53±3.7 in the study eye and 45.64±1.4 in the fellow eye; **this difference was also statistically significant (unpaired t test; t= 2.26 [df=18]; P = 0.04) (**Table 20; Figure 10; Figs.10.2.1 and 10.2.2)

One year follow up of operated eye showed mean average K value of 47.86±4.0 and fellow eye had 46.22±2.1; this difference was not statistically significant (unpaired t test; t = 1.13 [df=18]; P= 0.27) (Table 20; Figure 10; Figs.10.2.1 and 10.2.2)

3.3.7.3 GROUP C (7 patients, bilateral keratoconus; study eye = worse eye, operated first; fellow eye = better eye, operated after one week)

By one month follow up, the mean average K was stable 48.36±2.7 in the study eyes and 47.49±3.3 in the fellow eyes. No statistically significant difference was noted (unpaired t test; t = 0.53 [df=12]; P= 0.61) (Table 21; Figure 10; Figs.10.3.1 and 10.3.2)

In 6 month follow up, the mean average K was stable in both eyes with 48.16±2.8 in study eye and 47.11±3.4 in fellow eye; no statistically difference between these mean values was noted (unpaired t test; t= 0.62 [df=12]; P = 0.54) (Table 21, Figure 10; Figs.10.3.1 and 10.3.2)

In one year the mean average K value reduced in both study eye and fellow eye, with mean value of 47.86±2.7 in study eye and 46.97±3.4 in the fellow eye. This difference was not statistically significant (unpaired t test; t = 0.56 [df=12]; P = 0.59 (Table 21 and 22, Figure 10; Figs.10.3.1 and 10.3.2)

3.4 An attempt was made to compare the improvement in vision in operated eyes versus improvement in vision in unoperated eyes (Table 23). Twenty-eight eyes underwent C3R; vision improved in 20 (71.4%), was unchanged in six (21.4%) and worsened in two (7.2%); corresponding figures in the 14 unoperated eyes were four (28.6%), six (42.8%) and four (28.6%). T**hese differences approached statistical significance**

(Proportion of operated eyes with improved vision vs. Proportion of unoperated eyes with improved vision.**χ2 [df=2]=4.83; P=0.09).**

3.5 An attempt was made to compare improvement in vision in study eyes versus improvement in vision in fellow eyes in each of the groups.

3.5.1. In Group A, vision improved in all four study (keratoconic, operated) eyes, but remained unchanged in two and worsened in two fellow (non-keratoconic, unoperated eyes) (Table 24); this difference however, was not statistically significant (Yates' χ2 [df2]=3.25; P=0.20)

3.5.2 In Group B, in study eyes (n=10; keratoconic, operated), vision improved in nine (90%) and was unchanged in one (10%) and in fellow eyes (n=10, keratoconic, non-operated), vision improved in four (40%), was unchanged in four (40%) and worsened in two (20%). (Table 25); these differences however, were not statistically significant (Yates' χ2 [(df=2]= 2.53; P=0.28).

3.5.3 In Group C, in study eyes (n=7; keratoconic, worse eye operated), vision improved in four (57.1%), was unchanged in one (14.3 %) and worsened in two (28.6%), while in fellow eyes (n= 7, keratoconic, operated one week after study eye), vision improved in three (42.9%), was unchanged in four (57.1%) and did not worsen in any eye (Table 26); these differences

however, were not statistically significant (Yates' $\chi 2$ (degree of freedom=2)=1.3; P=0.52)

4. COMPLICATION

No intra-operative or post-operative complications were encountered in any of the operated eyes throughout the follow up period (one year)

Table 1.

Comparison of mean uncorrected visual acuity (UCVA) in eyes with unilateral keratoconus (Group A) undergoing corneal collagen cross-linking with riboflavin in the keratoconic eye at a tertiary eye care hospital

Examination time	Uncorrected visual acuity		Statistical Analysis by unpaired 't' test *p-value
	Study eye Mean ±SD (decimals)	Fellow Eye Mean ± SD (decimals)	
Baseline	0.212±0.075	0.19±0.11	-
1month	0.27±0.04	0.28±0.26	
6month	0.27±0.04	0.28±0.26	
1year	0.33±0.01	0.28±0.26	

Group A= (4 patients, unilateral keratoconus; study eye operated; fellow eye not operated)

Table 2.

Comparison of mean uncorrected visual acuity (UCVA) in eyes with bilateral keratoconus (Group B) undergoing corneal collagen cross-linking with riboflavin in one keratoconic eye at a tertiary eye care hospital

Examination time	Uncorrected visual acuity		Statistical Analysis by unpaired 't' test *p-value
	Study eye Mean ±SD (decimals)	Fellow Eye Mean ± SD (decimals)	
Baseline	0.23±1.8	0.27±0.20	0.66
1month	0.27±0.18	0.29±0.19	0.75
6month	0.34±0.26	0.295 ±0.19	0.65
1year	0.42±0.25	0.27±0.21	0.19

Group B= (10 patients, bilateral keratoconus; study eye operated; fellow eye not operated)

Table 3.

Comparison of mean uncorrected visual acuity (UCVA) in eyes with bilateral keratoconus (Group C) undergoing corneal collagen cross-linking with riboflavin first in the worse eye and then in the other eye at a tertiary eye care hospital

Examination time	Uncorrected visual		Statistical Analysis by unpaired 't' test *p-value
	Study eye Mean ±SD (decimals)	Fellow Eye Mean ± SD (decimals)	
Baseline	0.17±0.06	0.18±0.09	0.68
1month	0.19±0.08	0.23±0.14	0.99
6month	0.26±0.12	0.35±0.19	0.29
1year	0.39±0.19	0.52±0.29	0.31

Group C= (7 patients, bilateral keratoconus; study eye = worse eye, operated first; fellow eye = better eye, operated after one week)

Table 4.

Comparison of mean best corrected visual acuity (BCVA) in eyes with unilateral keratoconus (Group A) undergoing corneal collagen cross-linking with riboflavin in the keratoconic eye at a tertiary eye care hospital

Examination time	Best corrected visual acuity		Statistical Analysis by unpaired 't' test *p-value
	Study eye Mean ±SD (decimals)	Fellow Eye Mean ± SD (decimals)	
Baseline	0.71±0.20	0.83±0.19	0.32
1month	0.60±0.31	0.831±0.19	0.6
6month	0.71±0.20	0.79±0.24	0.64
1year	0.83±0.19	0.66±0.23	0.32

Group A= (4 patients, unilateral keratoconus; study eye operated; fellow eye not operated)

Table 5.

Comparison of mean best corrected visual acuity (BCVA) in eyes with bilateral keratoconus (Group B) undergoing corneal collagen cross-linking with riboflavin in one keratoconic eye at a tertiary eye care hospital

Examination time	Best corrected visual acuity		Statistical Analysis by unpaired 't' test *p-value
	Study eye Mean ±SD (decimals)	Fellow Eye Mean ± SD (decimals)	
Baseline	0.45±0.25	0.54±0.26	0.50
1month	0.52±0.21	0.56±0.24	0.74
6month	0.66±0.22	0.52±0.24	0.22
1year	0.75±0.17	0.49±0.39	0.08

Group B= (10 patients, bilateral keratoconus; study eye operated; fellow eye not operated)

Table 6.

Comparison of mean best corrected visual acuity (BCVA) in eyes with bilateral keratoconus (Group C) undergoing corneal collagen cross-linking with riboflavin first in the worse eye and then in the other eye at a tertiary eye care hospital

Examination time	Best corrected visual acuity		Statistical Analysis by unpaired 't' test *p-value
	Study eye Mean ±SD (decimals)	Fellow Eye Mean ± SD (decimals)	
Baseline	0.52±0.26	0.54±0.16	0.8
1month	0.56±0.22	0.64±0.17	0.48
6month	0.60±0.24	0.69±0.22	0.54
1year	0.64±0.28	0.81±0.24	0.25

Group C= (7 patients, bilateral keratoconus; study eye = worse eye, operated first; fellow eye = better eye, operated after one week)

Table 7.

Comparison of mean cylinder value (Dcyl) in eyes with unilateral keratoconus (Group A) undergoing corneal collagen cross-linking with riboflavin in the keratoconic eye at a tertiary eye care hospital

Examination time	Cylinder value		Statistical Analysis by unpaired 't' test *p-value
	Study eye Mean ±SD (diopters)	Fellow Eye Mean ± SD (diopters)	
Baseline	1.75±1.7	1.8±1.3	0.91
1month	2.12±1.15	2±1.4	0.93
6month	1.75±1.2	1.75±1.2	1.0
1year	1.5±1	2.00±0.21	0.47

Group A= (4 patients, unilateral keratoconus; study eye operated; fellow eye not operated)

Table 8.

Comparison of mean cylinder value (Dcyl) in eyes with bilateral keratoconus (Group B) undergoing corneal collagen cross-linking with riboflavin in one keratoconic eye at a tertiary eye care hospital

Examination time	Cylinder value		Statistical Analysis by unpaired 't' test *p-value
	Study eye Mean ±SD (diopters)	Fellow Eye Mean ± SD (diopters)	
Baseline	3.45±2.8	2.7±2.08	0.46
1month	3.3±2.00	2.7±1.9	0.57
6month	2.9±2.2	2.85±2.00	0.83
1year	2.65±1.8	2.85±2.00	0.82

Group B= (10 patients, bilateral keratoconus; study eye operated; fellow eye not operated)

Table 9.

Comparison of mean cylinder value (Dcyl) in eyes with bilateral keratoconus (Group C) undergoing corneal collagen cross-linking with riboflavin first in the worse eye and then in the other eye at a tertiary eye care hospital

Examination time	Cylinder value		Statistical Analysis by unpaired 't' test *p-value
	Study eye Mean ±SD (diopters)	Fellow Eye Mean ± SD (diopters)	
Baseline	2.85±1.3	2.71±1.6	0.85
1month	2.71±1.7	2.5±1.6	0.82
6month	2.25±1.16	2.28±1.3	0.87
1year	2.07±1.9	1.8±1.21	0.81

Group C= (7 patients, bilateral keratoconus; study eye = worse eye, operated first; fellow eye = better eye, operated after one week)

Table 10.

Comparison of mean spherical equivalent (SE) in eyes with unilateral keratoconus (Group A) undergoing corneal collagen cross-linking with riboflavin in the keratoconic eye at a tertiary eye care hospital

Examination time	Spherical equivalent		Statistical Analysis by unpaired 't' test *p-value
	Study eye Mean ±SD (diopters)	Fellow Eye Mean ± SD (diopters)	
Baseline	3.3±0.75	2.02±0.93	0.07
1month	3.31±0.55	2.25±1.19	0.16
6month	1.8±1.4	2.10±1.3	0.63
1year	1.5±1	2.5±1.5	0.33

Group A= (4 patients, unilateral keratoconus; study eye operated; fellow eye not operated)

Table 11.

Comparison of mean spherical equivalent (SE) in eyes with bilateral keratoconus (Group B) undergoing corneal collagen cross-linking with riboflavin in one keratoconic eye at a tertiary eye care hospital

Examination time	Spherical equivalent		Statistical Analysis by unpaired 't' test *p-value
	Study eye Mean ±SD (diopters)	Fellow Eye Mean ± SD (diopters)	
Baseline	2.02±0.93	2.21±1.9	0.27
1month	2.25±1.19	2.4±1.6	0.36
6month	2.10±1.3	2.5±1.2	0.84
1year	2.5±1.5	2.82±1.3	0.30

Group B= (10 patients, bilateral keratoconus; study eye operated; fellow eye not operated)

Table 12.

Comparison of mean spherical equivalent (SE) in eyes with bilateral keratoconus (Group C) undergoing corneal collagen cross-linking with riboflavin first in the worse eye and then in the other eye at a tertiary eye care hospital

Examination time	Spherical equivalent		Statistical Analysis by unpaired 't' test *p-value
	Study eye Mean ±SD (diopters)	Fellow Eye Mean ± SD (diopters)	
Baseline	4.21±2.17	3.97±1.6	0.83
1month	3.8±2.1	3.4±1.6	0.73
6month	3.44±1.79	3.28±1.25	0.79
1year	3.17±2.2	2.67±1.24	0.62

Group C= (7 patients, bilateral keratoconus; study eye = worse eye, operated first; fellow eye = better eye, operated after one week)

Table 13.

Comparison of mean Kmax value in eyes with unilateral keratoconus (Group A) undergoing corneal collagen cross-linking with riboflavin in the keratoconic eye at a tertiary eye care hospital

Examination time	K-max		Statistical Analysis by unpaired 't' test *p-value
	Study eye Mean ±SD (diopters)	Fellow Eye Mean ± SD (diopters)	
Baseline	50.76±2.2	45.83±2	0.02
1month	50.25±2.00	46.09±1.7	0.01
6month	49.75±2.4	46.02±1.9	0.0549
1year	49.24±2.1	45.66±2.11	0.0549

Group A= (4 patients, unilateral keratoconus; study eye operated; fellow eye not operated)

Table 14.

Comparison of mean Kmax value in eyes with bilateral keratoconus (Group B) undergoing corneal collagen cross-linking with riboflavin in one keratoconic eye at a tertiary eye care hospital

Examination time	K-max		Statistical Analysis by unpaired 't' test *p-value
	Study eye Mean ±SD (diopters)	Fellow Eye Mean ± SD (diopters)	
Baseline	52.34±4.4	47.26±1.8	0.59
1month	51.97±4.2	47.31±1.9	0.004
6month	50.46±4.5	47.31±1.9	0.005
1year	49.97±4.4	48.3±3.2	0.06

Group B= (10 patients, bilateral keratoconus; study eye operated; fellow eye not operated)

Table 15.

Comparison of mean Kmax values in eyes with bilateral keratoconus (Group C) undergoing corneal collagen cross-linking with riboflavin in theworse eye first and then in the other eye at a tertiary eye care hospital

Examination time	K-max		Statistical Analysis by unpaired 't' test *p-value
	Study eye Mean ±SD (diopters)	Fellow Eye Mean ± SD (diopters)	
Baseline	51.64±4.5	50.43±4.3	0.62
1month	51.36±4.7	50.28±4.3	0.67
6month	51.06±4.7	49.87±4.6	0.65
1year	50.74±4.7	49.63±4.4	0.66

Group C= (7 patients, bilateral keratoconus; study eye = worse eye, operated first; fellow eye = better eye, operated after one week)

Table 16.

Comparison of mean Kmin value in eyes with unilateral keratoconus (Group A) undergoing corneal collagen cross-linking with riboflavin in the keratoconic eye at a tertiary eye care hospital

Examination time	K- min		Statistical Analysis by unpaired 't' test *p-value
	Study eye Mean ±SD (diopters)	Fellow Eye Mean ± SD (diopters)	
Baseline	45.77±3.02	43.4±1.7	0.24
1month	45.38±3.3	44.01±1.4	0.48
6month	45.24±3.3	43.91±1.4	0.50
1year	45.17±3.3	43.91±1.44	0.51

Group A= (4 patients, unilateral keratoconus; study eye operated; fellow eye not operated)

Table 17.

Comparison of mean Kmin value in eyes with bilateral keratoconus (Group B) undergoing corneal collagen cross-linking with riboflavin in one keratoconic eye at a tertiary eye care hospital

Examination time	K- min		Statistical Analysis by unpaired 't' test *p-value
	Study eye Mean ±SD (diopters)	Fellow Eye Mean ± SD (diopters)	
Baseline	46.39±3.3	43.39±1.4	0.02
1month	46.32±3.7	43.81±1.7	0.07
6month	45.91±3.8	44.09±1.6	0.18
1year	45.75±3.8	44.54±1.6	0.38

Group B= (10 patients, bilateral keratoconus; study eye operated; fellow eye not operated)

Table 18.

Comparison of mean Kmin value in eyes with bilateral keratoconus (Group C) undergoing corneal collagen cross-linking with riboflavin first in the worse eye and then in the other eye at a tertiary eye care hospital

Examination time	K- min		Statistical Analysis by unpaired 't' test *p-value
	Study eye Mean ±SD (diopters)	Fellow Eye Mean ± SD (diopters)	
Baseline	45.64±1.9	45.13±2.4	0.68
1month	45.37±1.6	44.71±2.7	0.60
6month	45.26±2.0	44.36±2.6	0.49
1year	44.98±2.06	44.39±3.4	0.67

Group C= (7 patients, bilateral keratoconus; study eye = worse eye, operated first; fellow eye = better eye, operated after one week)

Table 19.

Comparison of mean K-avg value in eyes with unilateral keratoconus (Group A) undergoing corneal collagen cross-linking with riboflavin in the keratoconic eye at a tertiary eye care hospital

Examination time	K- avg		Statistical Analysis by unpaired 't' test *p-value
	Study eye Mean ±SD (diopters)	Fellow Eye Mean ± SD (diopters)	
Baseline	48.26±2.5	44.64±1.7	0.059
1month	47.81±2.6	45.05±1.5	0.09
6month	47.49±2.9	44.79±1.77	0.16
1year	47.20±2.7	44.78±1.77	0.19

Group A= (4 patients, unilateral keratoconus; study eye operated; fellow eye not operated)

Table 20. Comparison of mean K-avg value in eyes with bilateral keratoconus (Group B) undergoing corneal collagen cross-linking with riboflavin in one keratoconic eye at a tertiary eye care hospital

Examination time	K- avg		Statistical Analysis by unpaired 't' test *p-value
	Study eye Mean ±SD (diopters)	Fellow Eye Mean ± SD (diopters)	
Baseline	49.37±3.6	45.42±1.4	0.005
1month	49.11±3.6	45.55±1.5	0.01
6month	48.53±3.7	45.64±1.4	0.04
1year	47.86±4.0	46.22±2.1	0.27

Group B= (10 patients, bilateral keratoconus; study eye operated; fellow eye not operated)

Table 21.

Comparison of mean K-avg values in eyes with bilateral keratoconus (Group C) undergoing corneal collagen cross-linking with riboflavin first in the worse eye and then in the other eye at a tertiary eye care hospital

Examination time	K- avg		Statistical Analysis by unpaired 't' test *p-value
	Study eye Mean ±SD (diopters)	Fellow Eye Mean ± SD (diopters)	
Baseline	44.39±3.4	47.78±3.1	0.625
1month	48.36±2.7	47.49±3.3	0.61
6month	48.16±2.8	47.11±3.4	0.54
1year	47.86±2.7	46.97±3.4	0.59

Group C= (7 patients, bilateral keratoconus; study eye = worse eye, operated first; fellow eye = better eye, operated after one week)

TABLE 22

Statistical Analysis of significance of differences between mean values of different parameters across the duration of the study in the affected eyes and in the fellow eyes in the 3 groups

Statistical Analysis by one-way analysis of variance (ANOVA) with post-hoc test wherever relevant

Parameter	Eyes examined	Group A eyes (n=4)		Group B eyes (n=10)		Group C eyes (n=7)	
		Fischer 'F'	P	Fischer 'F'	P	Fischer 'F'	P
UCVA	Affected	1.59	0.24	1.49	0.23	**4.16**	**0.02**
BCVA	Affected	0.64	0.60	**3.59**	**0.03**	0.30	0.82
DCyl	Affected	0.095	0.96	0.33	0.80	0.38	0.77
SE	Affected	**3.81**	**0.04**	0.65	0.59	0.32	0.81
K1	Affected	0.43	0.73	0.50	0.69		
K2	Affected	0.42	0.75	0.84	0.48		
KAvg	Affected	0.43	0.73	0.45	0.72		
UCVA	Fellow	0.13	0.94	0.05	0.99	**4.33**	**0.01**
BCVA	Fellow	0.45	0.72	0.098	0.96	2.01	0.14
DCyl	Fellow	0.03	0.99	0.0091	0.9988	0.54	0.66
SE	Fellow	0.1	0.96	0.31	0.82	0.97	0.43
K1	Fellow	0.43	0.73	0.50	0.69		
K2	Fellow	0.42	0.75	0.84	0.48		
KAvg	Fellow	0.43	0.73	0.45	0.72		

Explanation of groups

Group A= 4 patients, unilateral keratoconus; study eye operated; fellow eye not operated

Group B= 10 patients, bilateral keratoconus; study eye operated; fellow eye not operated

Group C= 7 patients, bilateral keratoconus; study eye = worse eye, operated first; fellow eye = better eye, operated after one week

Post-hoc tests

SE, affected eye, Group A :Post-hoc test Spherical equivalent value in the study eye (Group A) revealed that the significant differences were in the pre-op vs. 1 year mean value and 1 month vs.1 year mean value

BCVA, affected eye, Group B: Post-hoc test of BCVA in study eye (Group B) revealed that the significant difference was in the pre-op vs.I year mean value

UCVA, affected eye, Group C: Post-hoc test of UCVA in study eye (Group C) revealed that the significant differences were in the pre-op vs.I year mean value and 1 month vs.1 year mean value

UCVA, fellow eye, Group C : Post-hoc test in fellow eye (Group C) revealed that the significant differences were in the pre-op vs.I year mean value and 1 month vs.1 year mean value

Table 23

Improvement in vision in operated eyes versus improvement in vision in unoperated eyes

Vision	Operated	Unoperated	Total	Proportion of operated eyes vs. Proportion of unoperated eyes with improved vision.$\chi 2$ (degree of freedom=2)=4.83; P=0.09
Improved	20	4	24	
No change	6	6	12	
Worsened	2	4	6	
Total	28	14	42	

Table 24.

Improvement in vision in study eyes versus improvement in vision in fellow eyes in Group A

Group A	Vision outcome			Statistical Analysis (chi-square test)
	Improved	No change	Worsened	Yates' $\chi 2$ (degree of freedom=2)=3.25; P=0.20
Study (n=4)	4	0	0	
Fellow (n=4)	0	2	2	

Group A= 4 patients, unilateral keratoconus; study eye operated; fellow eye not operated

Table 25.

Improvement in vision in study eyes versus improvement in vision in fellow eyes in Group B

Group B	Vision improved	No change in vision	Vision worsened	Statistical Analysis (chi-square test)
Study (n=10)	9	1	0	Yates' $\chi 2$ (degree of freedom=2)=2.53; P=0.28
Fellow (n=10)	4	4	2	

Group B= 10 patients, bilateral keratoconus; study eye operated; fellow eye not operated

Table 26.

Improvement in vision in study eyes versus improvement in vision in fellow eyes in Group C

Group C	Vision improved	No change in vision	Vision worsened	Statistical Analysis (chi-square test)
Study (n=7)	4	1	2	Yates' $\chi 2$ (degree of freedom=2)=1.3; P=0.52
Fellow (n=7)	3	4	0	

Group C=7 patients, bilateral keratoconus; study eye = worse eye, operated first; fellow eye = better eye, operated after one week

Figures:

Figure 1: Gender distribution of patients with keratoconus undergoing corneal collagen cross-linking at a tertiary eye care hospital

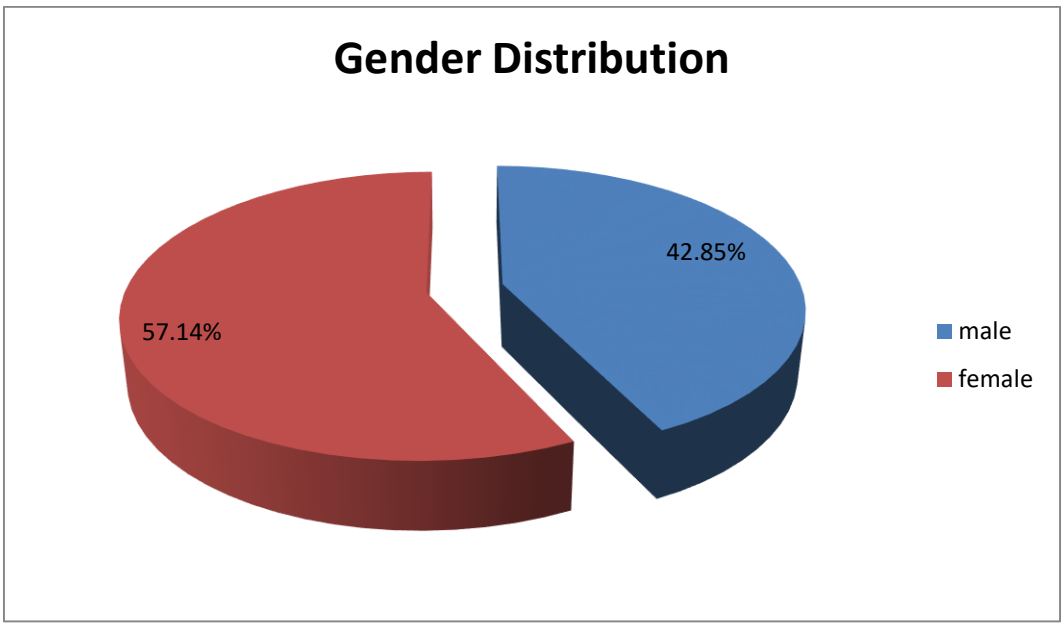


Figure 2: Age distribution of patients with keratoconus undergoing corneal collagen cross-linking at a tertiary eye care hospital

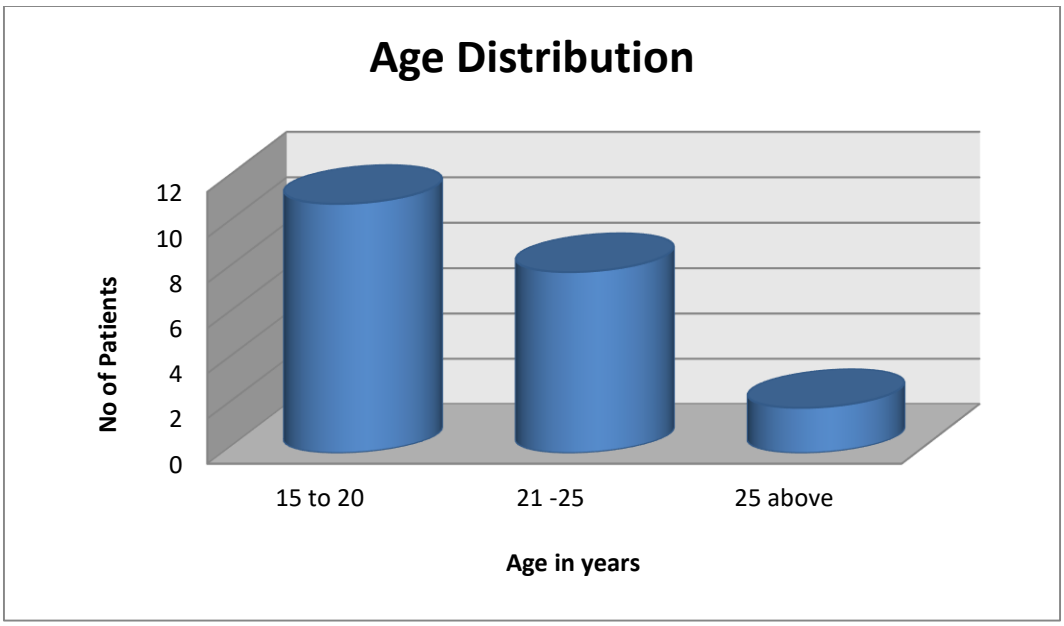


Figure 3: Laterality of the eye with keratoconus undergoing corneal collagen cross-linking at a tertiary eye care hospital:

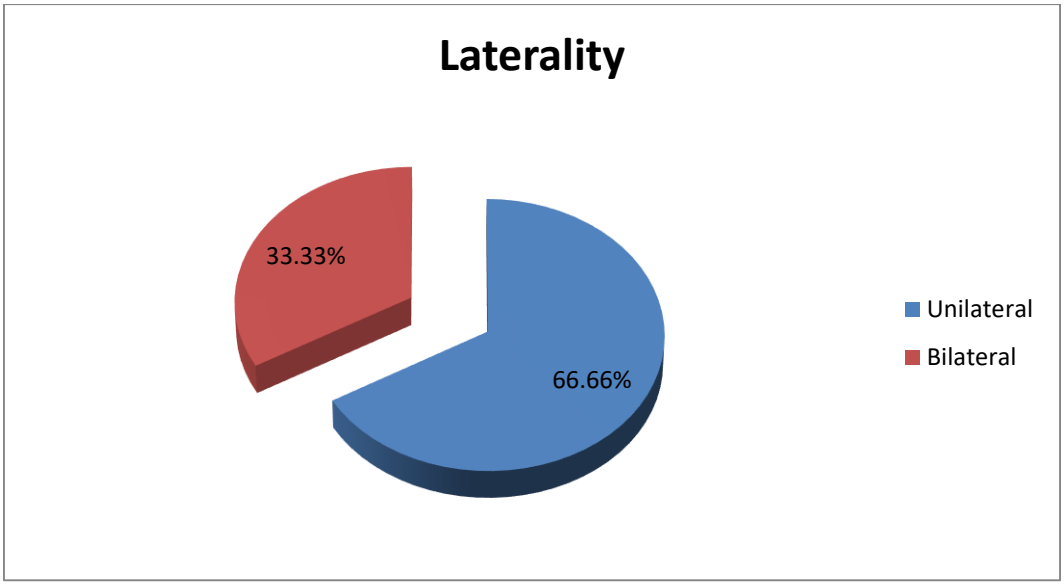
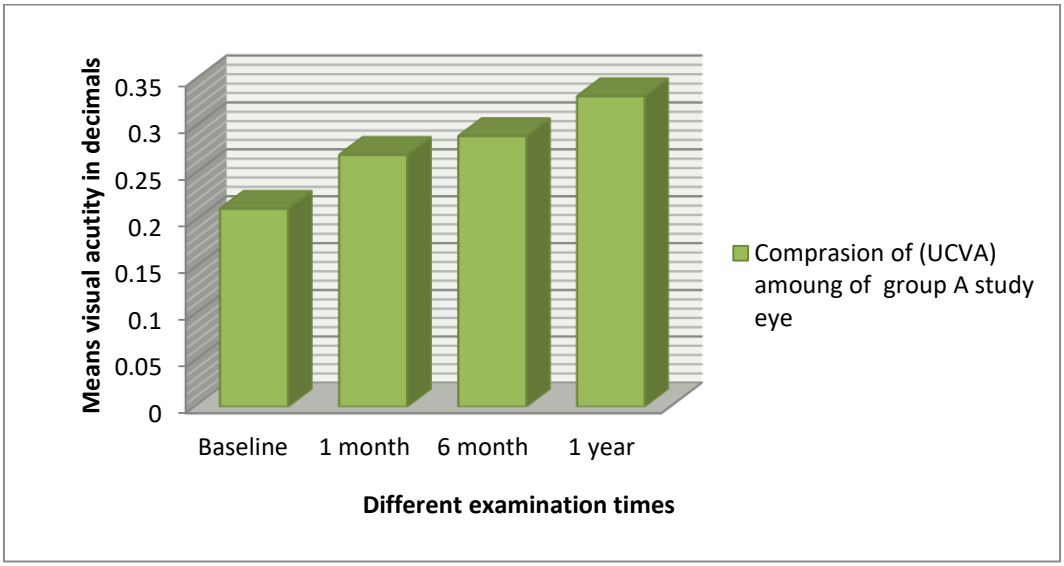


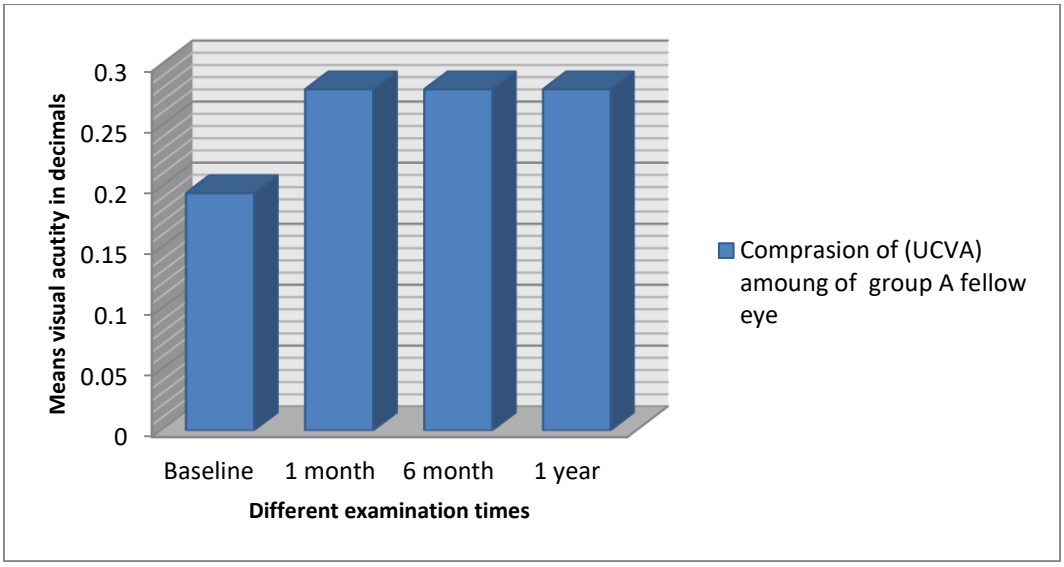
Figure 4 : Comparison of mean uncorrected visual acuity (UCVA) at different examination times in patients with keratoconus undergoing corneal collagen cross-linking at a tertiary eye care hospital:

FIGURE 4.1.1. Variations in mean uncorrected visual acuity (UCVA) at different examination times in four study (keratoconic operated) eyes in Group A



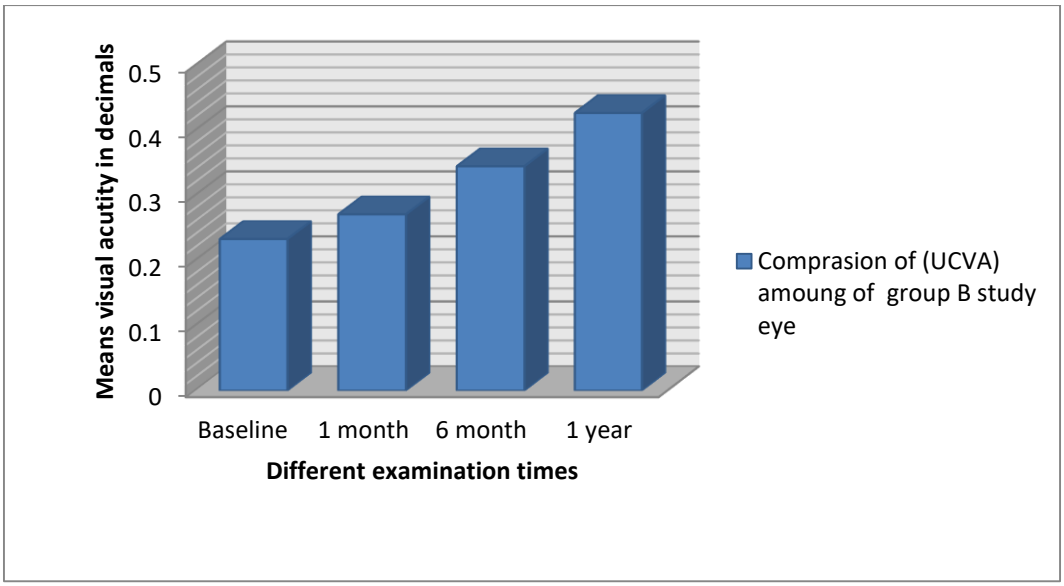
Group A (4 patients, unilateral keratoconus; study eye operated; fellow eye not operated)

FIGURE 4.1.2. Variations in mean uncorrected visual acuity (UCVA) at different examination times in four fellow (non-keratoconic, non-operated) eyes in Group A



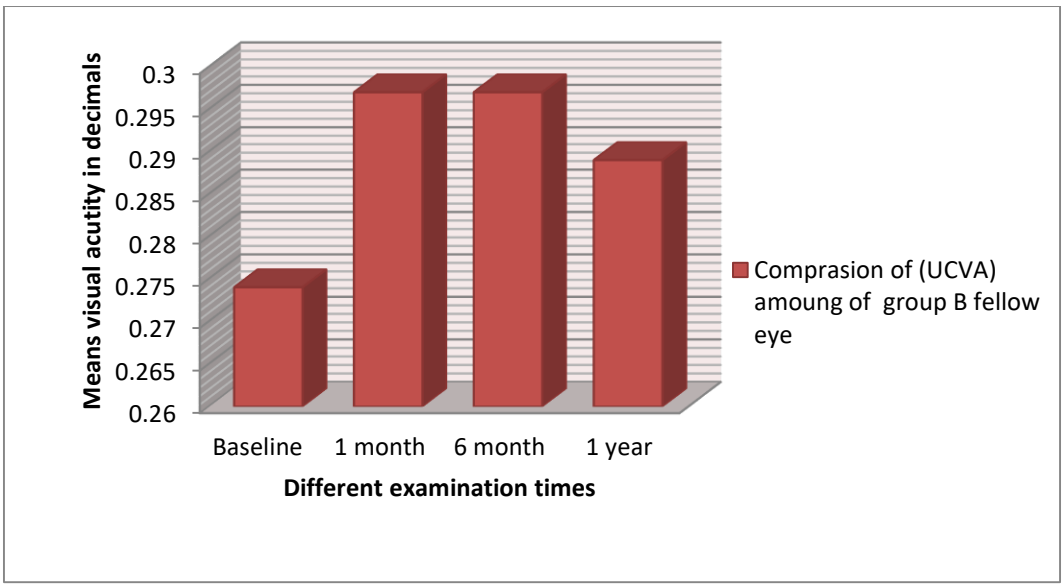
(4 patients, unilateral keratoconus; study eye operated; fellow eye not operated)

FIGURE 4.2.1. Variations in mean uncorrected visual acuity (UCVA) at different examination times in 10 study (keratoconic, operated) eyes in Group B



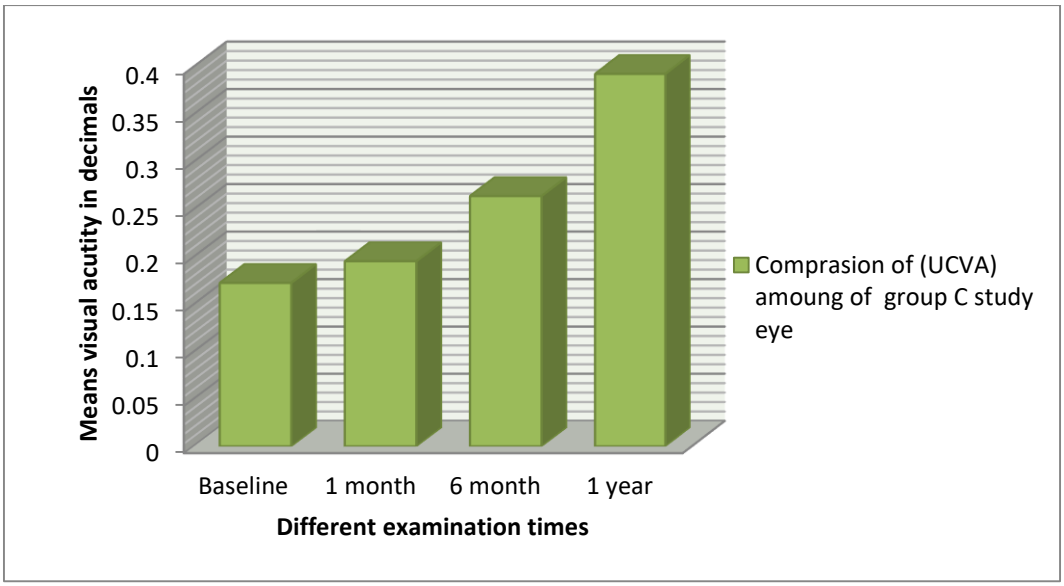
(10 patients, bilateral keratoconus; study eye operated; fellow eye not operated)

FIGURE 4.2.2. Variations in mean uncorrected visual acuity (UCVA) at different examination times in 10 fellow (keratoconic, non-operated) eyes in Group B



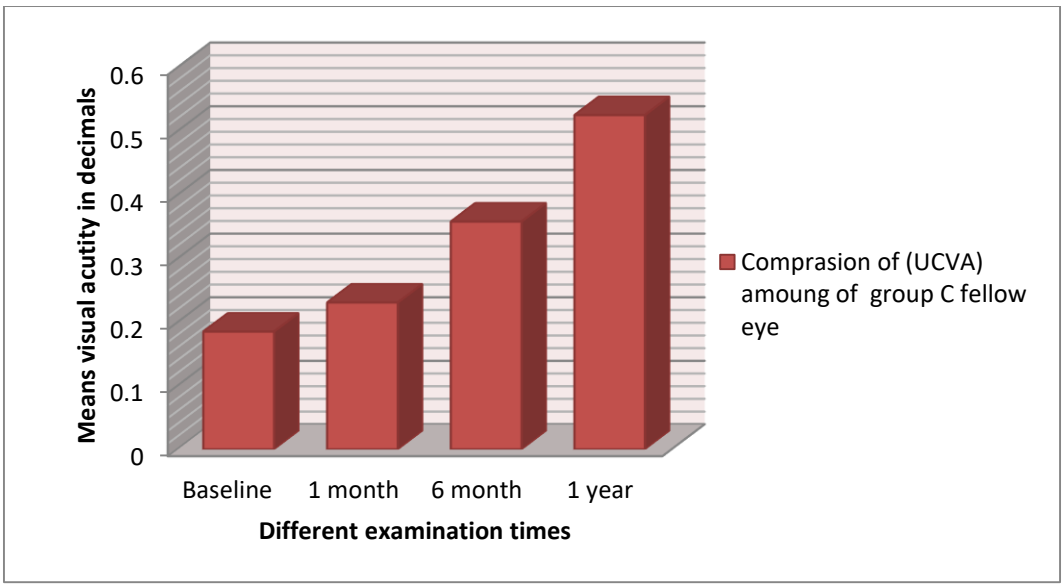
(10 patients, bilateral keratoconus; study eye operated; fellow eye not operated)

FIGURE 4.3.1. Variations in mean uncorrected visual acuity (UCVA) at different examination times in 7 study (keratoconic, worse eye, first operated) eyes in Group C



(7 patients, bilateral keratoconus; study eye = worse eye, operated first; fellow eye = better eye, operated after one week)

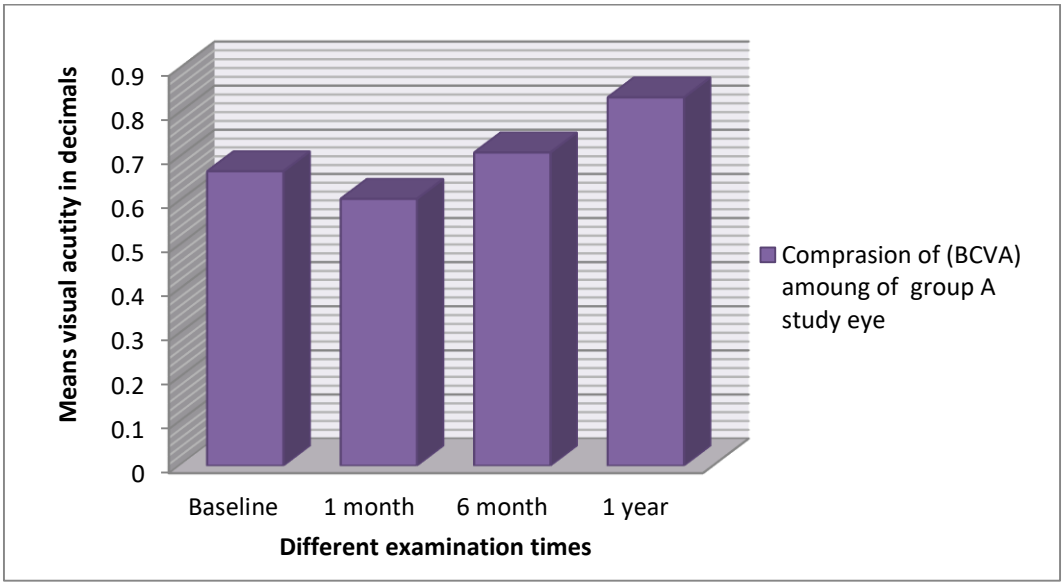
FIGURE 4.3.2. Variations in mean uncorrected visual acuity (UCVA) at different examination times in 7 fellow (keratoconic, better eye, operated second) eyes in Group C



(7 patients, bilateral keratoconus; study eye = worse eye, operated first; fellow eye = better eye, operated after one week)

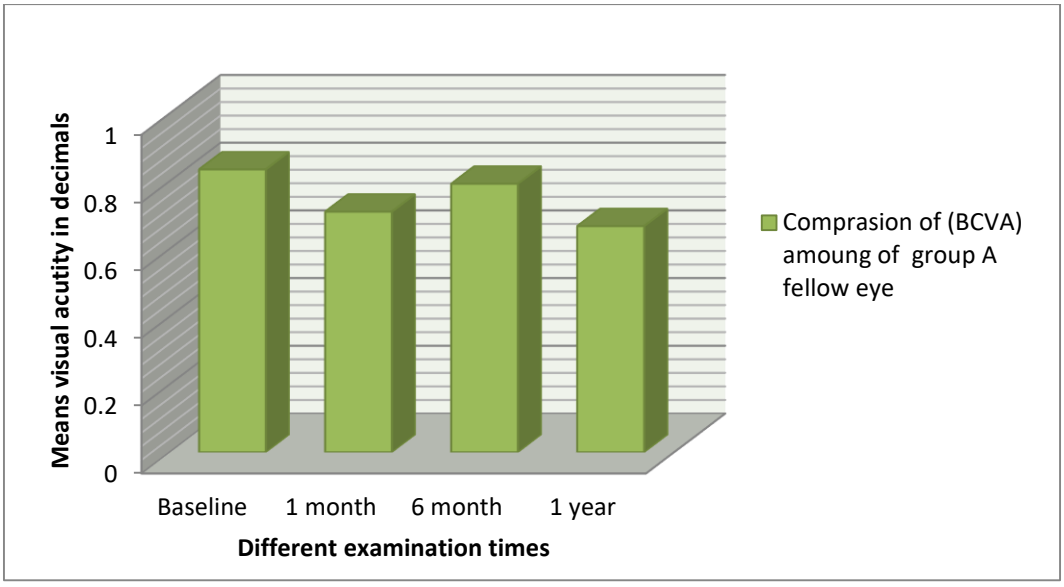
Figure 5 : Comparison of mean best corrected visual acuity (BCVA) at different examination times in patients with keratoconus undergoing corneal collagen cross-linking at a tertiary eye care hospital

FIGURE 5.1.1. Variations in mean best corrected visual acuity (BCVA) at different examination times in 4 study (keratoconic, operated) eyes in Group A



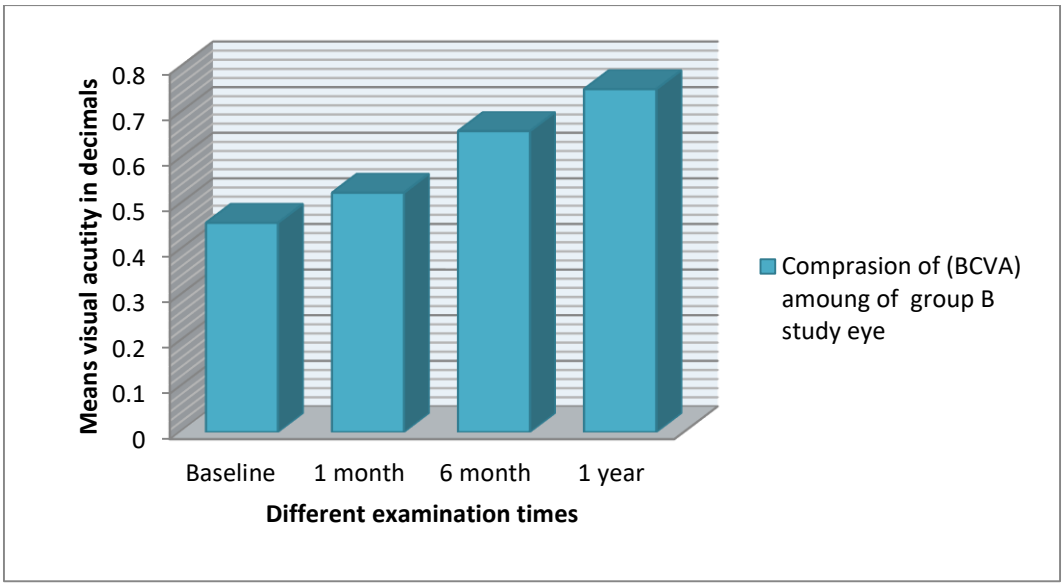
(4 patients, unilateral keratoconus; study eye operated; fellow eye not operated)

FIGURE 5.1.2. Variations in mean best corrected visual acuity (BCVA) at different examination times in four fellow (non-keratoconic, non- operated) eyes in Group A



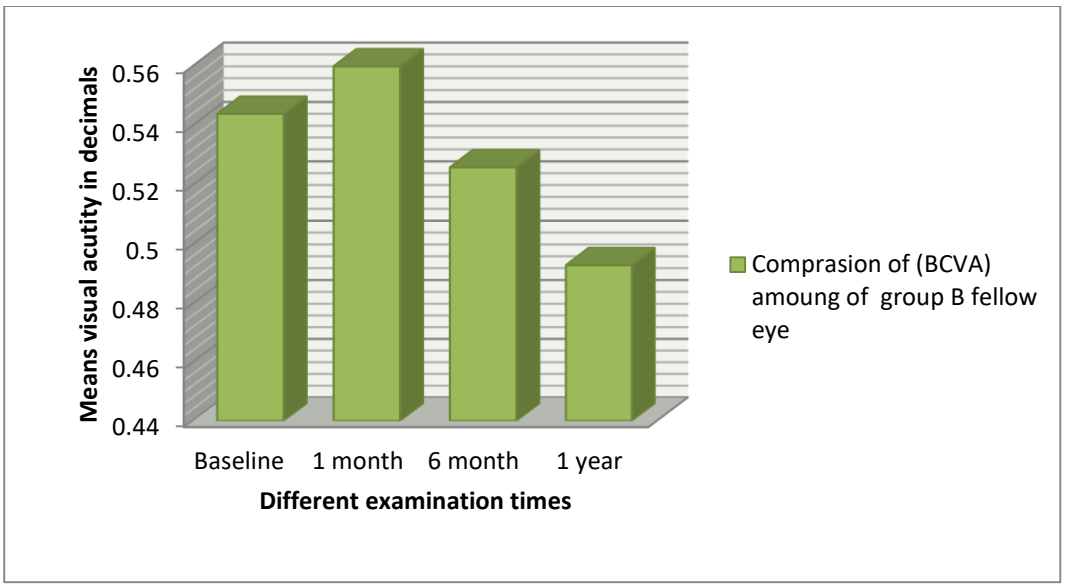
(4 patients, unilateral keratoconus; study eye operated; fellow eye not operated)

FIGURE 5.2.1. Variations in mean best corrected visual acuity (BCVA) at different examination times in 10 study (keratoconic, operated) eyes in Group B



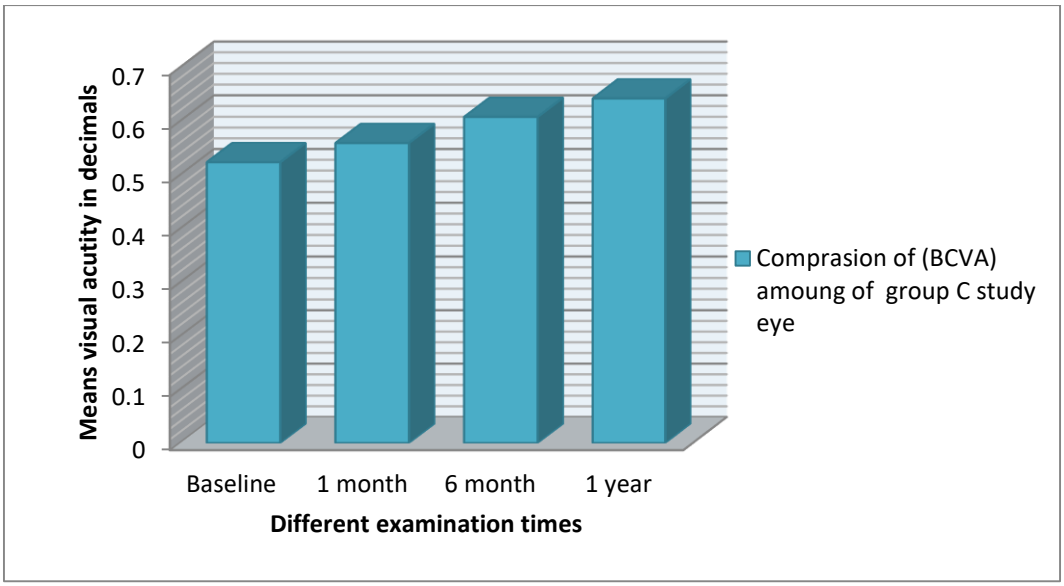
(10 patients, bilateral keratoconus; study eye operated; fellow eye not operated)

FIGURE 5.2.2. Variations in mean best corrected visual acuity (BCVA) at different examination times in 10 fellow (keratoconic, non-operated) eyes in Group B



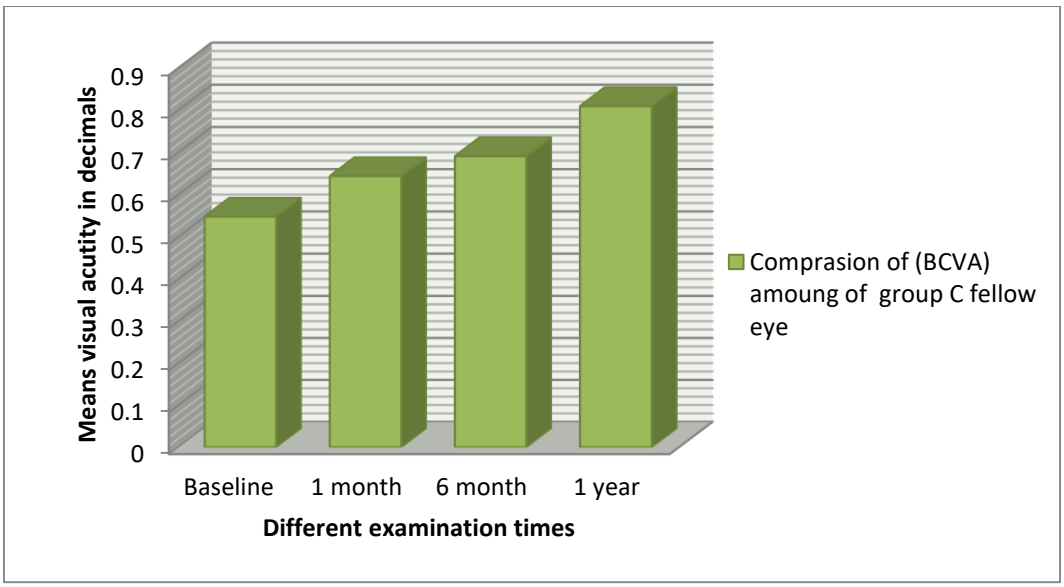
(10 patients, bilateral keratoconus; study eye operated; fellow eye not operated)

FIGURE 5.3.1. Variations in mean best corrected visual acuity (BCVA) at different examination times in 7 study (keratoconic, worse eye, first operated) eyes in Group C



(7 patients, bilateral keratoconus; study eye = worse eye, operated first; fellow eye = better eye, operated after one week)

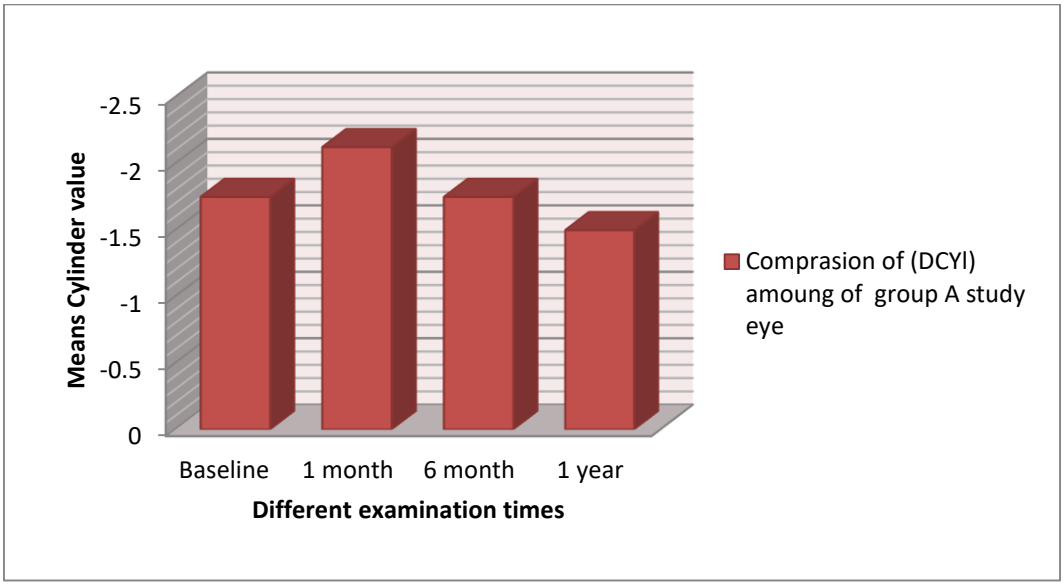
FIGURE 5.3.2. Variations in mean best corrected visual acuity (BCVA) at different examination times in 7 fellow (keratoconic, better eye, operated second) eyes in Group C



(7 patients, bilateral keratoconus; study eye = worse eye, operated first; fellow eye = better eye, operated after one week)

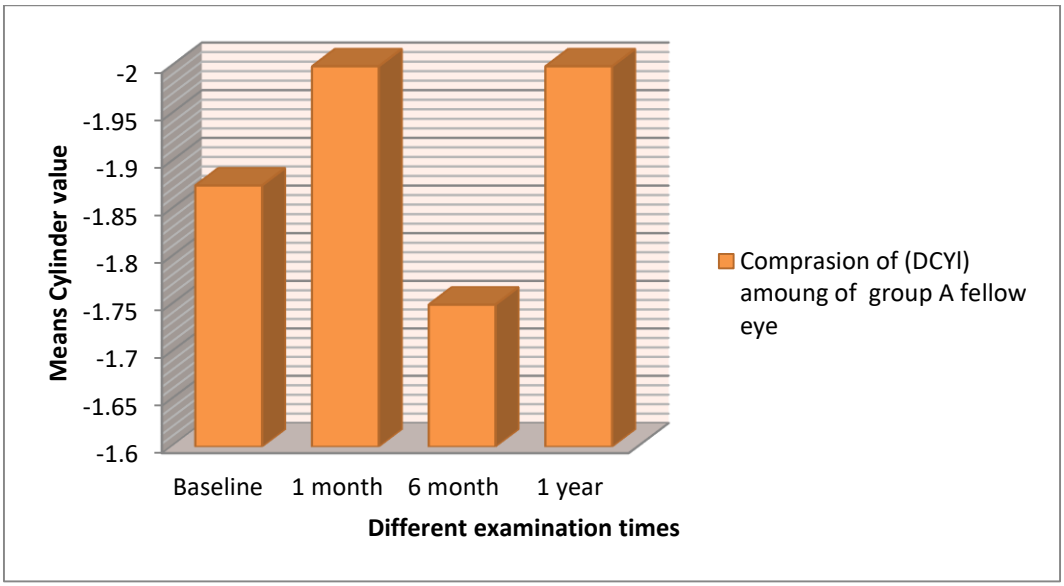
Figure 6: Comparison of mean cylinder value (Dcyl) at different examination times in patients with keratoconus undergoing corneal collagen cross-linking at a tertiary eye care hospital

FIGURE 6.1.1. Variations in mean cylinder value (Dcyl) at different examination times in 4 study (keratoconic, operated) eyes in Group A



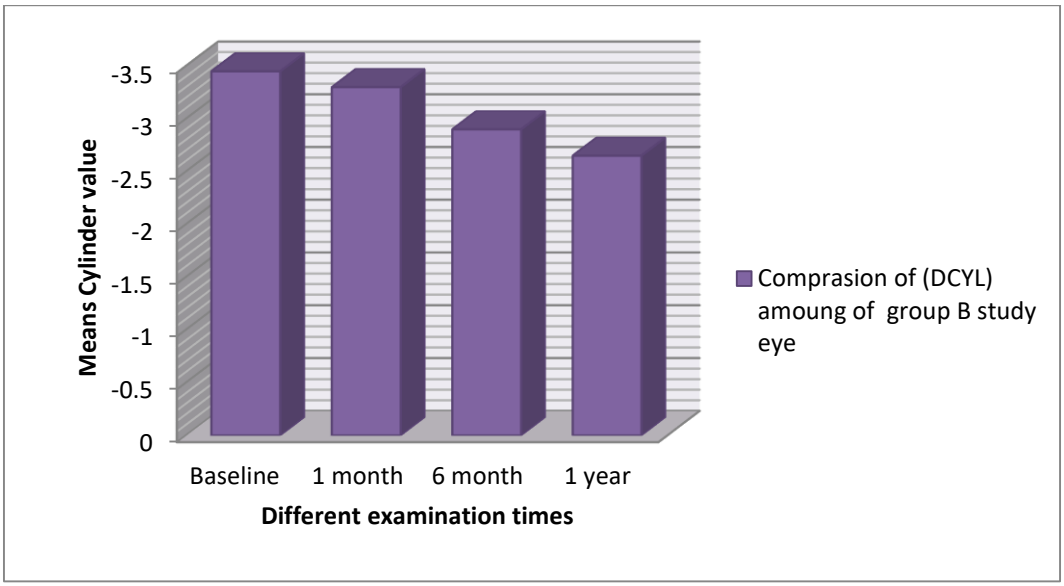
(4 patients, unilateral keratoconus; study eye operated; fellow eye not operated)

FIGURE 6.1.2. Variations in mean cylinder value (Dcyl) at different examination times in four fellow (non-keratoconic, non- operated) eyes in Group A



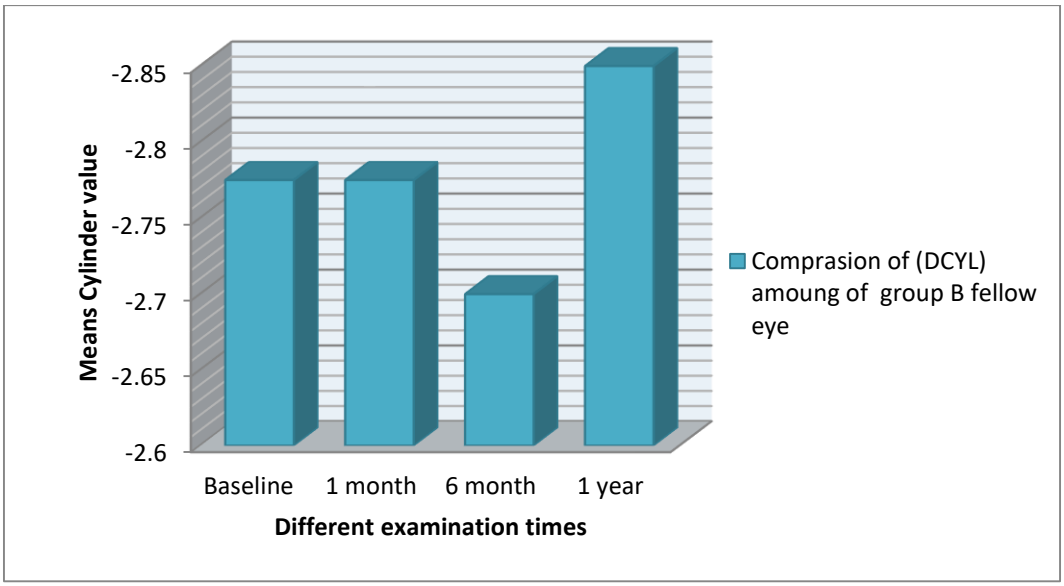
(4 patients, unilateral keratoconus; study eye operated; fellow eye not operated)

FIGURE 6.2.1. Variations in mean cylinder value (Dcyl) at different examination times in 10 study (keratoconic, operated) eyes in Group B



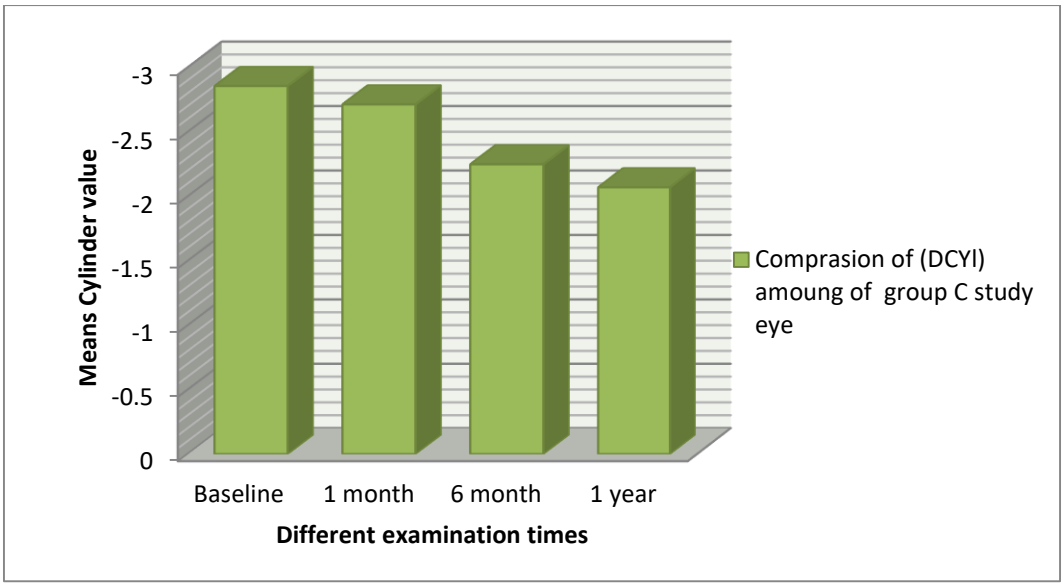
(10 patients, bilateral keratoconus; study eye operated; fellow eye not operated)

FIGURE 6.2.2. Variations in mean cylinder value (Dcyl) at different examination times in 10 fellow (keratoconic, non- operated) eyes in Group B



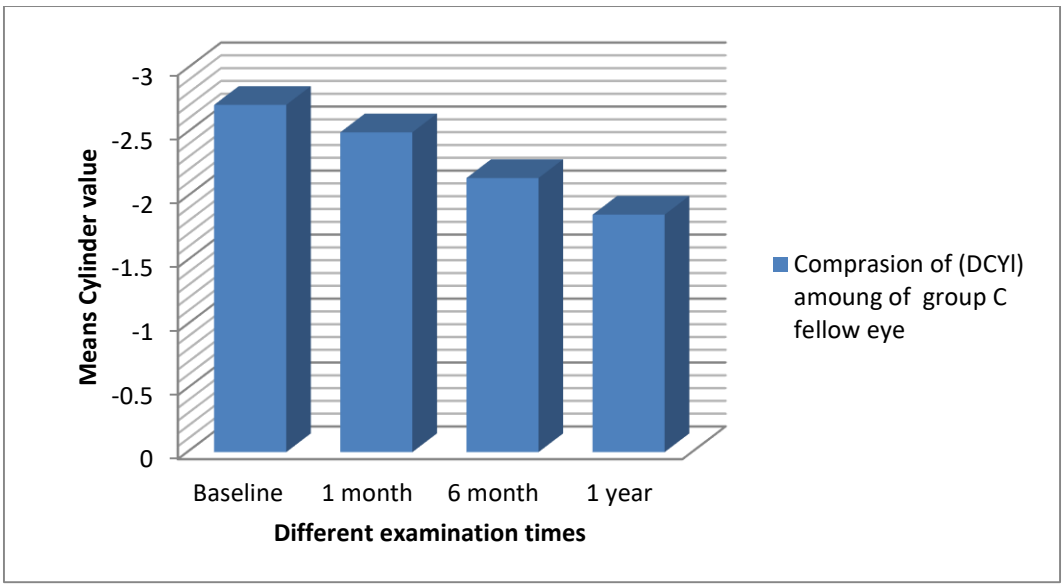
(10 patients, bilateral keratoconus; study eye operated; fellow eye not operated)

FIGURE 6.3.1. Variations in mean cylinder value (Dcyl) at different examination times in 7 study (keratoconic, worse eye, first operated) eyes in Group C



(7 patients, bilateral keratoconus; study eye = worse eye, operated first; fellow eye = better eye, operated after one week)

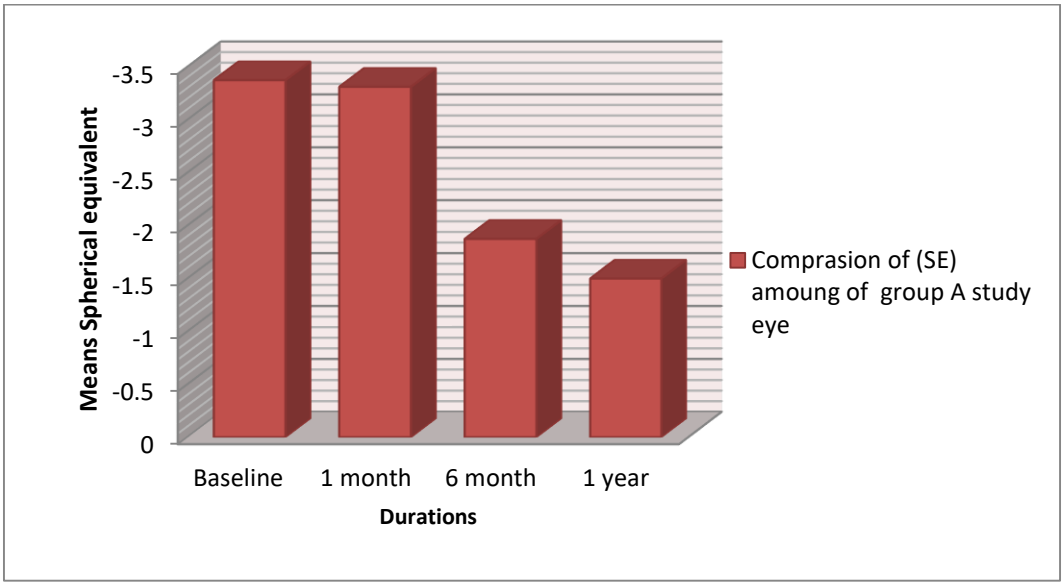
FIGURE 6.3.2. Variations in mean cylinder value (Dcyl) at different examination times in 7 fellow (keratoconic, better eye, operated second) eyes in Group C



(7 patients, bilateral keratoconus; study eye = worse eye, operated first; fellow eye = better eye, operated after one week)

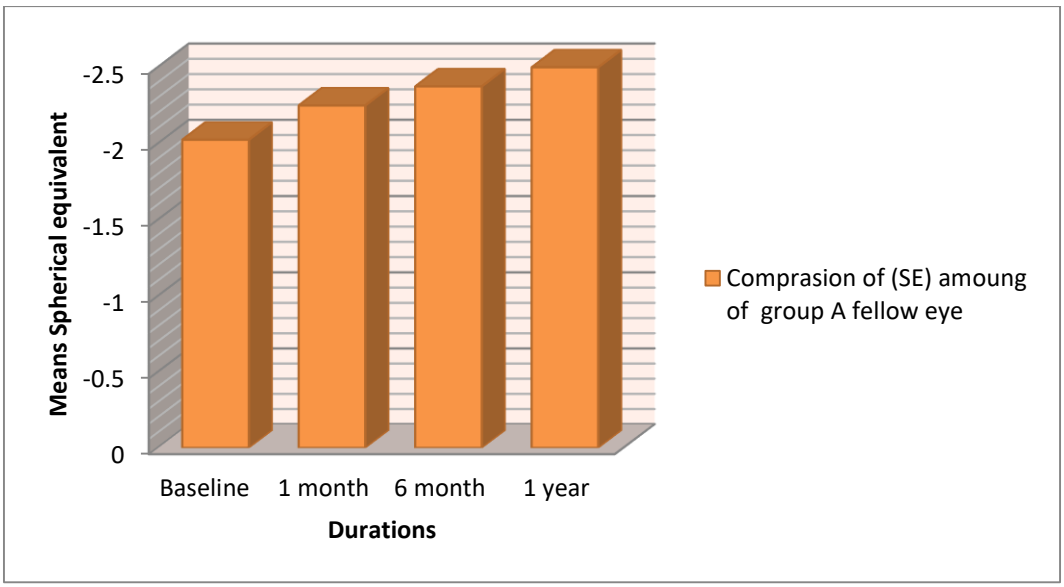
Figure 7: Comparison of mean Spherical equivalent (SE) at different examination times in patients with keratoconus undergoing corneal collagen cross-linking at a tertiary eye care hospital

FIGURE 7.1.1. Variations in mean spherical equivalent (SE) at different examination times in 4 study (keratoconic, operated) eyes in Group A



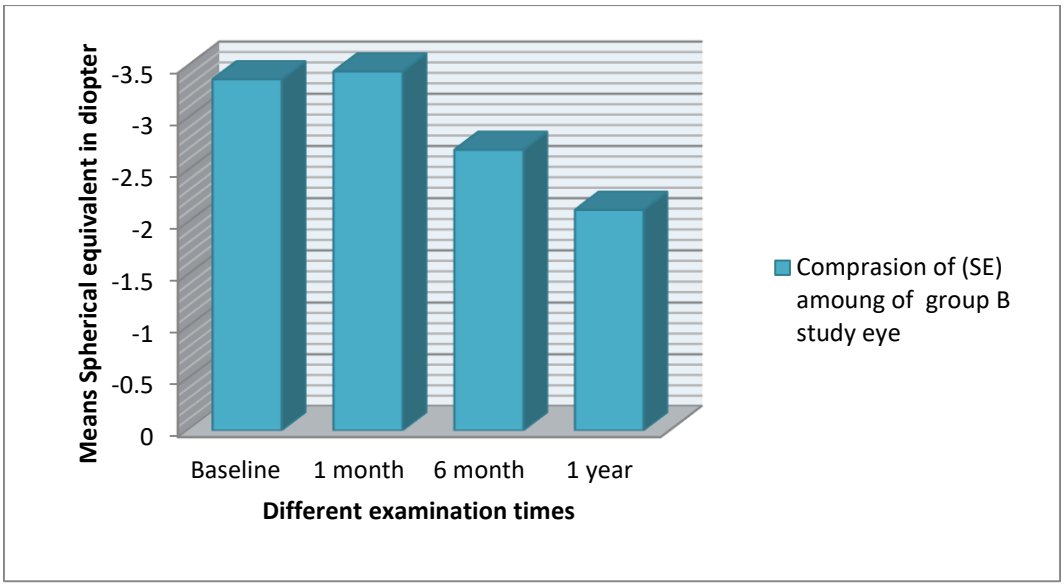
(4 patients, unilateral keratoconus; study eye operated; fellow eye not operated)

FIGURE 7.1.2. Variations in mean spherical equivalent (SE) at different examination times in four fellow (non-keratoconic, non-operated) eyes in Group A



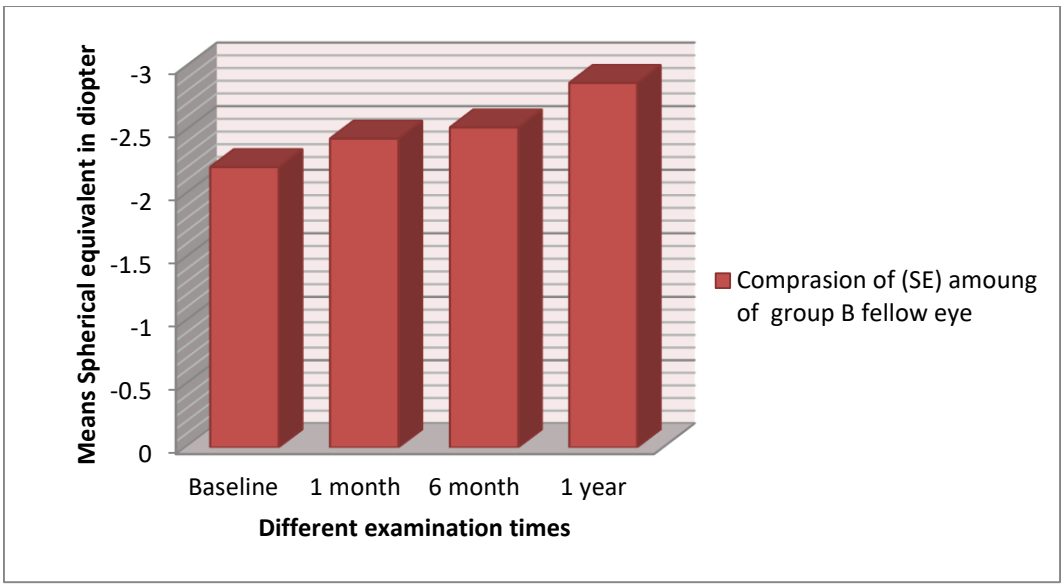
(4 patients, unilateral keratoconus; study eye operated; fellow eye not operated)

FIGURE 7.2.1. Variations in mean spherical equivalent (SE)at different examination times in 10 study (keratoconic, operated) eyes in Group B



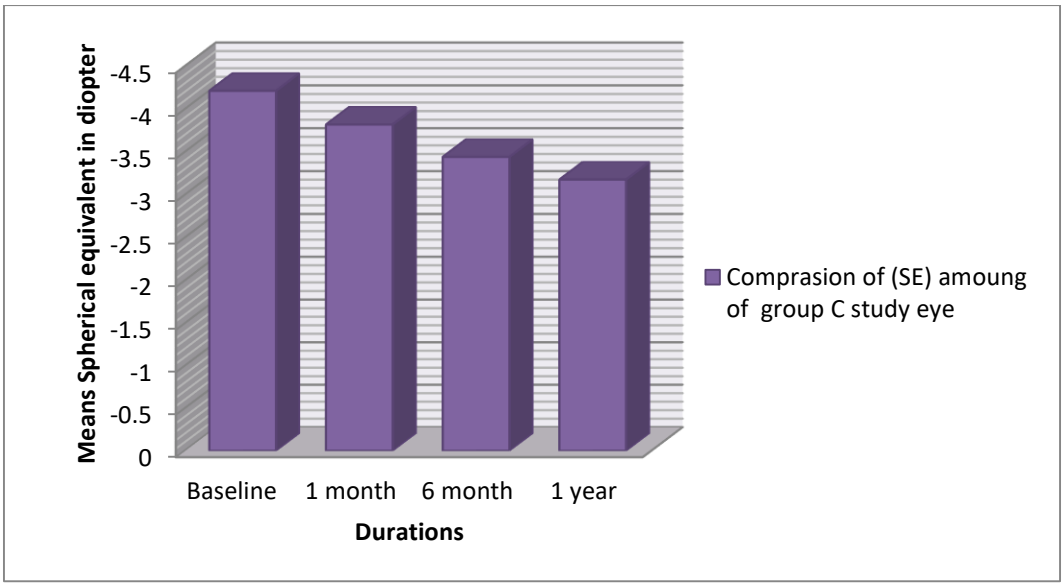
(10 patients, bilateral keratoconus; study eye operated; fellow eye not operated)

FIGURE 7.2.2. Variations in mean spherical equivalent (SE)at different examination times in 10 fellow (keratoconic, non- operated) eyes in Group B



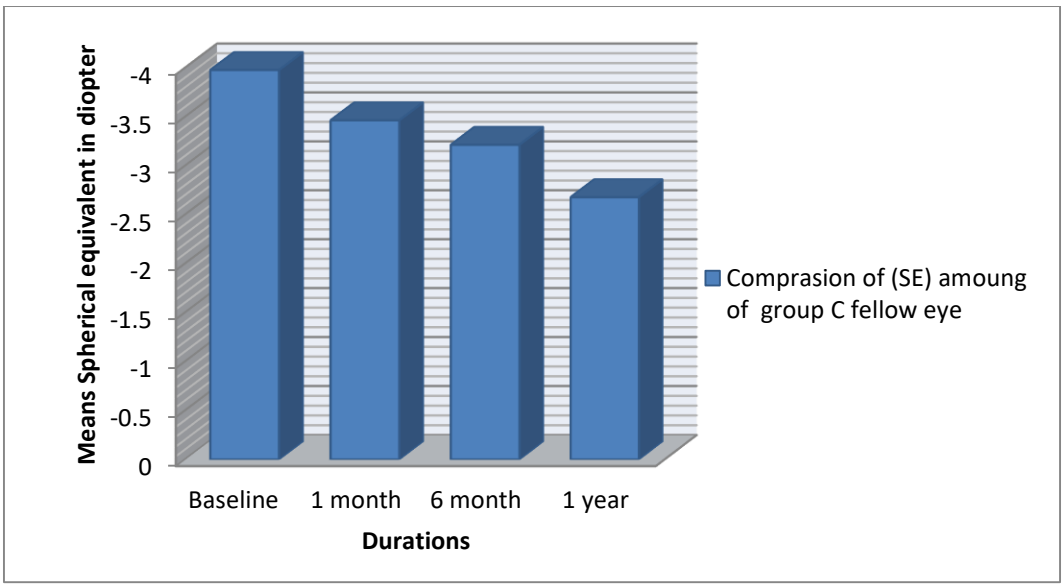
(10 patients, bilateral keratoconus; study eye operated; fellow eye not operated)

FIGURE 7.3.1. Variations in mean spherical equivalent (SE) at different examination times in 7 study (keratoconic, worse eye, first operated) eyes in Group C



(7 patients, bilateral keratoconus; study eye = worse eye, operated first; fellow eye = better eye, operated after one week)

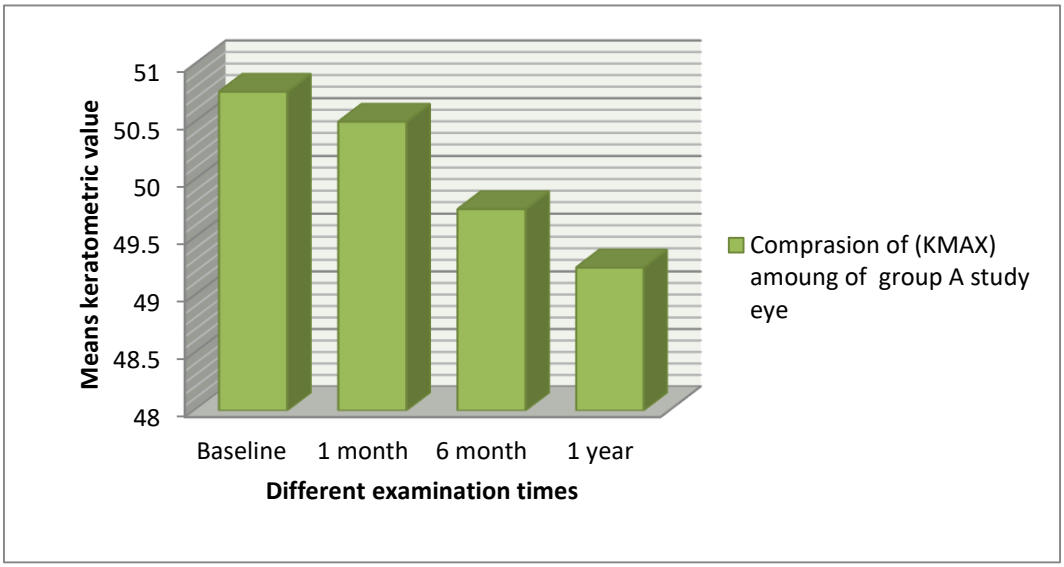
FIGURE 7.3.2. Variations in mean spherical equivalent (SE) at different examination times in 7 fellow (keratoconic, better eye, operated second) eyes in Group C



(7 patients, bilateral keratoconus; study eye = worse eye, operated first; fellow eye = better eye, operated after one week)

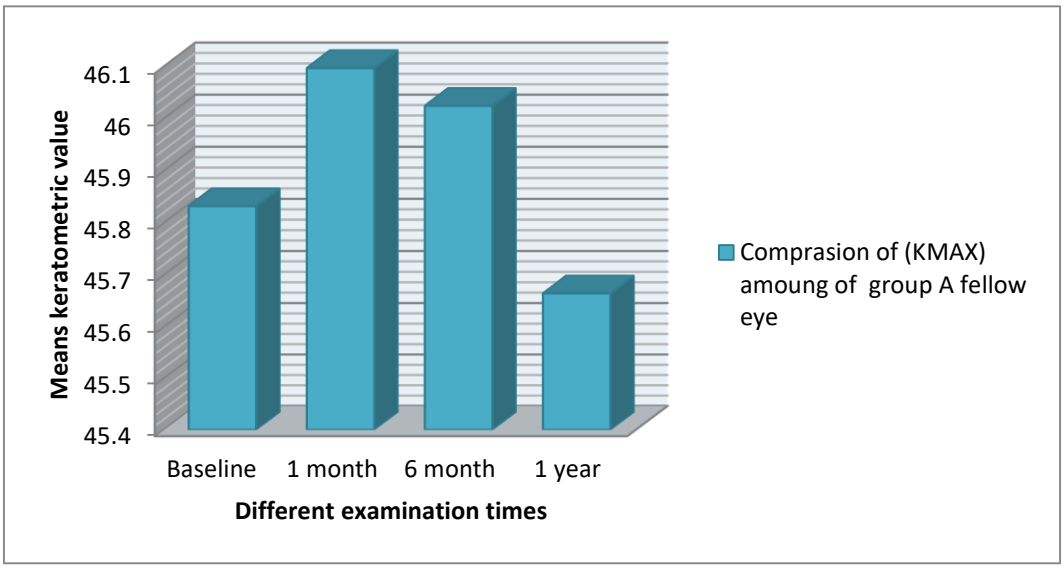
Figure 8 : Comparison of mean keratometric steep axis (Kmax) values at different examination times in patients with keratoconus undergoing corneal collagen cross-linking at a tertiary eye care hospital

FIGURE 8.1.1. Variations in mean keratometric steep axis (Kmax) values at different examination times in 4 study (keratoconic, operated) eyes in Group A



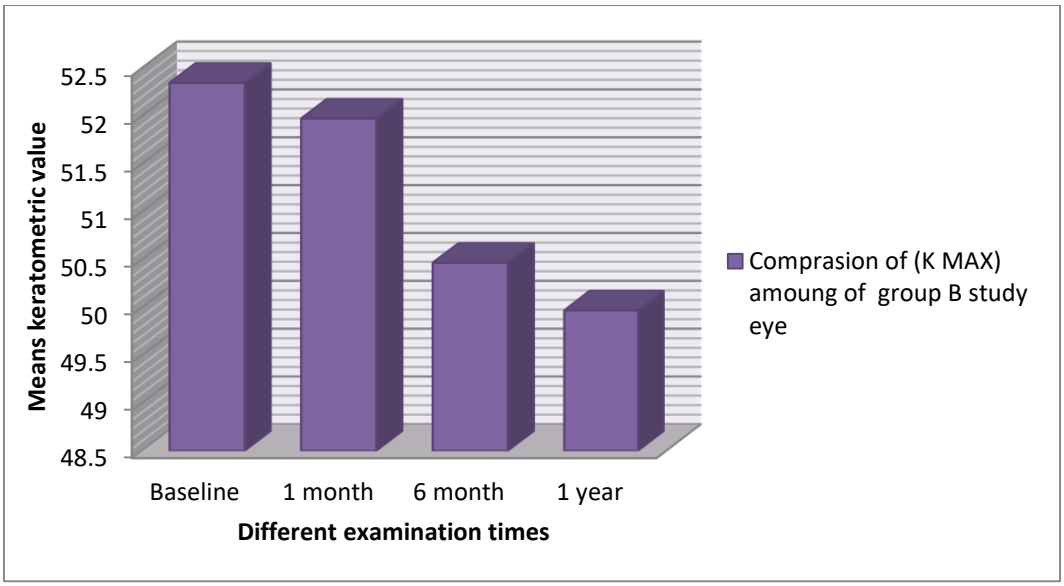
(4 patients, unilateral keratoconus; study eye operated; fellow eye not operated)

FIGURE 8.1.2. Variations in mean keratometric steep axis (Kmax) values at different examination times in four fellow (non-keratoconic, non- operated) eyes in Group A



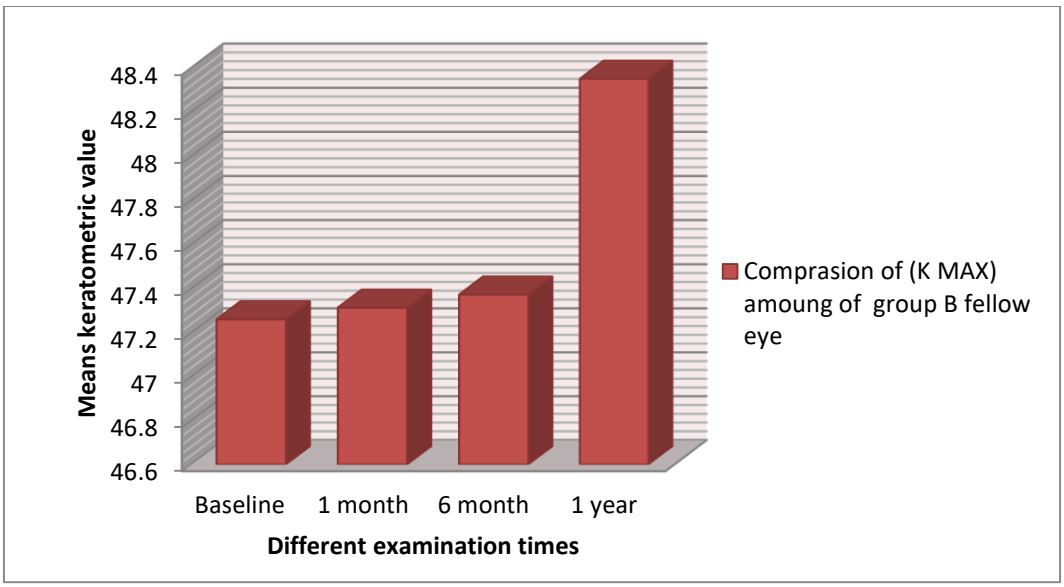
(4 patients, unilateral keratoconus; study eye operated; fellow eye not operated)

FIGURE 8.2.1. Variations in mean keratometric steep axis (Kmax) values at different examination times in 10 study (keratoconic, operated) eyes in Group B



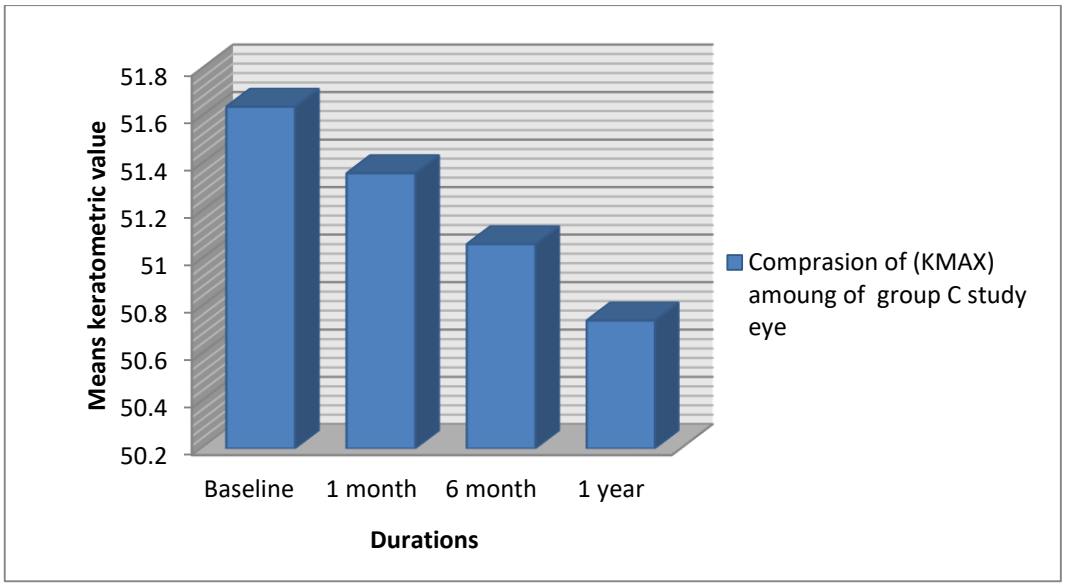
(10 patients, bilateral keratoconus; study eye operated; fellow eye not operated)

FIGURE 8.2.2. Variations in mean keratometric steep axis (Kmax) values at different examination times in 10 fellow (keratoconic, non-operated) eyes in Group B



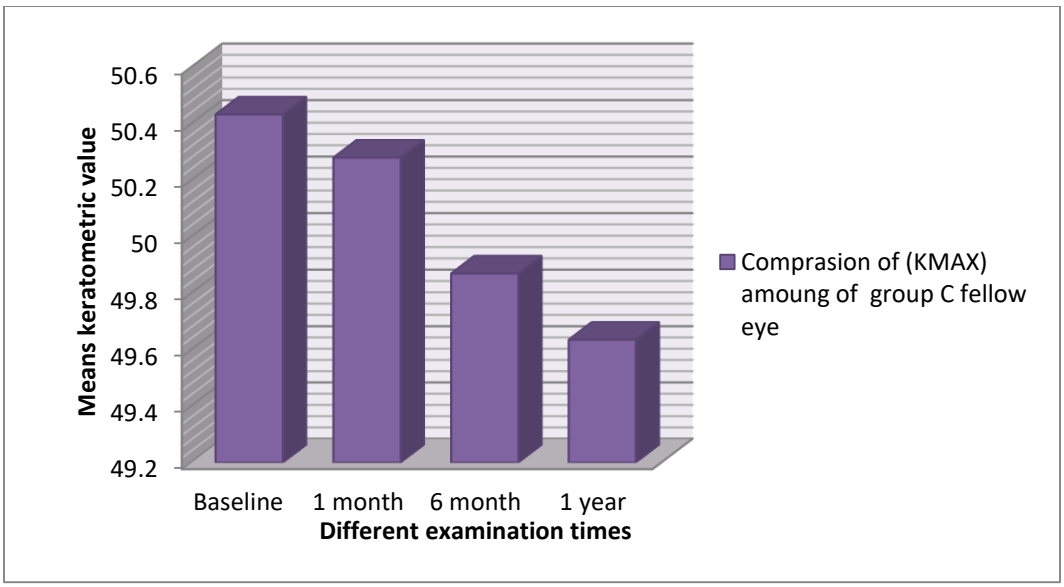
(10 patients, bilateral keratoconus; study eye operated; fellow eye not operated)

FIGURE 8.3.1. Variations in mean keratometric steep axis (Kmax) values at different examination times in 7 study (keratoconic, worse eye, first operated) eyes in Group C



(7 patients, bilateral keratoconus; study eye = worse eye, operated first; fellow eye = better eye, operated after one week)

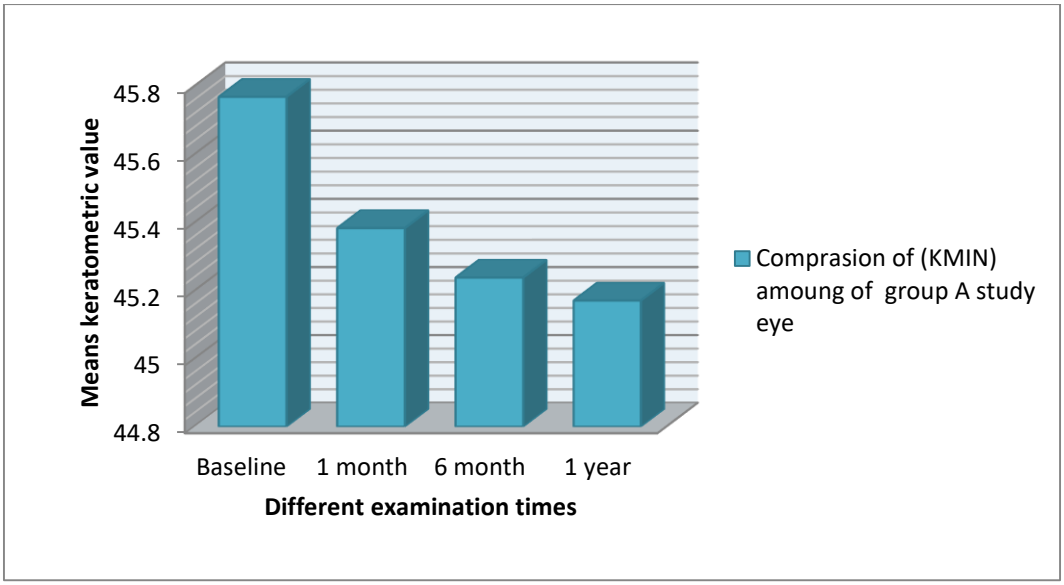
FIGURE 8.3.2. Variations in mean keratometric steep axis (Kmax) values at different examination times in 7 fellow (keratoconic, better eye, operated second) eyes in Group C



(7 patients, bilateral keratoconus; study eye = worse eye, operated first; fellow eye = better eye, operated after one week)

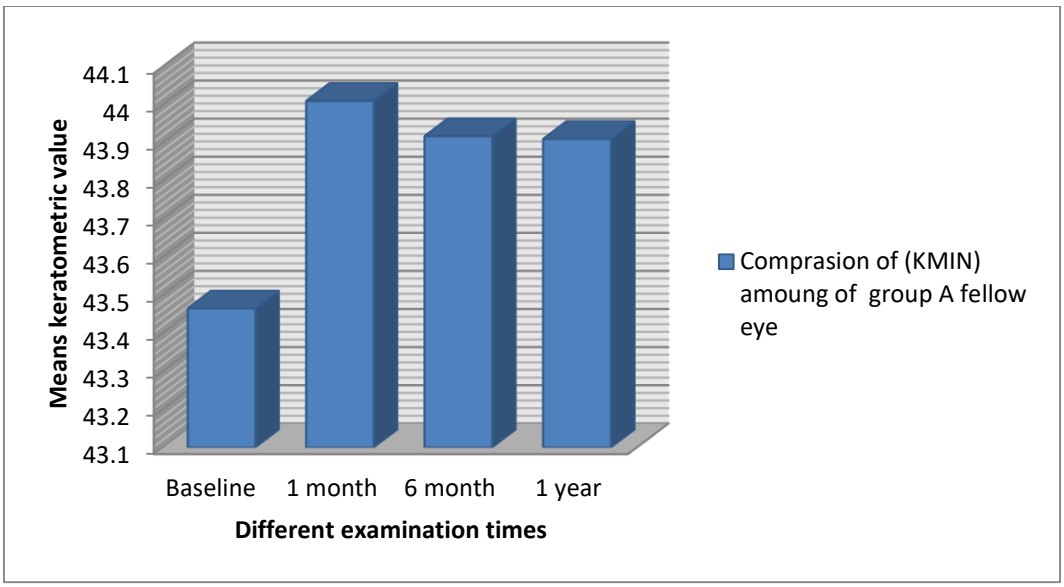
Figure 9: Comparison of mean keratometric flat axis (Kmin) values at different examination times in patients with keratoconus undergoing corneal collagen cross-linking at a tertiary eye care hospital

FIGURE 9.1.1. Variations in mean keratometric flat axis (Kmin) values at different examination times in 4 study (keratoconic, operated) eyes in Group A



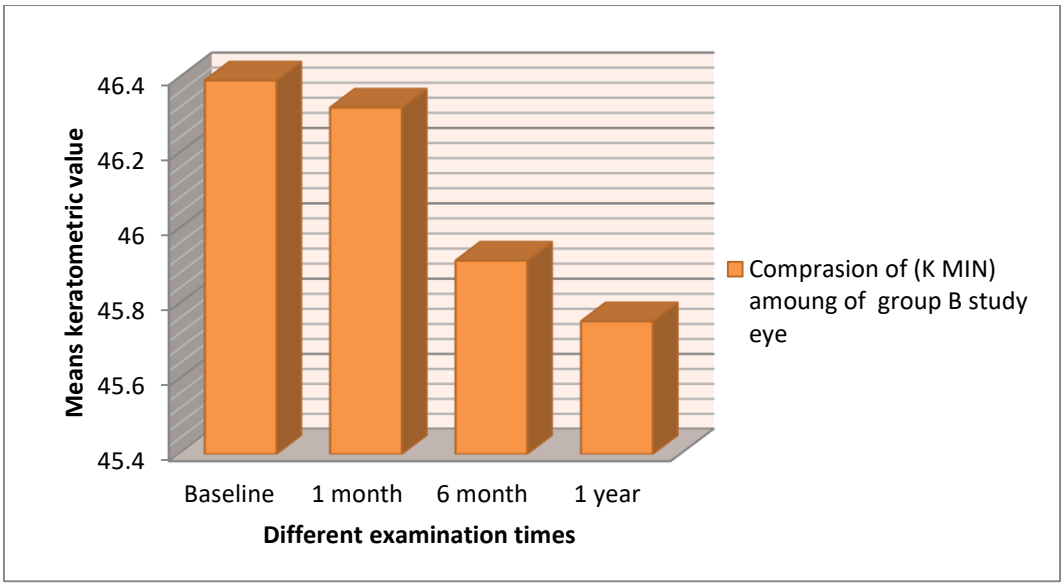
(4 patients, unilateral keratoconus; study eye operated; fellow eye not operated)

FIGURE 9.1.2. Variations in mean keratometric flat axis (Kmin) values at different examination times in four fellow (non-keratoconic, non- operated) eyes in Group A



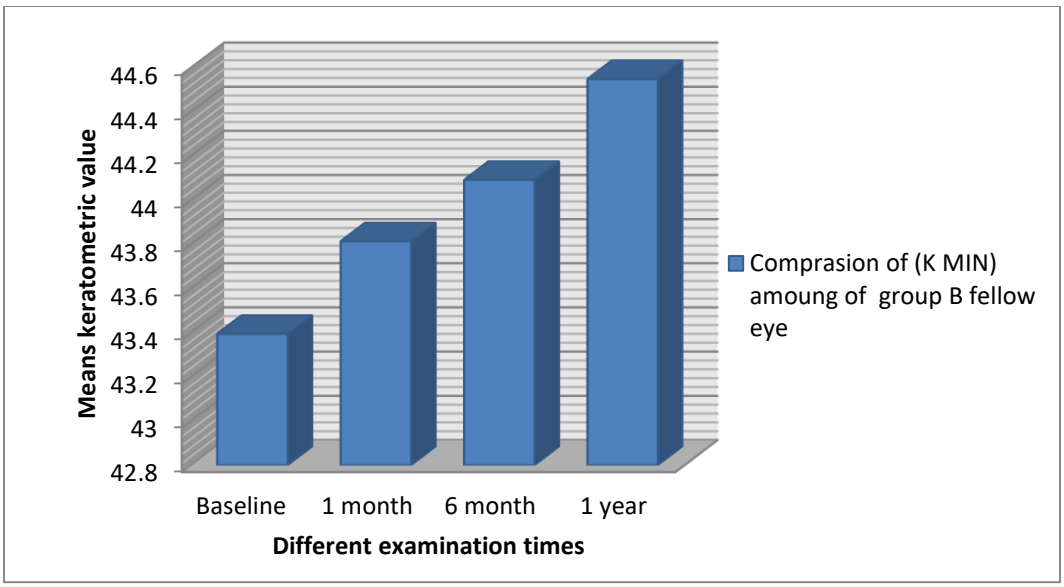
(4 patients, unilateral keratoconus; study eye operated; fellow eye not operated)

FIGURE 9.2.1. Variations in mean keratometric flat axis (Kmin) values at different examination times in 10 study (keratoconic, operated) eyes in Group B



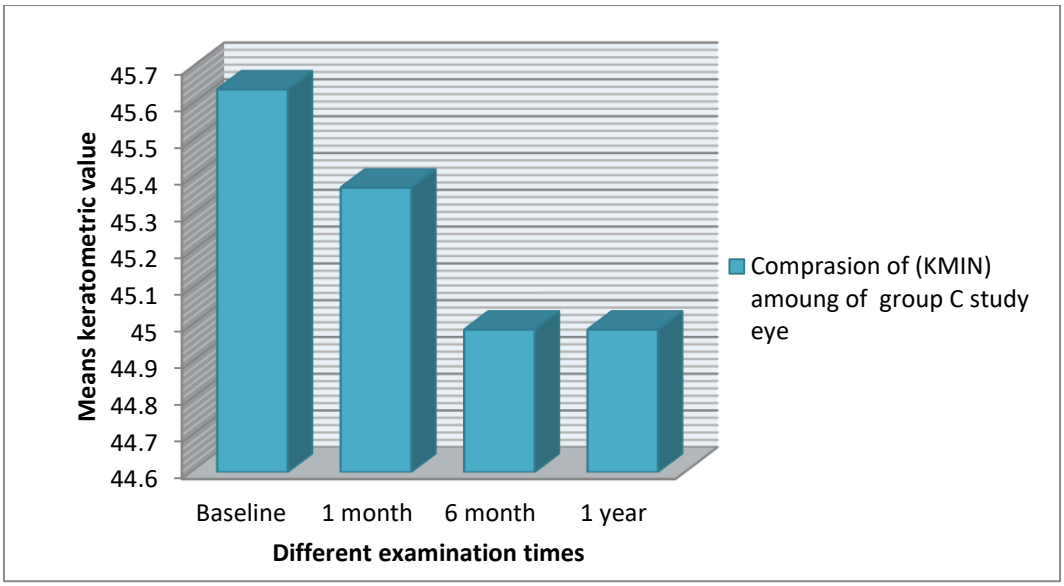
(10 patients, bilateral keratoconus; study eye operated; fellow eye not operated)

FIGURE 9.2.2. Variations in mean keratometric flat axis (Kmin) values at different examination times in 10 fellow (keratoconic, non-operated) eyes in Group B



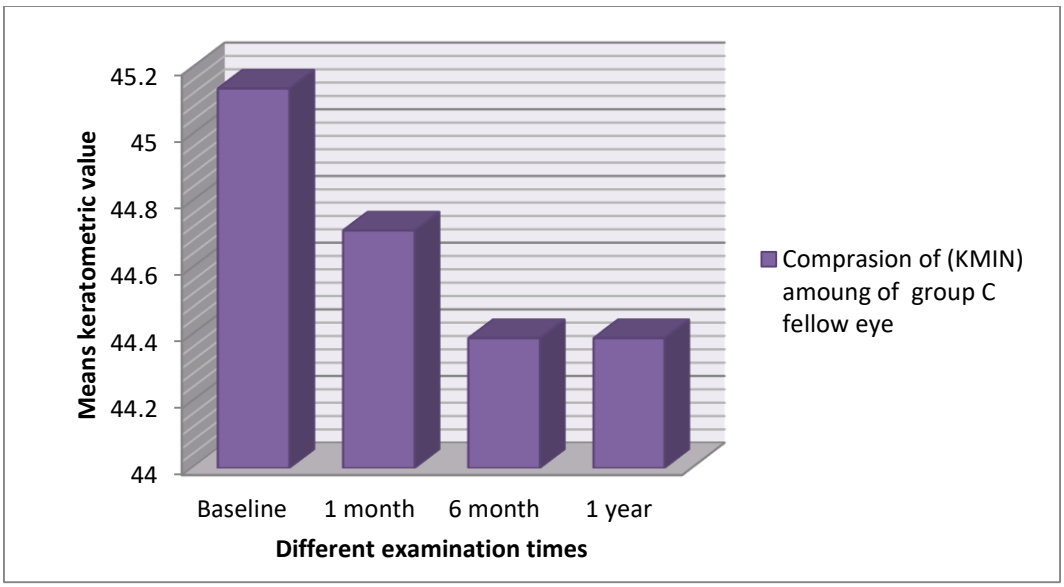
(10 patients, bilateral keratoconus; study eye operated; fellow eye not operated)

FIGURE 9.3.1. Variations in mean keratometric flat axis (Kmin) values at different examination times in 7 study (keratoconic, worse eye, first operated) eyes in Group C



(7 patients, bilateral keratoconus; study eye = worse eye, operated first; fellow eye = better eye, operated after one week)

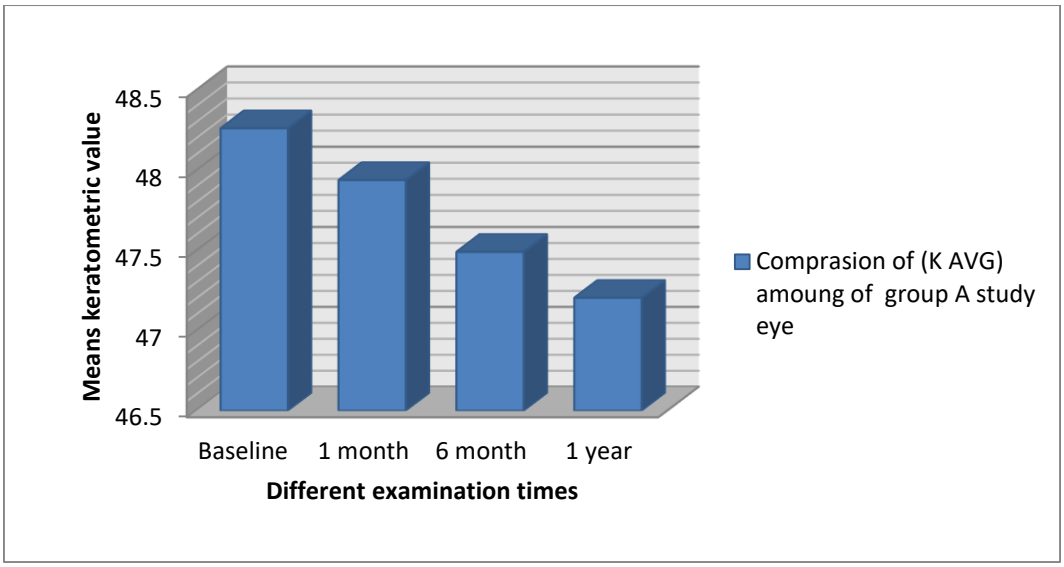
FIGURE 9.3.2. Variations in mean keratometric flat axis (Kmin) values at different examination times in 7 fellow (keratoconic, better eye, operated second) eyes in Group C



(7 patients, bilateral keratoconus; study eye = worse eye, operated first; fellow eye = better eye, operated after one week)

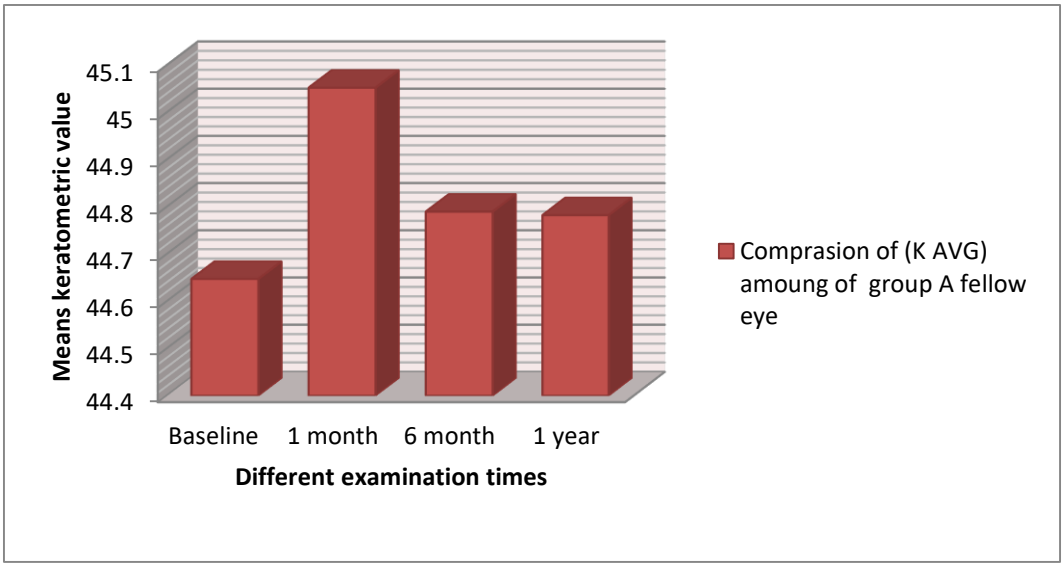
Figure 10 : Comparison of mean average keratometric (Kavg) values at different examination times in patients with keratoconus undergoing corneal collagen cross-linking at a tertiary eye care hospital

FIGURE 10.1.1. Variations in mean average keratometric (Kavg) values at different examination times in 4 study (keratoconic, operated) eyes in Group A



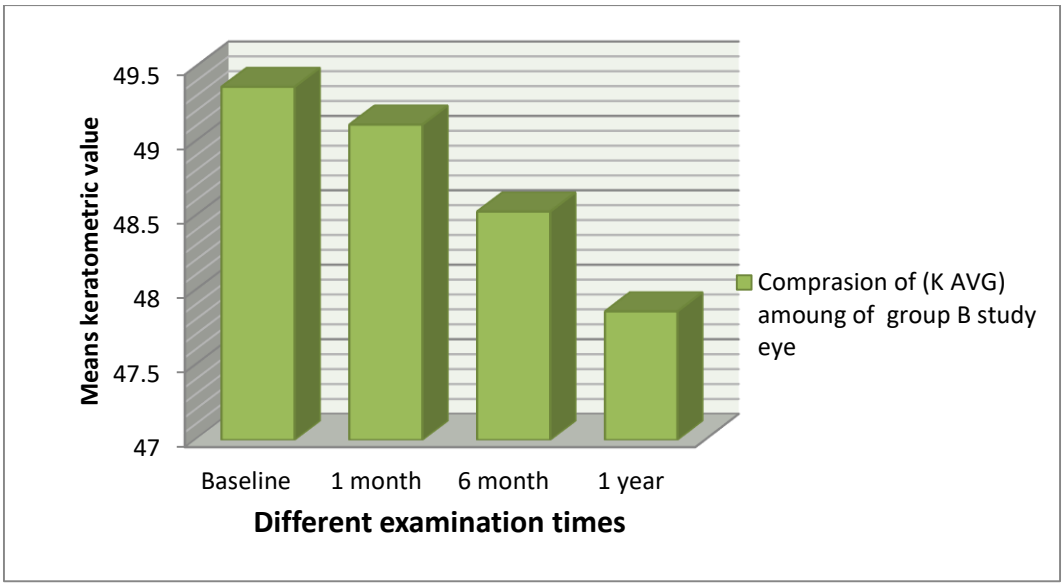
(4 patients, unilateral keratoconus; study eye operated; fellow eye not operated)

FIGURE 10.1.2. Variations in mean average keratometric (Kavg) values at different examination times in four fellow (non-keratoconic, non- operated) eyes in Group A



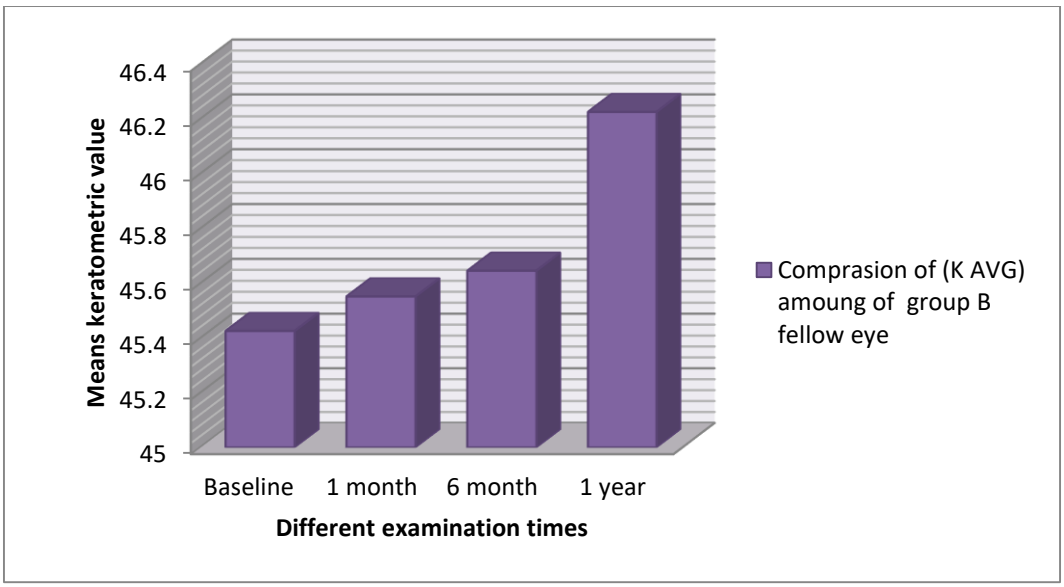
(4 patients, unilateral keratoconus; study eye operated; fellow eye not operated)

FIGURE 10.2.1. Variations in mean average keratometric (Kavg) values at different examination times in 10 study (keratoconic, operated) eyes in Group B



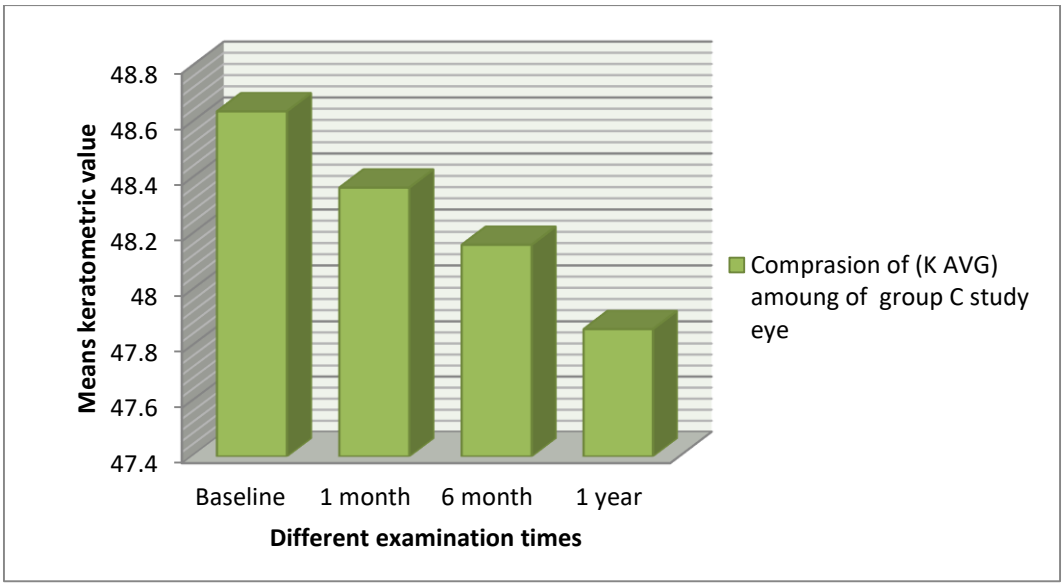
(10 patients, bilateral keratoconus; study eye operated; fellow eye not operated)

FIGURE 10.2.2. Variations in mean average keratometric (Kavg) values at different examination times in 10 fellow (keratoconic, non-operated) eyes in Group B



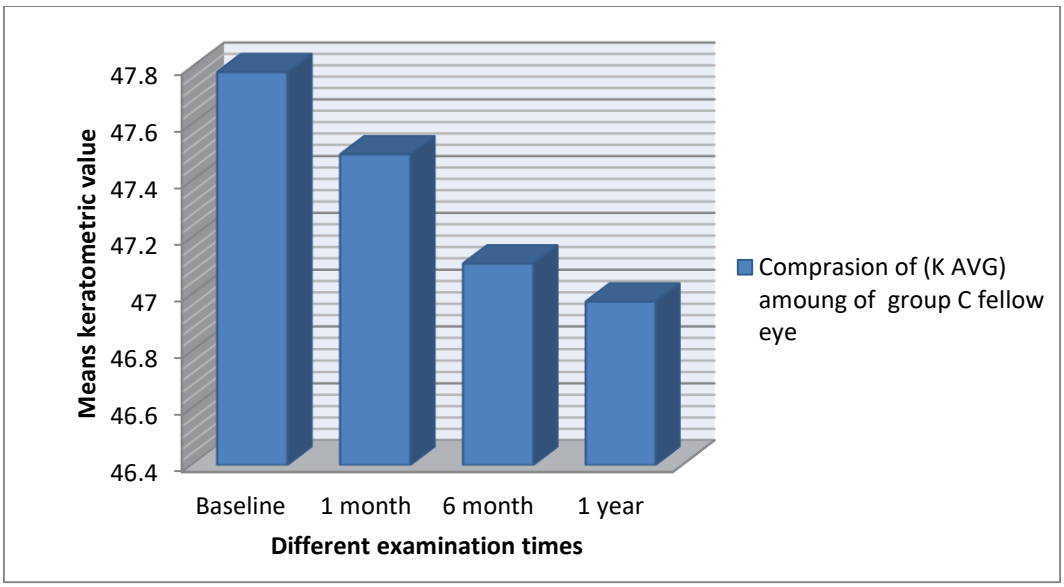
(10 patients, bilateral keratoconus; study eye operated; fellow eye not operated)

FIGURE 10.3.1. Variations in mean average keratometric (Kavg) values at different examination times in 7 study (keratoconic, worse eye, first operated) eyes in Group C



(7 patients, bilateral keratoconus; study eye = worse eye, operated first; fellow eye = better eye, operated after one week)

FIGURE 10.3.2. Variations in mean average keratometric (Kavg) values at different examination times in 7 fellow (keratoconic, better eye, operated second) eyes in Group C



(7 patients, bilateral keratoconus; study eye = worse eye, operated first; fellow eye = better eye, operated after one week)

Fig 11: UV-X ™ instrument used for performing C3R

Fig 12: Step1: Measurement of corneal diameter for epithelial debridement

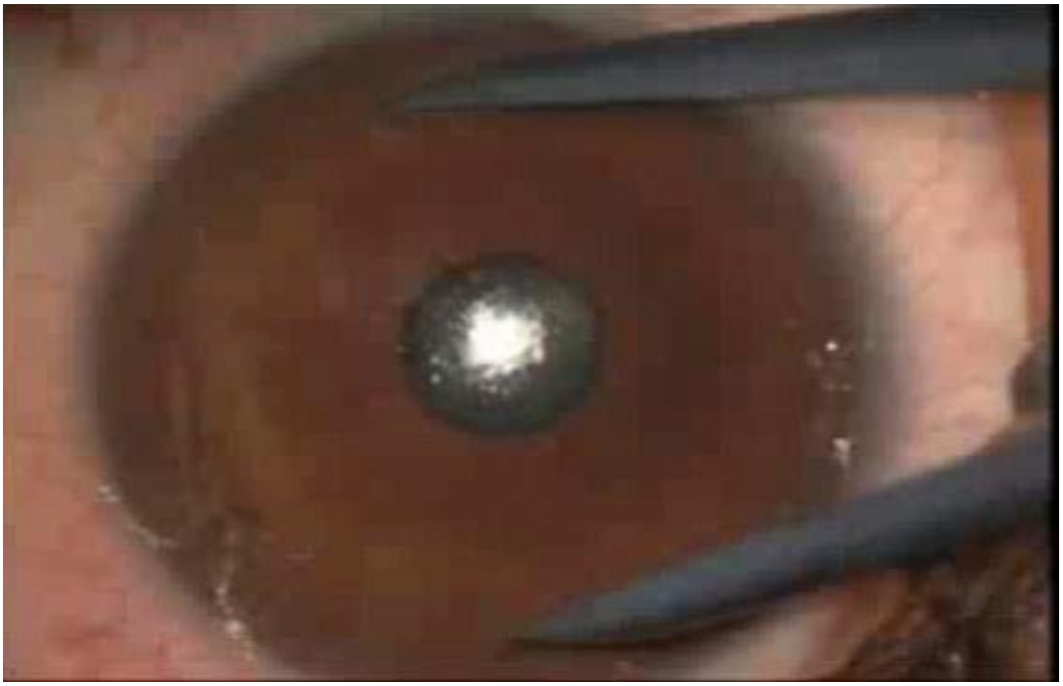


Fig13: Step 2: Mechanical debridement of corneal epithelium

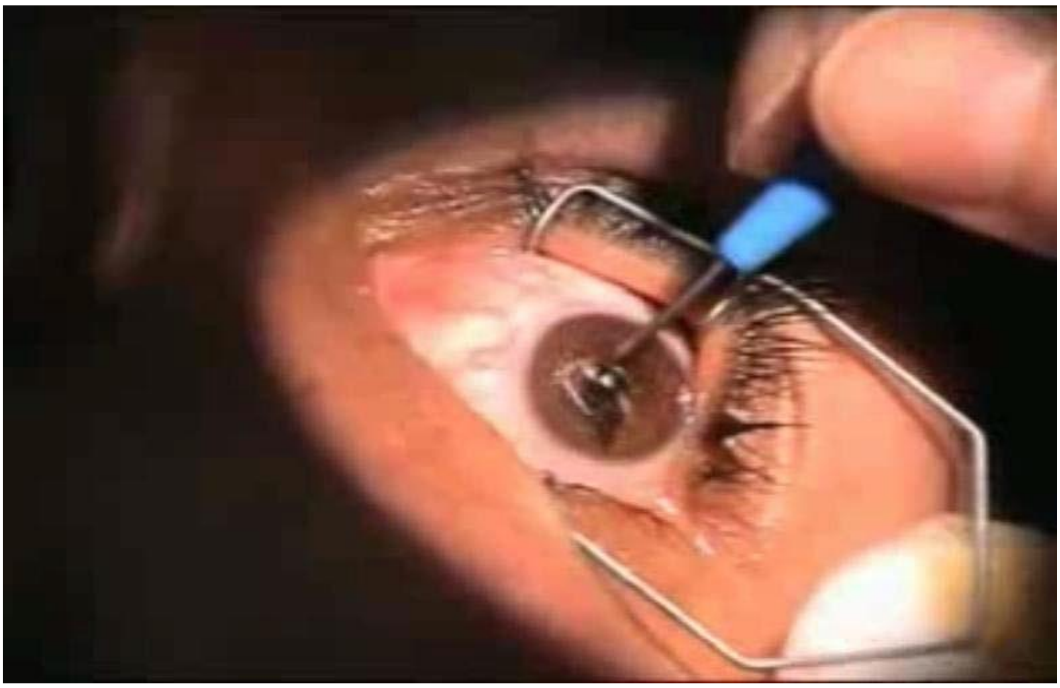


Fig 14: Step 3: Instillation of riboflavin (0.1%) drops every two minutes for 30 minutes

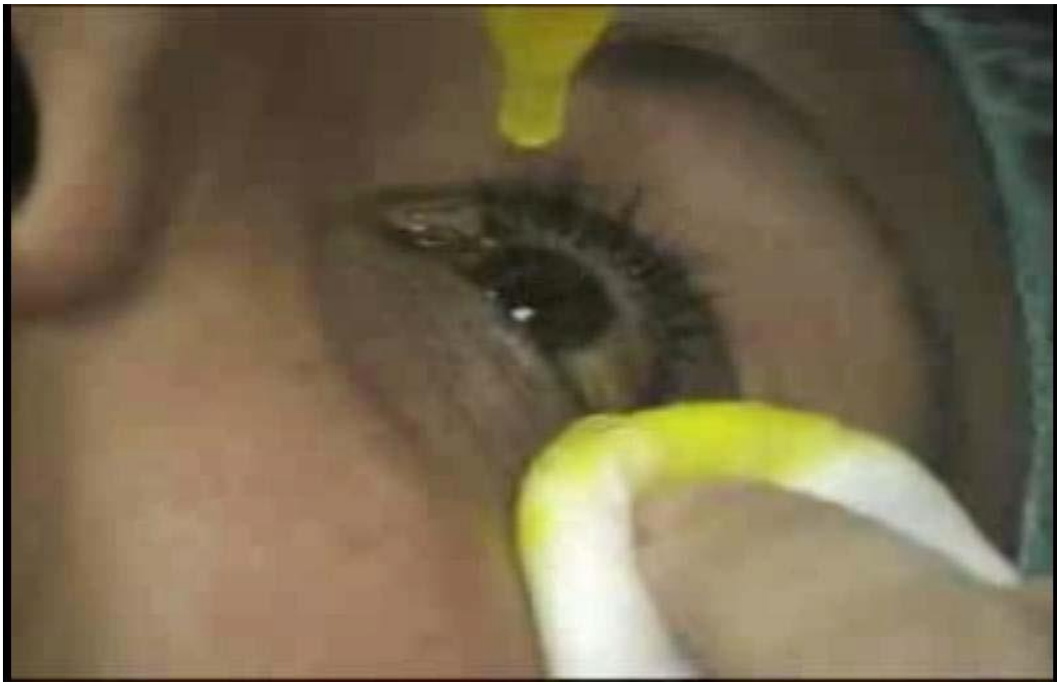


Fig 15: Step 4: Exposure to UV-A (370 nm) with sequential administration of riboflavin (0.1%) drops every two minutes for the next 30 minutes.

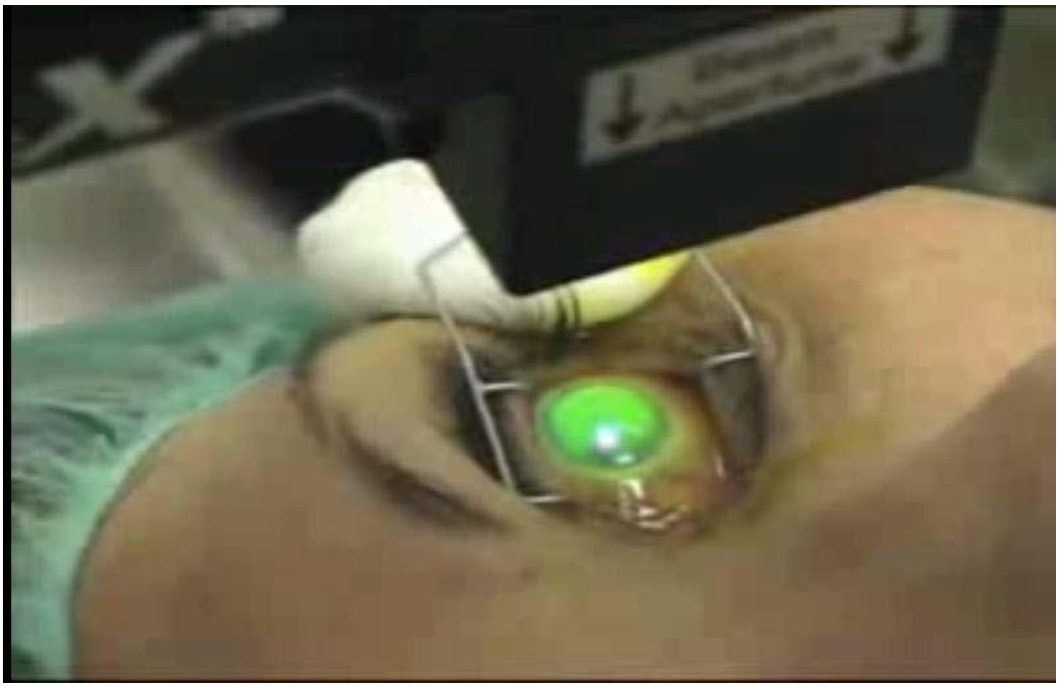
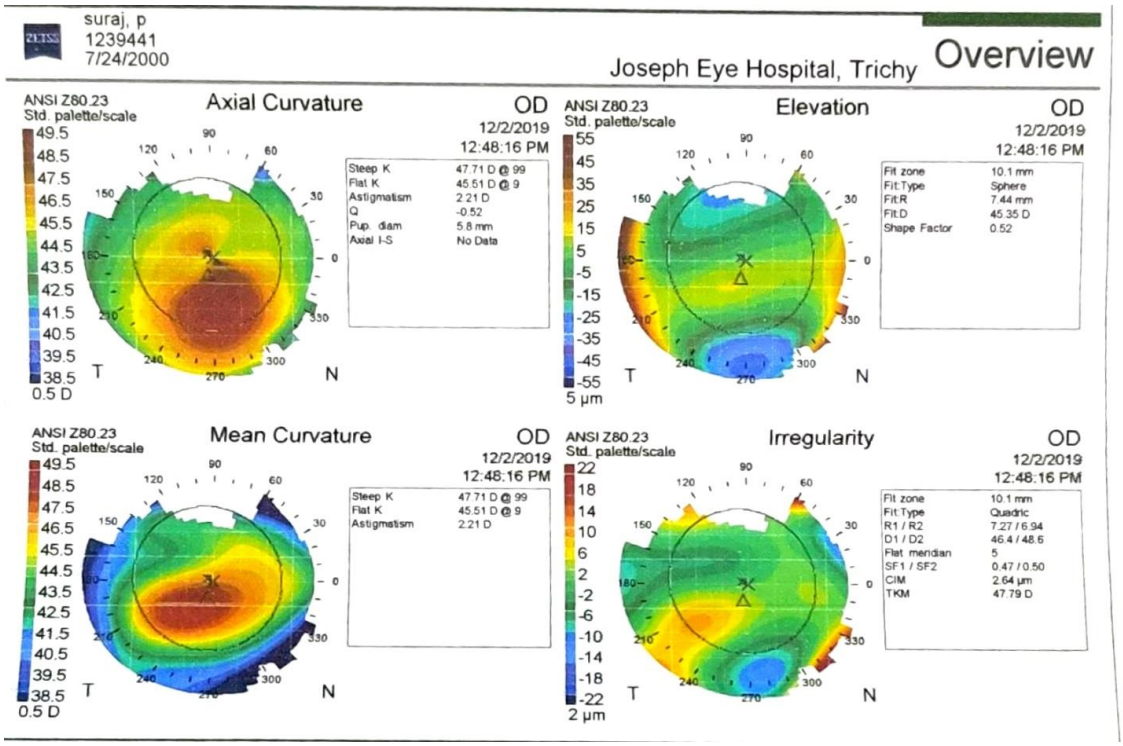
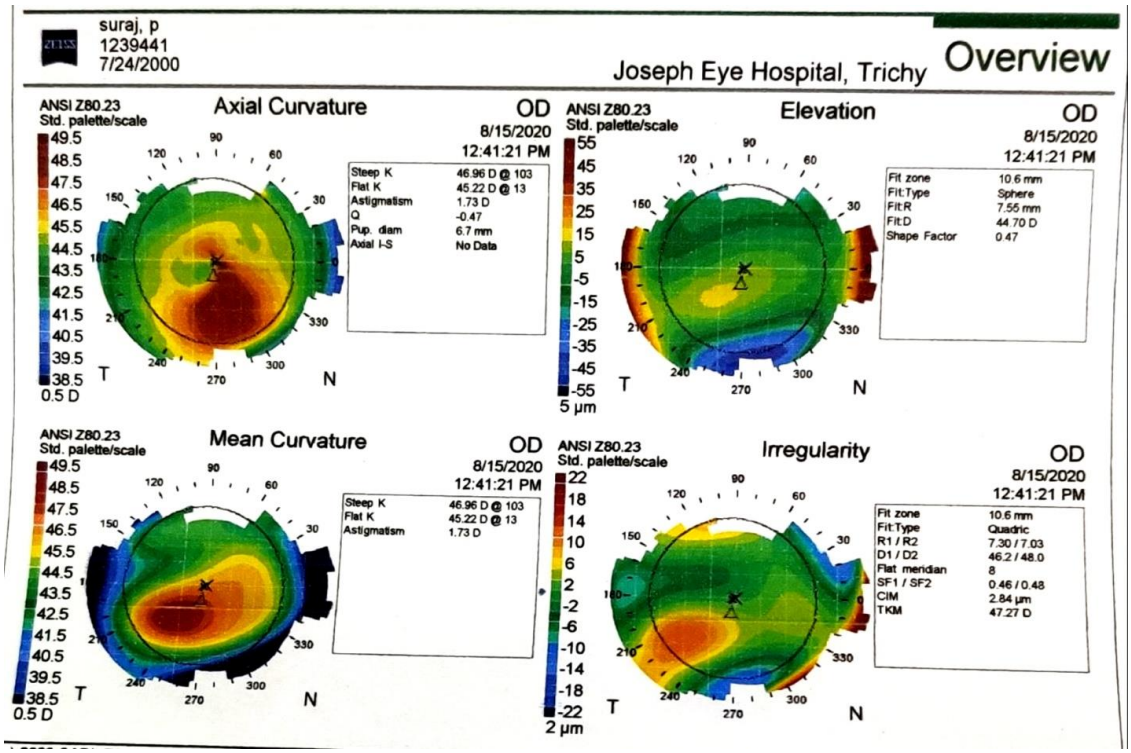


Fig.16: Corneal topography map of the study eye showing an improvement in the keratometric readings post-C3R





DISCUSSION

Corneal collagen cross-linking with riboflavin (C3R) is a promising treatment modality for keratoconus patients as it provides various advantages over other treatment modalities for corneal ectasia. The specific advantage of C3R over the other modalities is that it halts the progression of the disease; in some cases, it also causes a partial reversal of the pre-existing ectasia, and also defers the need for keratoplasty.

The C3R procedure increases the mechanical stability of the corneal tissue by creating additional covalent bonds in corneal stroma by means of polymerization.[4]

This causes either slowing down, or arrest, of progression of the ectatic condition.[4]

In addition to keratoconus, C3R is now being sucessfully tried for the treatment of pellucid marginal degeneration, progressive post-LASIK keratectasia (PPLK), bullous keratopathy, infectious keratitis, and corneal melts.

The investigation described in this dissertation was a prospective study in which an attempt was made to analyze the effect of C3R procedure

in halting the progression of keratoconus over a follow up period of one year.

The parameters which were taken for analysis included uncorrected visual acuity (UCVA), best corrected visual acuity (BCVA), cylinder value (Dcyl), spherical equivalent (SE) and keratometry values (K1, K2 and Average K value using corneal topography); these were all recorded at baseline, and at different follow-up periods of 1 month, 6 months and 1 year post- procedure. Any post-operative complications were also looked for at every follow- up visit.

Much research has been done on this topic in the western population where promising results have been obtained when the C3R procedure was used to treat keratoconus patients. Only a few studies have been undertaken using this procedure on the Asian population. Hence this study is of much relevance.

Keratoconus is a bilateral condition, It may sometimes present asymmetrically, with one eye involved earlier and the other eye later. Hence, in the current investigation, the fellow eye of all the patients who underwent the C3R procedure in one eye (four patients in Group A and 10 patients in Group B) was examined simultaneously during each follow- up visit to determine if the fellow eye was stable or had progressed to keratoconus. Eyes which presented with bilateral progressive keratoconus underwent

C3R procedure in both eyes (seven patients in Group C) within an interval of 1 week; the stability of both operated eyes was assessed simultaneously at each follow-up visit to analyze the effectiveness of the C3R procedure to halt the progression of keratoconus.

With reference to demography, in the current study, 42 eyes of 21 patients (21 study eyes and 21 fellow eyes) were followed up for a period of 1 year; of 21 patients, 14 pts underwent the procedure in one eye and seven patients, who presented with bilateral progressive keratoconus, underwent the procedure in both eyes within a week interval. All patients were within the age group of 15 to 40 years (mean age of all 21 patients was 21.23±5.3 years), which included nine males (42.85%) and 12 females (57.14%) (Fig.1)

A few other studies, such as by Raiskup *et al.* (2008)[39], studied 480 eyes of 272 patients; thus, sample size included in the current study was relatively small.

Keratoconus, being a bilateral, asymmetric disease, presents with one eye affected more than the other in most circumstances. Thus, of the 21 patients included in the study, unilateral keratoconus accounted for four (19.04%) and patients who presented with bilateral keratoconus were 17 (80.95%).

With reference to improvement in UCVA, in the current study, the mean UCVA showed a improvement following C3R at one -month follow-up, and this improvement was sustained during subsequent examinations at six months and at one year post C3R, when compared to the preoperative mean UCVA; this was seen in operated eyes in all three groups (Groups A, B and C).In Group A, the preoperative mean UCVA (decimals) improved from 0.212±0.075 to 0.33±0.01 at the final examination (one year postoperatively) in the study eye. In group B, the preoperative mean UCVA (decimals) improved from 0.23±1.8 to 0.42±0.25 at the final examination (one year postoperatively) in study eye. In Group C, a statistically significant improvement in mean UCVA was noted in the study (first operated) eyes at one year from baseline (One way ANOVA with Post hoc test Fisher 'F'= 4.16; P=0.02) (Table 22). The mean UCVA (decimals) improved from 0.17±0.06 (baseline) to 0.39±0.19 (1 year post-procedure) in study eye and 0.18±0.09 (baseline) to 0.52±0.29 in fellow (second operated) eye respectively (Table 1, 2 and 3; Fig.4)

Studies conducted in the west, such as the one done by Caporossi *et al.* (2010)[29], demonstrated a statistically significant improvement in terms of Snellen lines at all follow-up visits upto two years after the procedure.In the Sienna CXL trial, conducted on paediatric patients, Caporossi *et al.* (2012)[40] observed a statistically significant improvement in the mean

UCVA. Studies conducted on the Indian population have shown comparable results, which are encouraging. Arora *et al* (2012)[41] demonstrated an improvement in mean UCVA at the end of one year. Thus, a statistically significant improvement in mean UCVA post- the C3R procedure has been reported uniformly across several studies.

With reference to improvement in BCVA, in the current study, following the C3R procedure, the mean BCVA showed a significant improvement, when compared to the preoperative mean BCVA, at the 6 month follow- up visit; this improvement was sustained during subsequent examinations at one year post- procedure, This was seen in all operated (study) eyes in the 3 groups (Groups A, B and C). There was no significant difference in the mean BCVA between the three groups at pre operative (baseline) and post- operatively at first and sixth month follow up and the first year follow up (Fig.4, Tables 4, 5 and 6).In Group A study eyes, the mean BCVA (decimals) improved from preoperative 0.71±0.20 to 0.83±0.19 at the final examination (one year postoperatively).In Group B, the mean BCVA (decimals) showed a statistically significant improvement from the preoperative (baseline) value (0.45±0.25) to that at one year follow-up (0.75±0.17) (one way ANOVA with post hoc test, Fisher 'F' =3.59; P value = 0.03) (Table 22).In group C, the mean BCVA improved from 0.52±0.26 (pre-operative) to 0.64±0.28 at final examination (one year

postoperatively) in study eye and 0.54±0.16 to 0.81±0.24 in the fellow eye, respectively (Fig.5)

A study by Caporossi *et al.* (2010)[40] demonstrated an improvement in mean BCVA at all the follow-up visits until two years from the procedure. Raiskup *et al.* (2008)[42], in their long- term study, showed an improvement in mean BCVA in terms of Log MAR value at the end of 6 years. Studies conducted in the Indian population had comparable results, Arora *et al.* (2012)[43] found an improvement in mean BCVA at the end of 1 one year. In another study by Agrawal *et al.* (2009)[44], an improvement in terms of Snellen lines was observed at the end of one year

Spherical equivalent was calculated as the sum of the spherical value (DS) and half of the cylindrical value (1/2DC).In the current study, the mean pre-operative SE value was found to show reduction in operated eyes in all groups (A, B, C) at end of 1 year follow up (Table 22).In group A study eye, there was a statistically significant improvement in SE in at one year post-procedure, when compared with that of the baseline (One way ANOVA with post hoc test Fisher 'F'=3.81; P value= 0.04) (Table 22) (Tables 10, 11 and 12; Fig 7). Agrawal *et al.* (2009)[44], in a study conducted in the Indian population, also observed a similar reduction in the values of both the sphere and the SE. Another study by Vinciguerra *et al.* (2012)[45] observed a 62% reduction in the spherical equivalent value, two years after the CXL

procedure. Thus, it appears that reduction of the value of spherical equivalent post-C3R occurs in both the western and Asian patients

In terms of Cylinder value, no statistically significant difference was noted among the three groups. The current study also compared the mean reduction of the cylinder value in operated eyes in all three groups (Fig 6). Pre operative mean cylinder values (diopters) were 1.75±1.7 in group A, 3.45±2.8 in group B and 2.85±1.3 in group C study eyes which reduced to 1.5±1 in group A, 2.65±1.8 in group B and 2.07±1.9 in group C by the end of 1 year follow up. In the un-operated fellow eye, the cylinder value actually increased at one year follow up from baseline of 1.8±1.3 to 2.00±0.21 in group A and from baseline of 2.7±2.08 to 2.85±2.00 in group B (Tables 7, 8 and 9). Studies by Caporossi *et al.* (2006)[26] and Saffarian L *et al.* (2010)[46] demonstrated a similar reduction in cylinder value, which might be indicative of gradual corneal flattening post-C3R.

The mean values of topographic indices, K1 (the steeper meridian), K2 (the flatter meridian) and the Kavg (average keratometry) over each of the follow-up visits at one month, 6 months and one year were observed in the present study

In this study, K1 (Steep K) and K2 (Flat K) showed a very gradual and a steady flattening, in comparison with the pre-operative mean values, in study eye at all the post-operative visits in groups A, B and C. The Kavg

values also showed a similar trend. In this current study, the pre operative mean K1 was 50.76±2.2, 52.34±4.4 and 51.64±4.5 (Tables 13, 14 and 15; Fig 8), mean K2 was 45.77±3.02, 46.39±3.3 and 45.64±1.9 (Tables 16, 17 and 18; Fig 9) and mean Average k was 48.26±2.5, 49.37±3.6 and 48.64±2.7 (Tables 19, 20 and 21; Fig 10) in groups A, B and C, respectively. Post-operatively, these values showed a gradual fall of mean K1 (49.24±2.1, 49.97±4.4 and 50.74±4.7), mean K2 (45.17±3.3, 45.75±3.8 and 44.98±2.06) and mean Average K (47.20±2.7, 47.86±4.0 and 47.86±2.7) in groups A, B and C, respectively, by the end of 1 year follow up (Tables 13-21, Figs.8-10).

In other studies conducted on the western population, a similar trend was observed. Witting Silva *et al.* (2008)[47] and Hersh *et al.* (2011)[48] observed a reduction in the value of Kmax at the end of their one-year study. Greenstein *et al.* (2013)[49] observed a flattening of the steeper meridian (Kmax) in patients with severe disease having K value more than 55 D.

A study conducted by Agrawal *et al.* (2009)[44] in the Indian population also observed similar results at the end of one year. These results were comparable to that of the present study. Caporossi *et al.* (2010)[27] studied the topographic findings and observed the reduction in the mean average K in a statistically significant manner over a period of two years. This reduction was gradual and statistically significant. Another long- term study with a

large sample size by Raiskup *et al.* (2008)[42] demonstrated similar results. Also, Kankaria *et al.* (2013)[50] noticed a transient worsening in the topographic indices in the early post-operative period. These indices stabilized on subsequent visits without any intervention. Thus, many studies in the literature have shown a stable or gradual reduction in the mean keratometric values after C3R procedure.

Thus, in the current study, all the visual and topographic indices observed over the period of one year after the procedure, showed a trend of either halting or partially reversing the disease process. The improvement was seen irrespective of the demographical factors, such as age and gender, and other pre-operative indices such as the average keratometry value.

SUMMARY

Corneal collagen cross- linking is a simple and very effective procedure to halt corneal ectasia. The objective of the current study was to evaluate the safety and efficacy of corneal collagen cross-linking with riboflavin, and to assess its role in halting the progression of keratoconus.

The outcome measures evaluated were uncorrected visual acuity (UCVA), best corrected visual acuity (BCVA), spherical equivalent (SE), cylinder (Dcyl) values along with Keratometric readings by corneal topography (Steep K, Flat K and Average K) and also to note any complications, if any.

The current investigation was a prospective interventional study on patients with keratoconus who presented a tertiary eye care hospital over a 15 month period (June 2018 to august 2019) and were followed up for 12 months thereafter.

Forty two eyes of 21 patients were included in this study (21 eyes were study eyes; 21 were fellow eyes). There were nine males (42.85%) and 12 females (57.14%). Mean age of the patients was 21.09±3.9 years (range 15 to 40 years). The patients who presented with progressive keratoconus unilaterally (4 patients) or bilaterally (17 patients) during the study period,

who satisfied the inclusion criteria and who provided consent for undergoing C3R, were enrolled in the study.

Among these 21 patients, Group A had four patients who presented with unilateral progressive keratoconus (19.04%), Group B had 10 patients with bilateral keratoconus with progression in one eye only (47.61%)and Group C had seven patients with bilateral progressive keratoconus (33.33%) at the time of presentation.Of this, Group A (four study eyes operated) and Group B (10 study eyes operated) underwent C3R procedure in one eye only.In Group C (seven patients), first one eye underwent the procedure (seven study eyes) and then, within a week, the other eye underwent the procedure (seven fellow eyes); thus, 14 eyes underwent C3R procedure in group C, and both eyes were followed- up simultaneously at each post-operative visit.

The mean UCVA (decimals) pre procedure in study eye was 0.212±0.075 in group A (n=4), 0.23±1.8 in Group B (n=10) and 0.17±0.06 in group C (n=7).In all three groups, there was a gradual improvement in mean UCVA by 6 months to 0.29±0.04 in group A, 0.34±0.26 in group B and 0.26±0.12 in group C. By the end of 1 year follow- up, the mean UCVA had increased (improved) to 0.33±0.01 in group A, 0.42±0.25 in group B and 0.39±0.19 in Group C, when compared to that of the pre- operative mean UCVA.

The mean BCVA (decimals) pre- procedure in study eyes was 0.71±0.20 in group A, 0.45±0.25 in Group B and 0.52±0.26 in group C.In all three groups, there was a gradual increase (improvement) in mean BCVA by 6 months to 0.71±0.20 in group A, 0.66±0.22 in group B and 0.60±0.24 in group C. By the end of 1 year follow up, mean BCVA had increased (improved) to 0.83±0.19 in group A, 0.75±0.17 in group B and 0.64±0.28 in Group C, when compared to the pre operative BCVA.

The baseline mean Dcyl value (diopters) was 1.75±1.7 in group A study eyes (n=4), which remained stable at the 6 month follow up (mean of 1.75±1.2) and by end of 1 year follow up, it showed a slight fall to a mean of 1.5±1.In Group B study eyes (n=10), mean baseline Dcyl value was 3.45±2.8, which reduced to 2.9±2.2 by 6 months and further dropped to mean of 2.65±1.8 by the end of 1 year.

Spherical equivalent (SE, diopters) in study eyes of all groups showed a decrease at 1 year from the baseline mean value. Group A study eye baseline mean (diopters) was 3.3±0.75, which showed a shift to 1.8±1.4 in 6 months and 1.5±1 in 1 year follow up. Group B study eye mean values (diopters) were 3.3±2.5 at baseline, decreasing to 2.7±2.3 by 6 months and 2.1±1.7 at 1- year follow- up. Group C study eyes showed baseline SE (diopters) of 4.21±2.17, 6 month mean value of 3.44±1.79 and 1 year value remained almost stable (mean of 3.17±2.2).

Mean keratometric (K1) value at base line in study eye Group A was 50.76±2.2, which decreased by end of 1 year to a mean value of 45.17±3.3; mean K2 at baseline was 45.77±3.02 which remained stable by the end of 1 year at 45.17±3.3 and mean Average K value at baseline was 48.26±2.5 which, by the end of 1 year follow- up, showed a slight fall to 47.20±2.7

In group B study eyes, the baseline K1 mean value was 52.34±4.4 which showed a fall of mean 49.97±4.4 by the end of 1 year follow up, K2 at baseline mean value was 46.39±3.3 which was nearly stable to a mean value of 45.75±3.8 by the end of 1 year follow up and mean Average K at base line was 49.37±3.6, which was 47.86±4.0 by 1 year follow up.

In group C, where both eyes underwent C3R procedure, mean K1 in study eye (the eye operated first) at baseline was 51.64±4.5, which by 1 year follow-up reduced to 50.74±4.7. The K2 mean value was 45.64±1.9 at baseline which was 44.98±2.06 by 1 year follow up and the Average K mean value was 48.64±2.7 at baseline which was reduced to 47.86±2.7 by 1 year follow up.

The fellow eye in group C, which also underwent the C3R procedure within one week after the study eye, showed mean baseline K1 of 50.43±4.3, which reduced to 49.63±4.4 in 1 year, mean K2at baseline of 45.13±2.4 which was reduced to 44.39±3.4 by 1 year, and a mean Average K baseline

value of 47.78±3.1, which showed a decrease to 46.97±3.4 by end of 1 year follow up.

In this study, eyes that showed reduction in BCVA value of more than 0.5 from the baseline, at the end of one year follow-up, were considered improved and those eyes which showed reduction of less than 0.5 D were considered stable.

In group A (N=4) all four study eyes (operated) showed improvement and among 4 fellow eyes (un-operated), four eyes were stable at 1 year follow up, when compared with that of the baseline BCVA (P=0.20).

In group B (N=10), nine study (operated) eyes showed improvement and one study eye had stable vision at one year post-procedure; among the fellow eyes (un-operated), four improved, two remained stable and four worsened during the period of follow up from baseline BCVA (P=0.28).

In group C (N=7) study eyes (eyes operated first), four eyes showed improvement and two eyes remained stable, while in fellow eyes (operated after a week) three eyes showed improvement and four eyes remained stable (P=0.52).

Improvement in vision in operated eyes (4 [Group A]+10 [Group B]+14 [Group C]=28) versus improvement in vision in unoperated eyes (4 [Group A]+10 [Group B]=14) was analyzed; the difference approached

statistical significance, suggesting that there was a halt of progression of keratoconus in the operated eyes in unilateral and bilateral keratoconus (χ^2=4.83 [df=2]; P=0.09)

None of the operated eyes in all three groups showed any complications during the procedure or throughout the follow up period (1 year).

This study found C3R to be an effective method for treating keratoconus, providing good outcome in terms of maintaining vision and topographic indices. These results were comparable to that of other studies so far conducted.

A small sample size and short follow-up period were limiting factors of the current study.

CONCLUSION

This current study aimed at assessing the safety and efficacy of corneal collagen cross linking (C3R) procedure in patients with progressive keratoconus at a tertiary eye care hospital in a specific setting; various parameters were followed-up for a period of one year, comparing these with the pre operative mean values and the following conclusions were made.

The uncorrected visual acuity and the best corrected visual acuity improved from the mean baseline values in all the operated eyes in all three groups (A, B and C); in the fellow unoperated eye (Groups A and B), the mean UCVA and BCVA were either stable or reduced by the end of one year follow up. This shows stability of vision after the C3R procedure.

The study also observed no statistically significant difference in pre and post operative cylinder value and spherical equivalent in all operated eyes, suggesting halt of disease progression, and fellow unoperated eyes showed either stable or increase in cylinder and spherical equivalent values by end of one year follow up.

All the topographic values (K1, K2 and Average K) showed a gradual flattening in all follow up visits in all operated eyes in all three groups when compared to that of the unoperated eyes, where there was either stable value or gradual steepening was noted by end of one year follow up.

All the visual and topographic indices observed over the period of one year after the procedure showed a trend of either halting or partially reversing the disease process in operated eyes, when compared to that of the fellow unoperated eyes.

Thus, corneal collagen cross-linking with riboflavin appears to be a simple, safe and an effective modality of treatment for progressive keratoconus, with good success rate and minimal incidence of complications. However, a study on a larger number of patients with longer follow-up is required for assessing the longevity of this procedure and its long- term side effects.

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Annexure 1-Informed consent form (Page 1)

JEH/R/CF-10/0

ஜோசப் கண் மருத்துவமனை

திருச்சிராப்பள்ளி -620 001

மருத்துவம் / அறுவை மருத்துவத்திற்கான ஒப்புதல்

உங்களுடைய கண்களில் உள்ள குறைகளும், அதற்குத் தேவைப்படும் மருத்துவம், அறுவை மருத்துவம் அல்லது சோதனை முறைகள் அனைத்தும் உங்களுக்கு விளங்குமாறு உங்களுக்கு விரிவாகச் சொல்லப்பட்டுள்ளது. உங்கள் கண் தொடர்பாக உங்களுக்கு சொல்லப்பட்ட செய்திகளையும், குறிப்பிடத்தக்க முக்கியமான சில மருத்துவ செய்திகளையும் எழுத்துப்பூர்வமாக உறுதிப்படுத்த இந்த ஒப்புதல் பெறப்படுகிறது உங்களுக்கு செய்யவிருக்கும் சோதனைகளுக்கு ஒப்புதல் கொடுக்கவோ அல்லது மறுக்கவோ ஏதுவாக இப்படிவம் விரிவான தகவல்களைத் தரும் வகையில் அமைக்கப்பட்டுள்ளது.

1. மருத்துவர் என் கண்களில் கீழ்க்கண்டவை இருப்பதாக விளக்கினார்.
2. என் கண்களுக்குத் தேவைப்படும் மருத்துவம் மேற்கொள்ள கீழ்க்கண்ட சோதனைகளை செய்ய வேண்டும் என்பதை நான் அறிவேன்.

   வலதுகண்:

   இடதுகண்:

3. மருத்துவம், அறுவைமருத்துவம் இவற்றால் பயன்கள் இருந்தாலும் ஒவ்வாமை, இரத்தக்கசிவு, இரத்த உறைவு, நோய்த்தொற்று, மருந்துகளின் பின்விளைவுகள், பார்வை இழப்பு, உடல் செயல்பாடுகள் இழப்பு, மிக அரிதாக உயிரிழப்பு, போன்ற அபாயகரமான விளைவுகள் உண்டு என்பதை நான் அறிவேன். என் கண்களுக்காக செய்யப்படும் சில சோதனைகளுக்கென்று குறிப்பிட்ட விளைவுகள் உள்ளன என்பதையும் நான் அறிகிறேன்.

4. இதுவரை விவாதிக்கப்படாத அல்லது எதிர்பாராத நிலைகள், பின் விளைவுகள் மருத்துவத்துறையில் ஏற்படலாம் என்பது எனக்குத் தெரியும். சோதனைகளை செய்து கொண்டிருக்கும் போதே மேற்கொண்டு வேறு சோதனைகள் தேவைப்படும் நிலை எதிர்பாராமல் வரலாம் என்பதையும் நான் அறிவேன். சோதனைகளுக்கும், மருத்துவத்திற்கும் உரிய முடிவுகளைப் பற்றி எனக்கு எவ்வித உத்தரவாதமும், வாக்குறுதியும் தரப்படவில்லை என்பதை நான் ஒப்புக்கொள்கிறேன்.

5. கீழ்க்கண்ட மாற்றுமுறைகள், அதன் பலன்கள், பின்விளைவுகள், அதை மேற்கொள்ளாவிட்டால் விளைவுகள் ஏற்படக்கூடிய ஆகியவை எனக்கு விளக்கப்பட்டது. எனக்கு விளக்கப்பட்ட செய்திகளும், இந்த தெளிவாக புரிகிறது ஒப்புதல் படிவத்திலுள்ள செய்திகளும் எனக்குத் தெளிவாக புரிகிறது. என் ஐயங்களைத் தெளிவுபடுத்திக் கொள்ள கேள்விகள் கேட்க வாய்ப்பு தரப்பட்டது. அவைகளுக்கு எனக்குத் திருப்தியான பதில்களும் கிடைத்தன.

6. மேற்சொல்லப்பட்ட சோதனைகளையும், மருத்துவத்தையும் என் மருத்துவர் அல்லது அவரது உதவியாளர், மருத்துவமனை ஊழியர்கள், பயிற்றுவிக்கப்பட்ட நபர்கள் உதவியுடன் பார்வையாளர்கள் முன்னிலையில் செய்வதற்கு, இப்படிவத்தைப் படித்துப் பார்த்து, மருத்துவர்களுடன் கலந்து பேசியபின் நானாக முன்வந்து என் ஒப்புதலைத் தருகிறேன்.

நோயாளி (அல்லது நோயாளிக்காக அங்கீகரிக்கப்பட்ட நபரின் கையொப்பம்)
இடது கை பெருவிரல் ரேகை.

சாட்சி 1_____

சாட்சி 2_____

_____

தேதி

JOSEPH EYE HOSPITAL

Tiruchirapalli 620001

General Consent for Medical and Surgical Procedures

You have been given information about your condition and the recommended surgical, medical or diagnostic procedure(s) to be used. This consent form is designed to provide a written confirmation of such discussions by recording some of the more significant medical information given to you. It is intended to make you better informed so that you may give or withhold your consent to the proposed procedure(s).

1. **Condition:** My ophthalmologist has explained to me that the following condition(s) exist in my case:

_____

_____

_____

2. **Proposed Procedure(s):** I understand that the procedure(s) proposed for evaluating and treating my condition is/are: _____

_____

_____ Right eye _____ Left eye _____

3. **Risks/Benefits of Proposed Procedure(s):**
   A. Just as there may be benefits to the procedure(s) proposed, I also understand that medical and surgical procedures involve risks. These risks include allergic reaction, bleeding, blood clots, infections, adverse side effects of drugs, blindness, and even loss of bodily function or life.
   B. I also realize that there are particular risks associated with the procedure(s) proposed for me and that these risks include, but are not limited to, those enumerated in the addendum.
4. **Complications; Unforeseen Conditions; Results:** I am aware that in the practice of medicine, other unexpected risks or complications not discussed may occur. I also understand that during the course of the proposed procedure(s) unforeseen conditions may be revealed requiring the performance of additional procedures, and I authorize such procedures to be performed. I further acknowledge that no guarantees or promises have been made to me concerning the results of any procedure or treatment.
5. **Acknowledgments:** The available alternatives, the potential benefits and risks of the proposed procedure(s), and the likely result without such treatment, have been explained to me. I understand what has been discussed with me as well as the contents of this consent form, and have been given the opportunity to ask questions and have received satisfactory answers.
6. **Consent to Procedure(s) and Treatment:** Having read this form and talked with the physicians, my signature below acknowledges that: I voluntarily give my authorization and consent to the performance of the procedure(s) described above including by my ophthalmologist and/or his/her associates assisted by hospital personnel and other trained persons as well as the presence of observers.

_____ _____

Patient (or person authorized to sign for patient) Date

_____ _____

Witness Date

Annexure 2- Study proforma

NAME -

MR NO –

AGE -

SEX -

ADDRESS –

CONTACT NO –

SYSTEMIC DISEASES-

EYE	RE	LE
Uncorrected Visual Acuity (UCVA)		
Best Corrected Visual Acuity (BCVA)		
AR		
CCT		
K1		
K2		
CIM		

DATE OF SURGERY -

OPERATED EYE -

PROCEDURE DONE -

SURGERY DONE BY –

		Follow up after 1 month	Follow up after 6 month	Follow up after 1 year
Vision	RE			
	LE			
RE	BCVA			
	AR			
LE	BCVA			
	AR			
K1				
K2				
CIM				

Annexure 3- Key to master chart

Abbreviations used in the master chart

Mrd no – Medical record number

M – Male patient

F – Female patient

RE – Right eye

LE – Left eye

UCVA- Uncorrected visual acuity

BCVA – Best corrected visual acuity

Dsph - Sphere (Diopters)

Dcyl – cylinder (Diopters)

SE – Spherical equivalent

K1- Keratometry reading 1

K2 – Keratometry reading 2

Aveg K – Average K

Annexure 4 – Master chart

Group A [Patient with unilateral keratoconus with affected eye C3R done during study period;Fellow eye Normal with no keratoconus] N=4

				PRE-OPERATIVE [Baseline]									1 MONTH								6 MONTH								1 YEAR								
Mrd no	Age	Sex	Eye		Pre UCVA	pre BCVA	Dsph	Dcyl	Axis	SE	K1	K2	AVG K	UCVA	BCVA	Dsph	Dcyl	Axis	SE	K1	K2	AVG K	UCVA	BCVA	Dsph	Dcyl	Axis	SE	K1	K2	AVG K	UCVA	BCVA	Dsph	Dcyl	Axis	SE	K1	K2	AVG K	COMPLICATION
1326213	18	F	Operated eye	LE	0.1	0.67	0.5	-4	150	-2.5	47.72	41.83	44.77	0.25	0.67	0	-5.5	150	-2.75	48.55	40.86	44.7	0.25	0.67	0	-3	140	-1.5	46.22	40.68	43.45	0.25	1	0	-2	140	-1	46.14	40.69	43.41	NIL
1327383	25	M	Operated eye	RE	0.25	1	-2	-2	50	-3	52.05	48.45	50.25	0.33	1	-2	-2	50	-3	52.05	48.45	50.25	0.33	1	0	-2	60	-1	51.62	48.24	49.93	0.33	1	0	-2	40	-1	50.98	48.22	49.6	NIL
1228247	20	M	Operated eye	RE	0.25	0.5	-3.5	-1	170	-4	50.63	45	47.81	0.25	0.25	-3	-1	160	-3.5	50	44.93	47.46	0.33	0.67	0	-2	160	-1	49.78	44.82	47.3	0.5	0.67	0	-2	180	-1	49.54	44.76	47.15	NIL
1319341	25	F	Operated eye	LE	0.25	0.5	-4	0	0	-4	52.67	47.8	50.23	0.25	0.5	-4	0	0	-4	51.43	47.3	49.36	0.25	0.5	-4	0	0	-4	51.38	47.22	49.3	0.25	0.67	-3	0	0	-3	50.32	47.02	48.67	NIL
FELLOW EYE																																								
1326213	18	F	fellow eye	RE	0.25	0.67	-1	-2	180	-2	43.81	42.61	43.21	0.25	0.5	-1	-2	180	-2	43.92	42.52	43.22	0.25	0.5	-2	-2	180	-3	43.98	42.53	43.25	0.25	0.5	-2	-2	180	-3	43.98	42.57	43.27	NIL
1327383	25	M	fellow eye	LE	0.33	1	0	-2.5	100	-1.25	46.64	41.82	44.23	0.67	1	0	-3	100	-1.5	46.62	43.88	45.25	0.67	1	0	-3	100	-1.5	45.82	43.98	44.9	0.67	1	0	-3	100	-1.5	45.96	43.94	44.94	NIL
1228247	20	M	fellow eye	LE	0.1	1	-3.25	0	0	-3.35	44.55	43.52	44.03	0.1	0.67	-4	0	0	-4	45.66	43.72	44.69	0.1	0.67	-4	0	0	-4	45.72	43.24	43.76	0.1	0.5	-4	-1	20	-4.5	44.18	43.22	43.7	NIL
1319341	25	F	fellow eye	RE	0.1	0.67	0	-3	20	-1.5	48.33	45.91	47.12	0.1	0.67	0	-3	20	-1.5	48.19	45.92	47.05	0.1	1	0	-2	20	-1	48.58	45.92	47.25	0.1	0.67	0	-2	20	-1	48.54	45.91	47.22	NIL

Group B [Patient with Bilateral keratoconus with one eye C3R done and the fellow eye stable during study period] N=10

				PRE-OPERATIVE [Baseline]									1 MONTH								6 MONTH								1 YEAR								
Mrd no	Age	Sex	Eye		Pre UCVA	pre BCVA	Dsph	Dcyl	Axis	SE	K1	K2	AVG K	UCVA	BCVA	Dsph	Dcyl	Axis	SE	K1	K2	AVG K	UCVA	BCVA	Dsph	Dcyl	Axis	SE	K1	K2	AVG K	UCVA	BCVA	Dsph	Dcyl	Axis	SE	K1	K2	AVG K	COMPLICATION
1180150	22	M	perated ey	LE	0.1	0.5	0	-3	160	-1.5	49.41	45.41	47.41	0.1	0.5	0	-3	160	-1.5	49.45	45	47.22	0.1	0.67	0	-4	150	-2	48.92	45.02	46.97	0.1	0.67	-0.25	-4	150	-2.5	48.21	45	46.6	NIL
1350245	25	F	perated ey	RE	0.1	0.17	-1.25	-6	10	-4.25	51.76	44.82	48.29	0.17	0.67	-1	-6	10	-4	50.72	44.87	47.8	0.17	0.67	-1	-8	10	-5	50.43	44.56	47.49	0.17	0.67	-1	-6	10	-4	49.88	44.12	47	NIL
1247005	23	M	perated ey	LE	0.33	0.5	-1	-4	140	-3	50.22	45.22	47.72	0.33	0.5	-1	-3	140	-2.5	50.1	44.54	47.32	0.5	0.67	0	-2	90	-1	49.97	44.1	47.03	0.5	0.67	0	-2	90	-1	49.21	43.98	46.59	NIL
1323013	23	F	perated ey	LE	0.1	0.17	-6	-6	140	-9	50.72	44.72	47.72	0.1	0.25	-6	-6	150	-9	49.94	44.65	47.29	0.1	0.25	-4	-3	180	-5.5	48.45	44.23	46.34	0.17	0.67	0	-4	140	-2	48.08	44.19	46.13	NIL
1214156	15	M	perated ey	RE	0.33	0.67	0	-2	180	-1	57.18	43.92	50.55	0.5	0.67	0	-2	180	-1	56.32	43.21	49.76	0.5	0.67	-0.5	-1	150	-1	52.05	42.78	47.41	0.5	1	0.5	-1	160	-1	51.56	42.5	47.03	NIL
1335869	18	F	perated ey	LE	0.1	0.25	0	-4	180	-2	48.45	44.48	46.46	0.17	0.33	0	-4	180	-2	48.29	44.46	46.37	0.25	0.5	0	-3	170	-1.5	47.66	44.23	45.94	0.5	0.67	0	-2	160	-1	47	44.2	45.6	NIL
1128678	27	F	perated ey	RE	0.17	0.5	-3	-1.5	180	-3.75	49.85	44.67	47.26	0.25	0.33	-3	-1	170	-3.5	50.02	44.82	47.42	0.25	1	-2	-1	50	-2.5	44.28	43.24	47.18	0.5	1	-2	-1	50	-2.5	44.24	43	43.62	NIL
1343542	18	M	perated ey	LE	0.1	0.33	-0.5	-3	120	-2	61.57	54.51	58.04	0.17	0.5	0	-3	120	-1.5	60.62	55.47	57.74	0.25	0.5	0	-3	90	-1.5	60.09	55.12	57.6	0.33	0.5	0	-2.5	90	-1.25	59.67	55	57.33	NIL
1348994	17	F	perated ey	RE	0.33	0.5	-6	-5	180	-6.25	56.28	50.26	53.27	0.25	0.5	-6	-5	180	-8.5	56.26	50.27	53.26	0.33	0.67	-5	-4	140	-7	55.52	50.24	52.88	0.5	0.67	-4	-4	140	-6	54.82	50.22	52.52	NIL
1345695	20	M	perated ey	RE	0.67	1	-1	0	0	-1	48.04	45.93	46.98	0.67	1	-1	0	0	-1	48.04	45.93	46.98	1	1	0	0	0	0	47.32	45.64	46.48	1	1	0	0	0	0	47.04	45.34	46.19	NIL
FELLOW EYE																																								
1180150	22	M	fellow eye	RE	0.1	0.5	0	-3	20	-1.5	49.14	45,41	47.21	0.1	0.5	0	-3	20	-1.5	49.22	47.01	48.1	0.1	0.5	0	-4	20	-2	49.24	47.12	48.1	0.1	0.67	0	-4	20	-2	50.12	47.54	48.1	NIL
1350245	25	F	fellow eye	LE	0.17	0.67	-1	-6	180	-4	46.84	42.32	44.58	0.25	0.67	-1	-6	160	-4	46.93	42.28	44.6	0.25	0.67	-1	-6	160	-4	46.92	42.24	44.58	0.25	0.67	-1	-6.5	160	-4.25	47	42.87	44.58	NIL
1247005	23	M	fellow eye	RE	0.25	0.25	0	-5	140	-2.5	44.43	40.24	42.33	0.25	0.25	0	-5	140	-2.5	44.44	40.32	42.32	0.25	0.25	0	-2.5	140	-1.25	44.62	40.92	42.77	0.25	0.5	0	-2.5	120	-1.25	44.78	41.23	42.53	NIL
1323013	23	F	fellow eye	RE	0.1	0.17	-4	-4	30	-6	50.22	44.02	47.17	0.25	0.33	-4	-4	40	-6	50.22	44.02	47.17	0.25	0.33	-3	-4	60	-5	50.26	44.04	47.15	0.17	-0.5	-3	-4	90	-5	50.54	44.65	47.13	NIL
1214156	15	M	fellow eye	LE	0.5	0.67	0	-2.25	180	1.12	49.75	43.18	46.46	0.5	0.67	0	-2.25	180	-1.12	50.32	43.23	46.7	0.5	0.67	0	-3	180	-1.5	50.44	44.88	46.88	0.5	0.67	0	-4	180	-2	56.33	45.02	50.52	NIL
1335869	18	F	fellow eye	RE	0.1	0.67	-3.5	0	0	-3.5	46.26	45.52	45.89	0.1	0.67	-3.5	0	0	-3.5	46.24	45.53	45.88	0.1	1	-3.75	0	0	-3.75	46.32	45.5	45.92	0.1	0.67	-4	0	0	-4	47.13	45.78	46.45	NIL
1128678	27	F	fellow eye	LE	0.1	0.17	0	-4	90	-2	46.52	43.19	44.85	0.1	0.17	0	-4	90	-2	46.64	43.34	44.99	0.1	0.17	-1	-3.5	90	-2.75	46.62	43.42	45.02	0.1	0.25	-1	-3.5	90	-4.25	46.66	43.92	47.18	NIL
1343542	18	M	fellow eye	RE	0.5	0.67	-1	-0.5	90	-1.25	46.22	44.02	45.12	0.5	0.67	-1	-0.5	90	-1.25	46.42	44.21	45.31	0.5	0.5	-1	-1	90	-1.5	46.42	44.21	45.31	0.5	1	-1	-1	90	-1.5	47.07	44.94	45.15	NIL
1348994	17	F	fellow eye	LE	0.25	0.67	0	-3	90	-1.5	46.44	43.64	45.05	0.25	0.67	0	-3	90	-1.5	46.28	43.72	45	0.25	0.67	-0.5	-3	90	-2	46.38	44.01	45.19	0.25	0.5	-1	-3	90	-2.5	46.87	44.56	45.07	NIL
1345695	20	M	fellow eye	LE	0.67	1	-1	0	0	-1	46.8	44.42	45.61	0.67	1	-1	0	0	-1	46.44	44.48	45.46	0.67	0.5	-1.5	0	0	-1.5	46.52	44.58	45.55	0.67	0.5	-2	0	0	-2	47.02	44.98	45.55	NIL

Group C [Patient with Bilateral progressive keratoconus at presentation with both eye C3R done within the study period with severe eye operated first followed by the fellow eye operated 1 week later for all patients in thi

Mrd no	Age	Sex	Eye	PRE-OPERATIVE [Baseline]									1 MONTH								6 MONTH								1 YEAR									
					Pre UCVA	pre BCVA	Dsph	Dcyl	Axis	SE	K1	K2	AVG K	UCVA	BCVA	Dsph	Dcyl	Axis	SE	K1	K2	AVG K	UCVA	BCVA	Dsph	Dcyl	Axis	SE	K1	K2	AVG K	UCVA	BCVA	Dsph	Dcyl	Axis	SE	K1	K2	AVG K	COMPLICATION
1192558	24	F	Operated eye	LE	0.17	0.5	-1	-4	90	-3	50.22	45.22	47.72	0.33	0.5	-1	-3	140	-2.5	49.22	45.38	47.3	0.25	0.67	-1	-3	120	-4	49	44.82	46.91	0.33	0.67	-1	-2	140	-2	49.23	44.02	46.62	NIL
1239441	19	M	Operated eye	RE	0.17	0.67	-3	-1	20	-3.5	47.37	45.57	46.47	0.17	0.67	-1.75	-1	20	-2.25	47.92	45.51	46.71	0.17	0.67	-1.75	-0.75	20	-2.1	47.77	45.51	46.64	0.25	1	-1.5	0	0	-1.5	46.96	45.22	46.09	NIL
1314383	17	M	Operated eye	RE	0.1	0.5	-6	-4	80	-8	51.47	47.36	49.41	0.1	0.5	-4.5	-4	90	-6.5	50.38	46.56	48.47	0.25	0.33	-4.5	-3	90	-6	50.6	46.23	48.41	0.25	0.33	-4	-3	90	-5.5	49.99	46.12	48.05	NIL
1334076	23	F	Operated eye	LE	0.1	0.17	-4	-4.5	120	-6.25	59.43	45.22	52.32	0.1	0.25	-4	-6	120	-7	59.74	45.02	52.38	0.1	0.25	-3	-4	140	-5	60.02	44.67	52.34	0.25	0.33	-4	-6	140	-7	59.84	44.05	51.94	NIL
1352052	20	F	Operated eye	RE	0.25	1	-1	-2	90	-2	46.75	44.49	45.62	0.25	1	-1	-2	50	-2	46.23	44.23	45.23	0.25	1	0	-2	50	-1	45.88	44.92	45.4	0.33	0.5	0	-1.5	50	-0.75	45.92	44.84	45.38	NIL
1258238	20	F	Operated eye	LE	0.17	0.5	-1.5	-2	160	-2.5	50.56	42.86	46.71	0.17	0.5	-1.5	-1	150	-2.5	50.34	42.92	46.63	0.5	0.67	-1	-1	170	-2	49.5	42.01	45.75	0.67	0.67	-1	-1	150	-2	49.22	42.01	45.61	NIL
1088399	27	F	Operated eye	RE	0.25	0.33	-3	-2.5	120	-4.25	55.69	48.77	52.23	0.25	0.5	-3	-2	120	-4	55.7	48	51.85	0.33	0.67	-3	-2	70	-4	54.67	48.72	51.69	0.67	1	-3	-1	70	-3.5	54.03	48.66	51.34	NIL
FELLOW EYE																																								
1192558	24	F	fellow eye	RE	0.1	0.67	-4	-4	40	-6	46.58	43.58	45.08	0.25	0.67	-2.5	-3	40	-4	45.62	41.92	43.77	0.25	0.67	-2.5	-3	40	-4	45.8	41.55	43.67	0.67	1	-2	-3	40	-3.5	45.34	41.23	43.28	NIL
1239441	19	M	fellow eye	LE	0.1	0.67	-3	0	0	-3	58.62	47.61	53.11	0.1	1	-3.5	0	0	-3.5	58.45	47.61	53.03	0.67	1	-2	-1	20	-2.5	58.7	47.22	52.92	0.67	1	-2	-1	20	-2.5	57.95	47.28	52.61	NIL
1314383	17	M	fellow eye	LE	0.33	0.67	-0.5	-3	170	-2	48.22	42.73	45.47	0.33	0.67	0	-3	180	-1.5	48.65	42.12	45.38	0.5	1	-1	-3	180	-2.5	47.62	42.16	44.89	1	1	0	-1	10	-0.5	47.85	42.22	45	NIL
1334076	23	F	fellow eye	RE	0.25	0.33	-2	-4.5	50	-4.25	50.25	45.37	47.81	0.17	0.5	-2	-4.5	50	-4.25	49.85	45.15	47.5	0.25	0.5	-2	-4	20	-4	49.5	44.85	47.17	0.5	1	-2.25	-1	90	-2.75	49.23	44.5	46.86	NIL
1352052	20	F	fellow eye	LE	0.1	0.33	-5	-1.5	140	-5.6	49.52	48.14	48.83	0.1	0.5	-4.5	-1	90	-5	49.45	47.88	48.66	0.17	0.5	-4.5	0	0	-4.5	48.8	47	47.9	0.17	0.5	-4	-1	90	-4.5	48.9	48.25	48.57	NIL
1258238	20	F	fellow eye	RE	0.25	0.67	-1	-2	30	-2	46.45	41.87	44.16	0.5	0.67	0	-2	40	-1	46.55	41.64	44.09	0.5	0.67	0	-2	30	-1	45.68	41.2	43.44	0.5	0.67	0	-4	30	-2	45.55	41.02	43.28	NIL
1088399	27	F	fellow eye	LE	0.17	0.5	-3	-4	130	-5	53.4	46.67	50.03	0.17	0.5	-3	-4	180	-5	53.4	46.67	50.03	0.17	0.5	-3	-2	180	-4	53	46.56	49.78	0.17	0.5	-2	-2	180	-3	52.64	46.23	49.23	NIL