Topographical corneal changes in keratoconus patients treated with collagen cross linking: A before and after intervention study with one year follow up

Dr. Kalpana Meena[1], Dr. J.K. Chouhan[2], Dr. Pankaj Sharma[3], Dr. Rajesh Goyal[4§], Dr. Laxman Singh Dhakad[5]

[1,5]3rdYear Resident, Department of Ophthalmology, SMS Medical College, Jaipur (Rajasthan) India
[2,3]Professor, Department of Ophthalmology, SMS Medical College, Jaipur (Rajasthan) India
[4]Assistant Professor, Department of Ophthalmology, SMS Medical College, Jaipur (Rajasthan) India
§Corresponding author's Email: meenadrkalpana@gmail.com

Abstract— *Keratoconus is a progressive asymmetrical, bilateral, non-inflammatory corneal ectasia casing refractive errors. Various techniques are used to manage these cases. Corneal collagen cross linking (accelerated method) is one of such technique. A hospital based follow up study was conducted on 30 Keratoconus patients to find out the effect of corneal collagen cross linking (accelerated method) on refractive variables of Keratoconus patients. After this procedure, there was improvement in Best Corrected Visual Acuity 0.382, decrease in Cylindrical Refractive Power at 0.73%, decrease in Spherical Refractive Power at 19.32%, decrease in Spherical Equivalent at -6.15%, decrease KMAX of 0.712%, decline Mean Irregularity of 9.09%, Corneal thickness (Thinnest Point) decreased by 3.48%, Anterior Best Fitted Sphere Values decreased by 1.49% and Posterior Best Fitted Sphere decreased by 1.16%. It can be concluded from this present study that there is a significant improvement in topographic corneal changes and refractive results in patients with corneal ectasia after C3R. These results can illustrate the efficacy and usage of CXL for keratoconus among Indian patients. However, more studies and clinical trials are required to establish definite conclusions on the efficacy of C3R.*

Keywords: Keratoconus, Corneal Changes, Collagen Cross Linking.

I. INTRODUCTION

Keratoconus is a progressive asymmetrical, bilateral, non-inflammatory corneal ectasia which is characterized by corneal thinning protrusion of central cornea leading to decreased vision and irregular astigmatism. Keratoconic eyes have altered corneal biomechanical profile and appear to be more elastic and less rigid than normal eyes. Its incidence is 54 in 100000.[1] It is aggravated by puberty, pregnancy, vernal kerato-conjunctivitis and lid rubbing.

Corneal cross linking is a recently introduced treatment for addressing progressive keratoconus. It is a minimally invasive procedure and the only option that halts or slows the progression of disease. Riboflavin and ultraviolet-A rays[2,3] induce crosslinking through photopolymerization of collagen mediated by reactive oxygen species. These induce generation of stiffer collagen fibrils and a rearrangement of corneal lamellae within the matrix and thus increase corneal biomechanical rigidity and biomechanical resistance by 300 percent.

Therefore, C3R could potentially reduce the need for corneal grafting in patients with keratoconus which occurs generally in young population.

In India, very few studies have been done on collagen cross linking and its long-term outcomes. It achieves a result not so far achieved by any other modality of treatment.[4] Keratoplasty is often the only

choice in many patients. The problem with treatment like keratoplasty for keratoconus in a country like India are compounded by lack of adequate tissue availability thus cross linking helps in various ways; it may improve vision, helps regression, stabilize future progression and thus probably may delay or avoid keratoplasty in a given patient. Therefore, any procedure that may improve the quality of life in a given disease deserves a closer look.

This present study was conducted with the aim to evaluate long term topographical corneal and refractive changes before treatment and after one year of follow up of patients treated with collagen cross linking.

II. METHODOLOGY

A hospital based follow up study was conducted on 30 patients who underwent corneal collagen cross linking (accelerated method) at department of Opthalmology, SMS Medical college, Jaipur (Rajasthan) India in year 2017

A sample size of 30 gave power of 80% at alpha error 5% to verify the expected difference in mean pre and post-operative spherical refractive error changes(D) 0.32 and standard deviation 0.44.[5] Hence for this study purpose 30 eyes were taken.

For selection of patients, early to moderate keratoconus (grade 1to3 according to Amsler – Krumeich classification) eye patients with clear cornea & corneal ectasia and corneal thickness >/= 400 micron at thinnest point., fulfilling Rabinowitz criteria i.e. central corneal power >47.2 D, inferior superior dioptric asymmetry > 1.2D and skewed radial axis >21degrees were included for study. Out of these cases, cases with corneal hydrops /scaring, sever dry eye, concurrent corneal infection and with previous corneal surgery were excluded. Patients with pregnancy and other diseases were also excluded from this study. Finaly 30 eligible cases were included for this study.

After explaining the study, surgical procedures, and possible complications, an informed consent was obtained and patients were planned for procedure after routine investigations.

- Best Corrected Visual Acuity (BCVA)
- Automated refraction
- Retinoscopic examination.
- Slit lamp examination
- Corneal Topography using scheimpflug imaging system

2.1 Surgical Procedure

All 30 surgeries were performed by the same experienced surgeon under topical anaesthesia using proparacaine 0.5% eye drop. All patients were instilled proparacain 0.5% and xylocaine 4% eye drops every 5 minute for 30 minutes. Central 7mm corneal area was measured using corneal trephine and marked, Corneal epithelium was removed with the help of a hockey stick. Isotonic 0.25% Riboflavin dye was instilled every 3 minutes for 30 minutes. It was followed by exposure to UV-A light (370nm, 30mw/cm^2) for 3 minutes. BCL was applied, pad and patch was done. Oral painkiller was prescribed and patient was shifted to ward.

Topographic corneal changes will be measured by schiempflug imaging system. It provides highly accurate direct anterior and posterior elevation, corneal volume, and pachymetry measurement values of cornea. It allows documentation of an obliquely tilted object with maximally possible depth of focus and

minimum image distortion under given conditions. The principle used here is, when an oblique tangent is extended from a lens plane, they meet at a line through which Plane of focus (POF) also passes, with this condition a planer subject that is not parallel to image plane can be completely in focus. Measurements with Schiempflug imaging system are operator independent and repeatable.

Corneal collagen cross linking is a procedure to strengthen the cornea by formation of inter and intra-fibrilar covalent bonds in collagen fibres of corneal stroma with the help of photosensitizer Riboflavin and UV-A rays.

2.2 Post-Operative Care

Pad & patch was removed after 4 hours & the following topical medication was started.

1. Moxifloxacin 0.5% e/d qid
2. Loteprednolol+ tobramycin e/d qid
3. Carboxymethycellulose 0.5% e/d 2 hrly

All drops were given for a month and tapered gradually during following weeks. BCL was removed 5 days after the procedure.

2.3 Follow up

Follow up examination was done at one year after surgery. All the examinations were performed by a single observer to avoid bias, both pre and postoperatively. During follow up, the patients were assessed for:

- Postoperative complications of surgery (patients with postoperative complications were excluded from the study).
- BCVA, SE
- Scheimpflug imaging [Pentacam® (Kmax, corneal thickness(thinnest) , irregularity(mm), best fitted sphere (anterior and posterior)]

2.4 Statistical analysis

Significance of difference in means of various quantitative variables were inferred by unpaired 't' test. P value of less than 0.05 was considered statistically significant.

III. RESULTS

Out of a group of 30 patients, 21 (70%) are male and 9 (30%) are female. Maximum age among the patients was 26 years whereas minimum age was 12 years with the mean age was 18.8± 4.10. (Table 1)

In this group, 56.66% patients had their right eye affected whereas 43.44% had keratoconus in their left eye. (Table 1)

Table 1
Characteristic of study Population

S. No.	Characteristic		Number	Percentage (%)
1	**Sex**	**Male**	21	70
		Female	9	30
2	**Side of Eye**	**Left Eye**	13	43.33
		Right Eye	17	56.66

Age: Age range 12 years to 26 years with mean age 18.80±4.10 years

Mean improvement in Best Corrected Visual Acuity after this procedure is 0.382. There was no significant effect on best corrected visual acuity with *F* (0.8254) and p value >0.05 as per the regression analysis. (Table 2)

Mean decrease in Cylindrical Refractive Power after this procedure was seen at 0.73%. There was a significant effect on Cylindrical Refractive Power with *F*=56.50, p value < 0.01 and t-stat=7.51. (Table 2)

Mean decrease in Spherical Refractive Power after this procedure was seen at 19.32%, which was not significant on Sphere with *4.93*, p value > 0.05 and t-stat=2.22. (Table 2)

Mean decrease in Spherical Equivalent after this procedure was seen at -6.15%. There was a **significant effect** on SE with *F*=7.48, p value < 0.05 and t-stat=2.73. (Table 2)

Mean KMAX witnessed a decrease of 0.712% after C3R among these patients. There was a **significant effect** on KMAX with *F*=323.39, p value < 0.001 and t-stat=17.98. (Table 2)

Change in Mean Irregularity among the patients after the procedure saw a decline of 9.09%. Statistical test showed a **significant effect** on Irregularity with *F*=31.31, p value < 0.001 and t-stat=5.59. (Table 2)

Corneal thickness (Thinnest Point) decreased by 3.48% in these patient after this procedure. It was found a **significant effect** on CT with *F*=266.68, p value < 0.001 and t-stat=16.33. (Table 2)

Anterior Best Fitted Sphere Values decreased by 1.49% in these patient after this procedure. It was found a **significant effect** on ANTR.BFS with *F*=76.54, p value < 0.001 and t-stat=8.74. (Table 2)

Posterior Best Fitted Sphere decreased by 1.16% in these patient after this procedure. Statistical test demonstrated a **significant effect** on ANTR.BFS with *F*=216.18, p value < 0.001 and t-stat=14.70. (Table 2)

Table 2
Comparison of Refractive Variables before and after Collagen cross linking procedure

S. No.	Refractive Variables	Pre-operative (Mean ± SD)	1 year after Surgery (Mean ± SD)	P Value LS
1	**BCVA**	-0.866±0.26	-0.4841.± 1.2	0.370 NS
2	**Cylindrical Refractive Power**	3.342± 1.25	2.958± 1.20	0.035 **S**
3	**Spherical Refractive Power**	1.608 ± 0.95	1.598 ± 0.95	0.056 NS
4	**Spherical Equivalent**	3.279± 1.11	3.078 ± 1.22	0.010 **S**
5	**KMAX**	54.908 ± 6.94	54.517 ± 6.54	<0.001 **S**
6	**Irregularity**	0.033 ± 0.02	0.030 ± 0.02	<0.001 **S**
7	**Corneal thickness (Thinnest Point)**	454.252 ± 29.85	438.4 ± 31.56	<0.001 **S**
8	**Anterior Best Fitted Sphere Values**	7.312 ± 0.32	7.203 ± 0.40	<0.001 **S**
9	**Posterior Best Fitted Sphere**	6.012 ± 0.26	5.942 ± 0.28	<0.001 **S**

IV. DISCUSSION

In this study, 30 patients were studied for topographic corneal changes after one year at upgraded department of Ophthalmology, SMS Hospital.

In a study[3] conducted on 23 eyes with moderate or advanced progressive keratoconus, showed mean preoperative progression of keratometry (KMAX) by 1.42D in 525 eyes. The study also showed reduction in spherical equivalent by 1.14D.

In an animal study[6], showed a significant increase in corneal rigidity of porcine and rabbit corneas after corneal cross-linking. Studies on humans with keratoconus have demonstrated satisfactory short-term and long-term findings with substantial topographic and refractive improvement following treatment. A considerable decline in topographic parameters such as keratometry, apical gradient curvature, inferior-superior index, cone area, and corneal aberrations after C3R has been reported.

Another study[5] showed changes in corneal thickness one year after C3R for keratoconus and corneal ectasia. Study demonstrated more topographic flattening in eyes with centrally located cones compared with that of the peripherally located cones 1 year after C3R treatment, whereas differences among cone groups were not found statistically significant with respect to change in visual acuity.

A study[7] reported that the mean baseline corneal pachymetry was 460.68 ± 46.59 μm (range: 400 to 576 μm). One year postoperatively, the mean corneal thickness decreased significantly to 445.07 ± 41.57 μm (range: 395 to 570 μm) ($P< 0.05$). Their results are similar to this study.

Similar to previous studies our study showed that the mean baseline corneal pachymetry was 452.17 ± 30 μm. One year postoperatively, the mean corneal thickness decreased significantly to 438 ± 32 μm ($P< 0.001$). This decrease in corneal pachymetry may be attributed to the fact corneal epithelium is removed during the procedure.

In 2008, Raiskup-Wolf *et al*[8] described what remains the largest published series comprising 241 eyes followed in Dresden for up to six years after cross-linking. This uncontrolled, retrospective study confirmed earlier findings with statistically significant improvements in astigmatism, best-corrected visual acuity (BCVA), and maximum simulated keratometry values (Kmax) at 12 months. Flattening was observed in 54% of eyes with a mean change in Kmax of -1.91 D ($P< 0.01$). The effects of cross-linking were maintained over the duration of follow-up with progression of the disease documented in only two patients (which responded to retreatment). Subsequent published reports from several other centers have described similar results.

In present study mean preoperative KMAX was 54.098 which reduced to 54.517, therefore similar to previous studies witnessed a decrease of 0.712% after C3R among the patients. There was a very significant effect on KMAX with F=323.39, p value < 0.001 and t-stat=17.98.

A study [9] found that progression of keratoconus stopped in all patients. There was a decrease in Kmax by more than 2D. SE decreased from -3.27±4.08D to -2.68±3.02. after the procedure no eyes lost lines of BSCVA, 12 eyes maintained BSCVA, and rest gained two lines of BSCVA.

Vinciguerra et al[10] in 40 eyes of 40 pediatric patients with progressive keratoconus found a significant improvement in uncorrected visual acuity (UCVA) and BCVA with a statistically significant reduction in mean spherical equivalent and a flattening effect of C3R on the Keratoconic cornea.

Shetty et al(2014)[11] showed that there was an improvement in the mean postoperative uncorrected distant visual acuity (from 0.76 ± 0.26 to 0.61 ± 0.25; $P = 0.005$), mean corrected distant visual acuity (from 0.24 ± 0.19 to 0.12 ± 0.12; $P < 0.001$), mean spherical refraction (from −3.04 DS ± 3.60 to −2.38 DS ± 3.37; $P = 0.28$), mean cylinder (from −3.63 DC ± 1.82 to −2.80 DC ± 1.48; $P = 0.008$), and spherical equivalent (from −4.70 D ± 3.86 to −3.75 D ± 3.49; $P = 0.15$).

A study[12] showed that after 1 year of treatment, both treatment groups had a significant improvement in UCVA (accelerated CXL, $p < 0.001$; conventional CXL, $p < 0.001$) and BCVA (accelerated CXL, $p < 0.021$; conventional CXL, $p < 0.022$). The magnitude of improvement was similar in both groups without any statistical significance ($p > 0.430$). Spherical equivalent also decreased significantly in both groups ($p < 0.026$), with no inter-group difference ($p = 0.554$). Postoperatively, maximum keratometry flattened by 1.6 diopters ($p < 0.023$) and minimum keratometry flattened by 2 diopters in the conventional CXL group ($p < 0.047$). The corresponding values in accelerated CXL group were 0.47 diopters ($p = 0.471$) and 0.19 diopters ($p = 0.120$).

Similarly in present study Mean BSCVA was -0.866±0.261 preoperatively which improved to -0.484± 1.203, therefore showed mean improvement 0.382 after this procedure. Mean decrease in Spherical Equivalent for the patient group after this procedure was seen at -6.15%. There was a significant effect on Cylindrical Refractive Power with F=7.48, p value < 0.05 and t-stat=2.73.

In present study, like above mentioned studies, showed that C3R with riboflavin is effective in arresting the progression of keratoconus. For example, it showed that mean of preoperative posterior best-fit sphere (BFS) was 6.022 ±0.25mm before procedure and that it improved to 5.942 ± 0.28mm after procedure making the difference significant. . Anterior Best Fitted Sphere Values decreased by 1.49% in the post-operative group. We found a significant effect on ANTR.BFS with F=76.54, p value < 0.001 and t-stat=8.74. Change in Mean Irregularity among the patients after the procedure saw a decline of 9.09%. Statistical test showed a significant effect on Irregularity with F=31.31, p value < 0.001 and t-stat=5.59.

Results from a study by Coscunseven et all[13] confirmed Wollensack et all's study the group treated with collagen cross linking, it showed a similar mean decrease in spherical equivalent(SE) of 1.03 ±2.22D(5.25D to 3.75D), decrease in cylinder by 1.04 ±1.44D(-2.00Dto 4.00D and decrease in Kmax by 1.57 ± 1.14D (0.00 to3.90D). in the Conseven et all study the non-treated group showed progression of all corneal parameters under study.

Present study showed similar results in mean spherical refractive error from 1.608 to 1.598 with p value of 0.34 and t stat 2.22. Also, Mean decrease in Cylindrical Refractive Power for the patient group after this procedure was seen at 0.73%. There was a very significant effect on Cylindrical Refractive Power with F=56.50, p value < 0.001 and t-stat=7.51.

Mean decrease in Spherical Equivalent for the patient group after this procedure was seen at -6.15%. There was a significant effect on spherical equivalent. It changed from mean SE 3.279±1.11 to 3.078±1.22 with F=7.48, p value < 0.05 and t-stat=2.73. The result here is similar to the research of Saffarian and colleagues.

Koller *et al*[14]found a significant improvement in four of seven Pentacam topography indices (central keratoconus index, keratoconus index, index of height asymmetry, minimum radius of curvature) one year after CXL.

Present study also showed a Change in Mean Irregularity among the patients after the procedure saw a decline of 9.09%. Statistical test showed a significant effect on Irregularity with F=31.31, p value < 0.001 and t-stat=5.59.

Hence from the above results we conclude that C3R is positive effects on topographic variables such as keratometry, irregularity, anterior and posterior best fitted sphere. Study also showed improvement or status quo in refractive variables such as spherical equivalent, spherical refractive, cylindrical refractive power, best corrected visual acuity. More importantly, these effects were maintained in the 12 months followup period.

The results are similar to those found in previous studies, hence the procedure of collagen cross linking can be considered as a primary treatment modality in patients with Keratoconus as it is a non-invasive procedure and carries less post-operative complications such as infection, graft rejection, cataracts, glaucoma and astigmatism as seen in in Keratoplasy.

These observations have led to the following hypothesis, that if collagen cross linking stops or slows the progression of keratoconus, then it can also be combined with other treatment methods such as intracorneal rings for better regularising and reshaping of cornea in keratoconus. Additionally Post-operative morbidity is insignificant.

It is a safe procedure as compared to keratoplasty which is now used only when C3R fails to arrest disease progression. Numerous clinical studies agreed that C3R treatment provides significant improvements in visual acuity and maximum keratometry as well as halting the progression of keratoconus. However, it is still unclear whether baseline demographic and topographic characteristics influence postoperative outcomes.

V. CONCLUSION

It can be concluded from this present study that the procedure of collagen cross linking with riboflavin and UVA radiation definitely has beneficial effects on improving corneal strength and stability, thereby playing a significant role in halting the further progression of keratoconus. All the variables under study showed improvement or status quo in long term. Moreover post-operative complications were minimal and tolerable, Hence making the procedure worthy of consideration as a first line of management in Keratoconic population. However more such studies are required for establishing the efficacy and safety of C3R in general use.

CONFLICT OF INTEREST

None declared till now.

REFERENCES

[1] Klintworth G.K., Damms T.Corneal dystrophies and keratoconus. Curr. Opin. Ophthalmol. 1995;6(4):44–56.

[2] Rabinowitz Y.S. Keratoconus. Surv. Ophthalmol. 1998;42(4):297–319.

[3] Rahi A., Davies P., Ruben M., Lobascher D., Menon J.Keratoconus and coexisting atopic disease. Br. J. Ophthalmol. 1977;61(12):761–764.

[4] Lu Y., Vitart V., Burdon K.P., Khor C.C. et al; NEIGHBOR Consortium Genome-wide association analyses identify multiple loci associated with central corneal thickness and keratoconus. Nat. Genet. 2013;45(2):155–163.

[5] Wit. Hafezi F, Wiltfang R, Kanellopoulos J, Seiler T. Corneal collagen cross linking riboflavin/UVA for the treatment of induced keratectasia after laser in situ keratomileusis. J Cat Refract Surg. 2007;33:2035–40

[6] Kymionis GD, Bouzoukis DI, Diakonis VF, Portaliou DM, Pallikaris AI, Yoo SH. Diffuse lamellar keratitis after corneal crosslinking in a patient with post-laser in situ keratomileusis corneal ectasia. J Cataract Refract Surg. 2007;33:2135–7.

[7] Kymionis GD, Kontadakis GA, Kounis GA, Portaliou DM, Karavitaki AE, Magarakis M, et al. Simultaneous topography-guided PRK followed by corneal collagen cross-linking for keratoconus. J Refract Surg. 2009;25:S807–11.

[8] Raiskup F, Hoyer A, Spoerl E. Permanent corneal haze after riboflavin-UVA-induced cross-linking in keratoconus. J Refract Surg. 2009;25:S824–8.

[9] Kymionis GD, Bouzoukis DI, Diakonis VF, Portaliou DM, Pallikaris AI, Yoo SH. Diffuse lamellar keratitis after corneal crosslinking in a patient with post-laser in situ keratomileusis corneal ectasia. J Cataract Refract Surg. 2007;33:2135–7.

[10] Vinciguerra P, Camesasca FI, Albe E, Trazza S. Corneal collagen cros11 wit. Hafezi F, Wiltfang R, Kanellopoulos J, Seiler T. Corneal collagen crosslinking h riboflavin/UVA for the treatment of induced keratectasia after laser in situ keratomileusis. J Cat Refract Surg. 2007;33:2035–40.

[11] Shetty R, Nagaraja H, Jayadev C, Pahuja NK, Kurian Kummelil M, Nuijts RM. Accelerated corneal collagen cross-linking in pediatric patients: Two-year follow-up results. Biomed Res Int 2014;2014:894095.

[12] Yeung SN, Lichtinger A, Ku JY, Kim P, Low SA, Rootman DS. Intracorneal ring segment explantation after intracorneal ring segment implantation combined with same-day corneal collagen crosslinking in keratoconus. Cornea 2013;32:1617-20.

[13] Coskunseven E, Jankov MR, Hafezi F. Comparative study of corneal collagen cross-linking with Riboflavin and UVA irradiation in patients with keratoconus. J Refract Surg. 2009;25:371–6.

[14] Koller T, Iseli HP, Donitzky C, Ing D, Papadopoulos N, Seiler T. Topography-guided surface ablation for forme fruste keratoconus. Ophthalmology 2006;113:2198-202.