Comparison of accelerated collagen cross linking & conventional collagen cross linking in management of keratoconus: An interventional study

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Abstract— *Keratoconus is a disease of corneal and is a growing disease in the young population of today and in recent years many new modalities of treatment have come up to try and stop its progression in the early stages. Corneal collagen cross linking (CXL) is one of those modality. there are two type of CXL surgeries one is conventional other one is accelerated one. This intervention study was conducted on 40 patients and 60 eyes compare the outcome of conventional CXL (30 eyes) and accelerated CXL(30 eyes) in treatment of Keratoconus. It was found that there was no significant difference in change in various parameters like Log MAR best corrected visual acuity (BCVA) on Snellen's Chart, Spherical Equivalent (SEQ), Kmax (D) and Central Corneal Thickness (CCT) after 3 months as well as after 6 months in both the type of modalities. It was conclude from this study that accelerated CXL shows comparable results with conventional CXL in arresting the progression of mild KC, but long-term follow-up evaluation is warranted to delineate any difference in the clinical and topographical effect between the conventional and accelerated protocols.*

Keywords: Keratoconus, Corneal collagen cross linking (CXL), best corrected visual acuity (BCVA), Spherical Equivalent (SEQ), Kmax (D), Central Corneal Thickness (CCT).

I. INTRODUCTION

Keratoconus (KC) is a common ectasia of the cornea [1,2]. Keratoconus is a progressive asymmetrical, bilateral, non-inflammatory corneal ectasia which is characterized by corneal thinning and irregular astigmatism. It is aggravated by puberty, pregnancy, vernal kerato-conjunctivitis and lid rubbing. It occurs due to enzyme imbalance, stromal keratocyte apoptosis. Its reported incidence ranges between 50-230 per 100,000 and the estimated prevalence is 54.5:100,000.[1,2] In India incidence is 2300 per 100,000(0.0003-2.3%).[3]

Keratoconus(from Greek: *kerato*-horn, cornea; *konos*-cone) is a growing disease in the young population of today and in recent years many new modalities of treatment have come up to try and stop its progression in the early stages.Natural progression of the disease usually led to vision threatening complications like hydrops, severe corneal thinning with astigmatism. Surgical intervention was the usual end stage of the progression. The results of keratoplasty, though good, but requires lifelong follow-up and management of rejection. Post keratoplasty astigmatism is also a leading cause of visual morbidity. Hence a technique for halting the progression of thinning and ectasia was investigated. One such modality is collagen cross linking with riboflavin and UV-A.

Corneal collagen cross linking is a procedure to strengthen the cornea by formation of inters and intra-fibrilar covalent bond in collagen fibers of corneal stroma with the help of photo-sensitizer Riboflavin and UVA rays.C3R was developed in 1998 by Theo Seiler.[4,5]

The original cross-linking procedure involved anaesthetizing the eye (for example with proxymetacainhydrochloride 0.5% drops), removing the central 8-10mm of the epithelium and applying a riboflavin solution (0.1% riboflavin-5-phosphate and 20% dextran T-500) to the corneal surface 30 minutes before irradiation and at 5 minutes intervals during the course of a 30 minute exposure to 370 nm UVA with an irradiance of 3 $mwcm^{-2.}$ On the basis of UVA irradiance and exposure time C3R is classified in two groups i.e. 'Conventional C3R' (3mw/cm^2 for 30 minutes) and 'Accelerated C3R' (30mw/cm^2 for 3 minutes). [6]

In India, very few studies have been done to compare the clinical outcomes of accelerated and conventional corneal collagen cross linking (CXL) in the treatment of progressive keratoconus, hence this study was conducted with the aim to compare the clinical outcomes of accelerated and conventional corneal collagen cross linking in the treatment of progressive keratoconus.

II. METHODOLOGY

This hospital based prospective double blind randozized comparative interventional study was carried out in the Department of General Opthalmology, SMS Medical College, Jaipur (Rajasthan) India, in the year 2016.

Sample size was calculated to be minimum 26 eyes in each of the two groups at an alpha error 0.05 and power of 80% with minimum detectable difference of mean of K_{Max} Spherical Equilant (SEQ) at 6 months 1.2 D with SD 1.5 D in conventional and accelerated collagen cross linking in treatment of Keratoconus[7]. In these study 30 eyes for each of group was taken with 10% atrition.

For this study, patients of keratoconus with one year of duration having clear cornea, keratoconus grade 1&2, corneal thickness ≥400µm at thinnest point, K_{max} ≥1.0D, manifesting cylinder ≥1.0D and manifesting spherical≥0.5D were included. Out of these patients, patients with known co-morbities, pregnancy, apical corneal opacity, severe dry eye, concurrent corneal infection, concomitant immune disease and patient having any previous corneal surgery were excluded from study. Patients with known co-morbities, pregnancy and /or refusing to take participate in this study were also excluded from study. Finaly 40 patients of keratoconus attending ophthalmology O.P.D & cornea clinic of SMS hospital were selected for this study.

After taking proper consent and counseling, subjects were evaluated thoroghly and full Ophthalmological checkup including best corrected visual acuity (BCVA) on Snellen's Chart, Spherical Equivalent (SEQ), Applanation Tonometry, Slit lamp examination for any anterior segment pathology and for any endothelium changes like Guttatae, Fundus examination, Specular microscopy study with Topcon SP-3000P specular microscope (Endothelial Cell count and Central Corneal Thickness) and Corneal topography (Scheimpflug imaging) were done. Pre-operative investigation like blood sugar, Complete blood count, urine complete and ECG etc. were also done.

Randomization of patients to allocate the group were done randomly through chi-box method. And blinding was followed throughout the study neither the patient nor the investigator investigating outcome were knowing that which type of operation was done on which patient. Operating surgeon was same for each of two group. Finally 30 eyes of 18 patients of 'Group A' underwent conventional CXL and 30 eyes of 22 patients 'Group B' underwent accelerated CXL.

All 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. Corneal epithelium was removed. Isotonic 0.25% Riboflavin dextran was instilled every 3 minutes for 30 minutes. Both groups were exposure to UVA light (370nm, 3mw/cm^2) for 30 minutes during which riboflavin was instilled every 3 minutes. BCL was applied in both groups, pad and patch was done. After 4 hours pad & patch was removed. Artificial tears e/d 2 hrly & Moxifloxacin 0.5% e/d qid with Loteprednol+tobramycin e/d qid were given to all of them for 4 week. BCL was removed after 5 days of operation.

On postoperative 3rd month and 6th month follow up examination was done. 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, SEQ and Scheimpflug imaging [Pentacam® (K_{max}, central corneal thickness)]. Topcon Specular Microscope SP-3000P was used for specular microscopy in order to record central corneal thickness (CCT).

Statistical analysis: Qualitative data was compared by Chi square test. Unpaired t test was used to infer the difference in means. For significance, "p" value <0.05 was accepted as significant. Analysis was done by trial version of SPSS statistical software.

III. RESULTS

In this study, **30 eyes of 18 patients of 'Group A'** underwent conventional CXL and **30 eyes of 22 patients ''Group B''** underwent accelerated CXL. Both these groups were comparable as per age and sex wise. (Table 1)

Table 1
Age and Sex wise Comparison of Both groups

Variables		'Group A' (N=18) (Conventional CXL)	'Group B' (N=22) (Accelerated CXL)	P Value LS
Age	**Mean ± SD in Years**	18.57 ± **4.19**	18.41 ± **3.98**	0.902* **NS**
Sex	**Male : Female**	12:6	14: 8	0.894** **NS**

** Unpaired 't'test **Chisquare test*

When outcome of these two groups were compared after 3 months of operation it was observed that the change in log MAR BCVA after 3 months, showing no statistically significant difference between two groups (P>0.05). Likewise there was no significant change in change in Kmax(D), SEQ(D) and CCT(µm) after 3 months of operation. (Table 2)

Table 2
Comparison of Change in Ophthalmologic Variables in both groups after 3 months of operation

Variables		'Group A' (N=18) (Conventional CXL)	'Group B' (N=22) (Accelerated CXL)	*P Value LS
1	**Log MAR BCVA**	0 ± 0.066	-0.038 ± 0.089	0.066 **NS**
2	**Kmax(D**	-0.03 ± 0.612	0.193 ± 0.399	0.100 **NS**
3	**SEQ(D)**	-0.691 ± 1.291	-0.491 ± 0.412	0.423 **NS**
4	**CCT(µm)**	4.366 ± 6.882	0.966 ± 6.720	0.058 **NS**

** Unpaired 't'test*

Likewise when outcome of these two groups were compared after 6 months of operation it was observed that the change in log MAR BCVA after 6 months, showing no statistically significant difference

between two groups (P>0.05). Likewise there was no significant change in change Kmax(D), SEQ(D) and CCT(µm) after 6 months of operation. (Table 3)

Table 3
Comparison of Change in Ophthalmologic Variables in both groups after 6 months of operation

Variables		'Group A' (N=18) (Conventional CXL)	'Group B' (N=22) (Accelerated CXL)	*P Value LS
1	Log MAR BCVA	-0.132 ± 0.121	-0.152 ± 0.119	0.510 NS
2	Kmax(D	0.75 ± 1.048	0.863 ± 0.516	0.597 NS
3	SEQ(D)	-1.208 ± 1.784	-1.016 ± 0.639	0.582 NS
4	CCT(µm)	1.366 ± 9.668	-2.866 ± 7.421	0.062 NS

** Unpaired 't'test*

IV. DISCUSSION

In this study in 'Group A' total patients were 18 (12 males & 6 females) with mean age18.57±4.19 years and in 'Group B' total patients were 22 (14 males & 8 females) with mean age18.41±3.98 years. Thus, both groups were age and sex matched.

In this study, there was no statistically significant difference in the postoperative BCVA between the two groups (P=0.66 and P=0.510 postoperatively at 3 & 6 months respectively). Similar improvement has been reported in several studies.[8-10] Hashemian *et al*[11] showed similar visual outcomes between conventional CXL and 30 mw/cm^2 accelerated CXL at one year. Hashemian *et al*[17] showed preoperative/postoperative UDVA (logMAR) in accelerated and conventional was 0.72±0.53/0.72±0.53 and 0.74±0.50/0.72±0.51 with P value 0.745.

In this study, in group 'A' the Kmax was decreased by 0.03±0.61 and 0.75±1.04 at 3 month follow up and 6 month follow up whereas in 'Group B' it was decreased by 0.19±0.39 and 0.86±0.51, which was with no statistically significant difference. Similarly Jankov *et al*(2008)[12] also found that progression of keratoconus stopped in all patients who were actively progressing 6 months prior to treatment. Max K decreased by more than 2 D (from 53.02 ± 8.42 D to 50.88 ± 6.05 D). Fournie et al (2009)[13] also reported almost similar observations in 22 patients trial.

In this study, in 'Group A' the mean decrease in SEQ at month 3 and month 6 was -0.69±1.29 and -1.20±1.78.In 'Group B' the mean decrease in SEQ at month3 and month 6 was -0.49±0.41 and -1.01±0.63. There was no statistically significant difference in the decrease of postoperative SEQ between the two groups (P =0.423 and P=0.582 postoperatively at 3 & 6 month respectively). Ng AL etall reported Change in Kmax in after 6 month follow up in conventional and accelarated collagen cross linking in treatment of Keratoconus -1.8±1.8D and -0.3±0.9 D respectivly. With difference of 1.2 D with SD 1.5 D in conventional and accelarated collagen cross linking in treatment of Keratoconus. This difference was found significant (p=0.015). Similarly Wollensak *et al*(2003),[14] which included 23 eyes with moderate or advanced progressive keratoconus, showed that CXL was effective in halting the progression of keratoconus and the SEQ was reduced by an average of 1.14 D over a period of 4 year.

In this study, in 'Group A' the mean change in CCT at month 3 and month 6 was 4.36±6.88 and 1.36±9.66. In 'Group B' the mean change in CCT at month3 and month 6 was 0.96±6.72 and -2.86±7.42. There was no statistically significant difference in the change of postoperative CCT between the two groups (P =0.058 and P=0.062 postoperatively at 3 & 6 month respectively).Similarly Derakhshan A et

al (2011)[9] study showed that the mean central corneal thickness (CCT) was 485 ± 29.6 μm before treatment and 494 ± 30.8 μm thereafter; CCT increased by an average of 9.1 ± 11.2 μm ($P < 0.001$).

The reduction inkeratoconus in both groups is less than the results reported by Greenstein and Hersh[8] (1.7 D) or Caporossi et al[15] (2.1 D) but are comparable to the results of Derakhshan et al[9] (0.65) and Vinciguerra et al[10] (1.1D). The explanation is that the former two groups included more advanced cases of KC, while the latter two groups included mild- to moderate-KC cases as the amount of flattening by CXL is directly proportional to the steepness of the cornea.[11]

In this study, accelerated group shows a significant reduction of the CCT, 6 months after surgery. A similar behaviour was observed in the conventional CXL group and is similar to previous reports. The early thinning may be attributed to the compression of collagen fibrils or keratocyte apoptosis, among other theories[16] significant improvement was observed in this present study in UCVA, BCVA and spherical equivalent in both groups. Previous studies have demonstrated similar functional improvement after CXL.[17,18] This has been attributed to an improved regularity of the corneal shape after CXL.

Both groups showed a statistically significant improvement in BSCVA, 6 month after surgery. Similar improvement has been reported in several studies.[8-10] These findings seem to suggest a similar clinical efficacy between the conventional and accelerated protocols. We did not observe visually significant corneal haze in any of cases in present study.

It can be conclude that accelerated CXL shows comparable results with conventional CXL in arresting the progression of mild KC, but long-term follow-up evaluation is warranted to delineate any difference in the clinical and topographical effect between the conventional and accelerated protocols. As other studies like Chow et al (2015)[19] and Hashemian et al(2014)[20] reported their observations.

Chow et al (2015)[19] 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 ($p = 0.120$). However, there were no inter-group differences in the changes in keratometry values between conventional CXL and accelerated CXL at 1 year postoperatively. The corneal thicknesses (thinnest corneal thickness and central corneal thickness) decreased significantly postoperatively in both groups ($p > 0.017$), although no inter-group difference was found. Central corneal thickness reduced by 23.56 μm in conventional CXL group and 22.63 μm in accelerated CXL group ($p = 0.606$).

Hashemian et al (2014)[20] (P value=0.64) conducted a study on 153 eyes of 153 patients with 15-month follow-up period after CXL (76 eyes in the conventional group and 77 eyes in the accelerated group). Measured variables include corrected distance visual acuity (CDVA), uncorrected distance visual acuity (UDVA), refraction, maximum keratometry, endothelial cell density, anterior and posterior stromal keratocyte density, and subbasalnerve density. Cylindrical and spherical components of refraction improved significantly during 15 months of follow-up. No difference was observed between the two study groups.

V. CONCLUSION

It can be concluded from this present study that accelerated CXL shows comparable results with conventional CXL in arresting the progression of mild KC, but long-term follow-up evaluation is warranted to delineate any difference in the clinical and topographical effect between the conventional and accelerated protocols.

CONFLICT OF INTEREST

None declared till now.

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