· Original article ·

Prospective analysis of treatment of mild to moderate keratoconus without awaiting progression

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Received:2016-04-29 Accepted:2016-11-10

核黄素角膜胶原交联治疗早期轻中度圆锥角膜的研究

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摘要

目的:核黄素角膜胶原交联早期治疗轻度至中度圆锥角膜的预后。

方法:三级眼科诊疗中心的前瞻性研究。共 38 例 47 眼轻至中度圆锥角膜接受核黄素角膜胶原交联治疗的患者纳入本研究。术前数据包括参与眼数,视力,眼压,角膜厚度与角膜地形图。术后数据包括最佳矫正视力,眼压,角膜厚度,角膜地形图和术后并发症。

结果:研究包含年龄 16~30 岁的患者 38 例 47 眼。平均术前视力为 0.58±0.40 logMAR,术后随访 2a 显著提高(0.40±0.27logMAR)(P=0.005)。平均术前角膜曲率为 50.5±4.6 D,术后显著降低。随访 2a 平均角膜曲率为 48.2±4.1 D(P=0.011)。术后随访 2a 眼压(15.1±3.0mmHg)较术前(12.9±2.5 mmHg)显著增加(P=0.035)。术前角膜厚度 467.9±38.8 μm,术后随访 2a(465.0±39.3 μm)明显降低。所有患者均无并发症出现。

结论:早期使用核黄素角膜胶原交联治疗轻至中度圆锥角膜可获得长期的良好视力,而不必等其发展为进展期。

关键词:角膜;圆锥角膜;角膜胶原交联

引用:Kelkar J, Kelkar A, Arora E, Kelkar S, Sayad M. 核黄素角膜胶原交联治疗早期轻中度圆锥角膜的研究. 国际眼科杂志 2017;17(2):200-204

Abstract

• AIM: To present the outcomes of early treatment with corneal collagen cross-linking with riboflavin in patients with mild to moderate keratoconus.

• METHODS: It is a prospective interventional study at tertiary eye care center. Forty-seven eyes of 38 patients with mild to moderate keratoconus who underwent collagen cross linking with riboflavin were enrolled. Preoperative data included eye involved, presenting visual acuity, intraocular pressure (IOP), pachymetry and corneal topography. Postoperative data included the best-corrected visual acuity (BCVA), IOP, pachymetry, corneal topography and postoperative complications.

• RESULTS: Study comprised of 47 eyes of 38 patients aged between 16-30y. The average preoperative vision was 0.58±0.40 logMAR which significantly improved to 0.40±0.27logMAR at 2y follow up (P=0.005). The average preoperative keratometry readings were 50.5±4.6 D which significantly decreased during the subsequent follow up and the average keratometry readings at 2y was 48.2±4.1 D (P=0.011). The average IOP significantly increased postoperatively and at 2y follow up was 15.1±3.0mmHg compared to preoperative IOP (12.9±2.5 mmHg) (P=0.035). The average preoperativepachymetry was 467.9±38.8 μm, which decreased significantly and was 465.0±39.3 μm at 2y follow up. No complications were noted in any of our cases.

• CONCLUSION: Early treatment with collagen cross-linking with riboflavin provide good long term visual outcomes in patients with mild to moderate keratoconus without awaiting for progression of the keratoconus.

• KEYWORDS: cornea; keratoconus; corneal collagen cross-linking

DOI:10.3980/j.issn.1672-5123.2017.2.02

Citation: Kelkar J, Kelkar A, Arora E, Kelkar S, Sayad M. Prospective analysis of treatment of mild to moderate keratoconus without awaiting progression. *Guoji Yanke Zazhi*(*Int Eye Sci*) 2017;17(2):200-204

INTRODUCTION

Keratoconus is a non-inflammatory progressive corneal disease with biomechanical resistance reduced to almost half of that seen in normal cornea. Corneal collagen cross-linking (CXL) employs riboflavin and ultraviolet-A (UVA) which induces crosslinking through photopolymerization of collagen mediated by reactive oxygen species and, thus, increases corneal biomechanical rigidity and biochemical resistance in progressive keratoconus[1]. CXL is indicated when progression of keratoconus is documented. Several

studies over period of time have proved the efficacy of cross linking in progressive keratoconus[2].

This study aims to assess the efficacy of treating patients with mild to moderate keratoconus on diagnosis with riboflavin-UVA induced cross-linking of corneal collagen without awaiting for progression to occur.

SUBJECTS AND METHODS

This prospective nonrandomized one arm cohort study with consecutive recruitment study was conducted at National Institute of Ophthalmology between Sep. 2011 to Nov. 2013 with approval from institutional ethics committee. Total 47 eyes of 38 patients aged between 16-30y attending with complains of diminution of vision due to keratoconus were included in the study with informed consent. For patients younger than 18y of age (legal age of giving consent), consents were taken from their parents.

This study comprised patients with the following inclusion criteria: 1) Mild to moderate keratoconus as per the Amsler-Krumeich classification; 2) Corneal thickness of at least 375 μm; 3) No slit-lamp evidence of corneal scarring or any other corneal pathology.

Sample size calculation was performed to detect a clinically significant difference of 1.0D for the mean K readings between pre-op and post-op 2-year follow-up, at a significance level of 0.05 and a power of 80% (type II error=0.20), assuming a standard deviation of pre-op and post-op difference of 3.5D. A drop-out rate of 10% over 2-year study period was anticipated, to give a sample size of 47. Thus a data on total of 47 eyes therefore was compared in this study.

Demographic variables were age, sex and eye treated. All the patients underwent complete preoperative evaluation including refraction; distance visual acuity testing using a log MAR chart at an effective distance of 3 meters from patient; anterior segment examination with a slit lamp bio-microscope (Topcon Corp, Japan), Intra ocular pressure (IOP) measurement with Goldman's applanation tonometer (GAT). The posterior segment was assessed using +90 Diopter lens and the slit lamp. Corneal topography (Sirius system, CSO, Italy) and pachymetry (Sirius system, CSO, Italy) were performed. The Sirius system combines a monochromatic 360-degree rotating Scheimpflug camera and a Placido disk to analyze the anterior segment by obtaining 25 radial sections of the cornea and anterior chamber. In a single scan, it provides tangential and axial curvature data of the anterior and posterior corneal surfaces, the global refractive power of the cornea, a biometric estimation of various structures, complete corneal pachymetry, and wavefront analysis. A 475 nm blue LED light is used to measure 35 632 points for the anterior corneal surface and 30 000 for the posterior cornea. A pachymetric map is then reconstructed using the point-by-point anterior and posterior corneal surface data. The system provides Keratometry (K) values along the flattest meridian as well as the K value in the steepest meridian. The mean *K* is calculated from the flattest and steepest meridian keratometry readings.

Table 1 The age and sex distribution

Characteristics	No. of cases (n=47)	Percentage (%)
Age (a)		
<20	19	40.4
20-24	16	34.0
≥25	12	25.6
Sex		
M	23	48.9
F	24	51.1

Each measurement consists of 25 consecutive scans in a single shot.

Patients with uncontrolled diabetes, uncontrolled vascular disease, pregnant and nursing mothers, uncontrolled glaucoma and patients who have undergone ocular surgery including refractive surgery and history of herpetic eye disease were excluded from study.

CXL was performed by a single surgeon under topical anaesthesia with 0.5% proparacaine eye drops. Eye was painted and draped. Lid was retracted with eye speculum. Epithelium was abraded with 70% alcohol and cotton tipped applicator. CXL was done following the Dresden protocol. Riboflavin eye drops (Peschke M, Switzerland) were put every 2min for 30min UV-A light (My Healthskape) was switched on for next 30min. Riboflavin eye drops were put every 5min for next 30min. Bandage contact lens was applied. We had one patient with pachymetry <400μm for whom we used the Hypo-osmolar riboflavin eye drops (Nano XL, Japan).

Post-operatively patients were started on topical moxifloxacin eye drops 3 times a day for 4wk, topical carboxy methyl cellulose eye drops, 3 times a day for 4wk, topical fluorometholone eye drops 3 times a day for 1mo. Bandage contact lens was removed after 3d. Patients were assessed post-operatively for BCVA, IOP and pachymetry, and topography was done at 1mo, 3mo, 6mo postoperative and yearly thereafter for 2y.

At each follow up visit best corrected visual acuity (BCVA), IOP and slit lamp examination were noted.

Complications like non-healing of epithelium, stromal haze, infiltrate and keratitis were noted.

RESULTS

Demographic parameters showed that 19(40.4%) cases were <20y of age, 16(34%) belonged to 20-24y and 12(25.6%) belonged to the age group of 25 and above. Twenty-three of 47 patients were males(48.9%) and the remaining were females (51.1%)(Table 1).

The mean pre-op logMAR visual acuity was found to be 0.58±0.40 and the mean 1mo post-op logMAR vision was found to be 0.56±0.33, which did not differ significantly from the pre op mean logMAR vision (P>0.05). However, average logMAR vision significantly improved at 6mo (0.44±0.32; P=0.002), 1-year (0.40±0.27; P=0.005) and 2-year (0.40±0.27; P=0.005) post-op follow-ups compared to pre-op logMAR vision (P<0.01 for all) (Table 2).

Table 2　The pre-op and post-op comparison of all parameters studied of operated eye only (n=47)　$\bar{x}\pm s$

Parameters	Preop	Postop 1mo	Postop 6mo	Postop 1a	Postop 2a	Pair-wise comparisons (P)			
						Preop *vs* Postop 1mo	Preop *vs* Postop 6mo	Preop *vs* Postop 1a	Preop *vs* Postop 2a
Vision (LogMar)	0.58±0.40 0.20-1.47	0.56±0.33 0.20-1.77	0.44±0.32 0.20-1.77	0.40±0.27 0.10-1.47	0.40±0.27 0.10-1.47	0.700 (Non-Significant)	0.002 (Significant)	0.005 (Significant)	0.005 (Significant)
Topo (Cylinder)	5.88±2.91 0.32-13.37	5.41±2.94 0.24-14.25	5.09±2.77 0.26-12.47	5.38±2.67 0.73-12.28	5.34±2.69 0.68-12.21	0.001 (Significant)	0.001 (Significant)	0.001 (Significant)	0.001 (Significant)
K readings	50.5±4.6 43.62-59.62	49.0±4.6 39.26-58.58	48.8±4.5 42.05-62.69	47.9±4.0 42.12-58.00	48.2±4.1 42.04-58.03	0.004 (Significant)	0.002 (Significant)	0.005 (Significant)	0.011 (Significant)
IOP (mmHg)	12.9±2.5 10.0-19.0	14.4±3.4 10.0-20.0	15.2±2.6 10.0-20.0	14.8±3.3 11.0-20.0	15.1±3.0 11.0-20.0	0.008 (Significant)	0.001 (Significant)	0.049 (Significant)	0.035 (Significant)
Pachymetry	467.9±38.8 390-543	445.6±39.6 363-524	455.9±39.3 372-535	461.7±39.2 380-540	465.0±39.3 385-546	0.001 (Significant)	0.001 (Significant)	0.001 (Significant)	0.001 (Significant)

IOP: Intraocular pressure; LogMAR: Logarithm minimum angle of resolution; SD: Standard deviation; Range: Min-max; P values are obtained using paired t-test (Paired analysis); P<0.05 is considered to be statistically significant.

Thirty-four cases (72.3%) had their pre-operative IOP ranging from 10-13 mmHg, 9 (19.2%) between 14-17 mmHg and 4 cases (8.5%) between 18-21 mmHg(Table 3).

The mean pre-operative IOP was 12.9±2.5 mmHg. The postoperative IOP was 14.4±3.4 mmHg, 15.2±2.6 mmHg, 14.8±3.3 mmHg and 15.1±3.0 mmHg during the 1st month, 6th month, 1st year and 2nd year follow up (Table 2).

One out of 47 cases (2.1%) had a pre-operative pachymetry value between 375-400 μm. Fifteen cases (31.9%) had their pre-operative pachymetry between 400-450 μm, 20 cases (42.6%) between 450-500μm, and 11 cases (23.4%) between 500-550 μm (Table 4).

The mean pre-operative pachymetry was 467.9±38.8 μm. The mean post-operative pachymetry reduced significantly to 445.6±39.6 μm after 1mo. The pachymetry values showed slight improvement in the subsequent follow ups, however, as compared to the pre-operative values, the reduction in the pachymetry was significant. The 6th month, 1st year and 2nd year follow ups showed a mean pachymetry of 455.9±39.3 μm, 461.7±39.2 μm and 465.0±39.3 μm respectively (Table 2).

The average topographic cylinder significantly improved throughout the follow up period. The mean pre-op cylindrical value was 5.88±2.91, which improved during the 1st month follow up to 5.41±2.94. During the 6mo follow up, it was 5.09±2.77, during the 1y follow up, it was 5.38±2.67 and during the 2y follow up, it was 5.34±2.69(Table 2).

The mean pre-operative K value was 50.5±4.6 D, which significantly improved to 49.0±4.6 D during the 1st month (P=0.004), 48.8±4.5 D during the 6th month (P=0.002), 47.9±4.0 D at 1y (P=0.005) and 48.2±4.1 D at the 2nd year (P=0.011) follow up (Table 2). Figure 1 shows tangential anterior topographic image and average K values of a patient with keratoconus, who underwent CXL.

Figure 2-4 shows the topography and K values of the same patient during the subsequent follow ups.

Table 3　The distribution of pre-op intraocular pressure

mmHg

IOP	No. of cases (n=47)	Percentage (%)
10-13	34	72.3
14-17	9	19.2
18-21	4	8.5
Total	47	100

Table 4　The distribution of pre-op pachymetry　μm

Pachymetry (Microns)	No. of cases (n=47)	Percentage (%)
375-400	1	2.1
400-450	15	31.9
450-500	20	42.6
500-550	11	23.4
Total	47	100.0

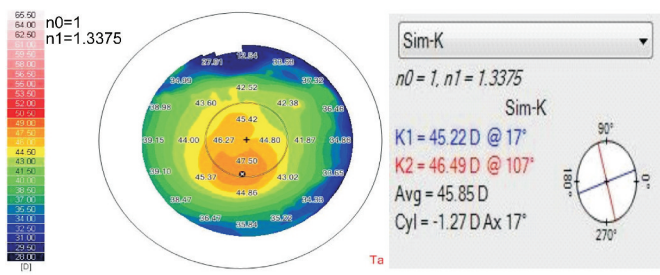

Figure 1　Pre-operative tangential anterior topographic image and average topographic K value.

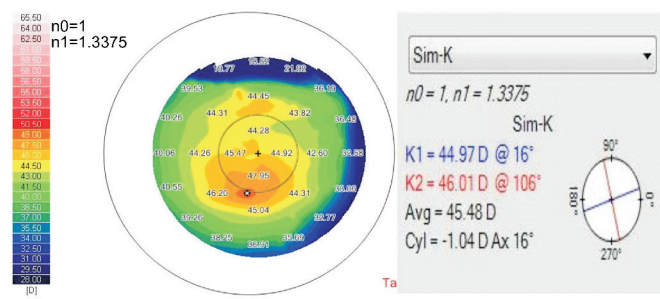

Figure 2　One month post-operative tangential anterior topographic image and average topographic K value.

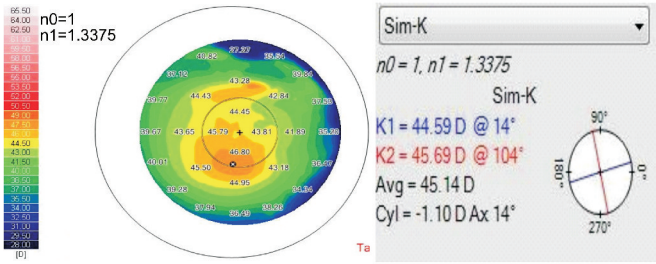

Figure 3 1-year post-operative tangential anterior topographic image and average topographic K value.

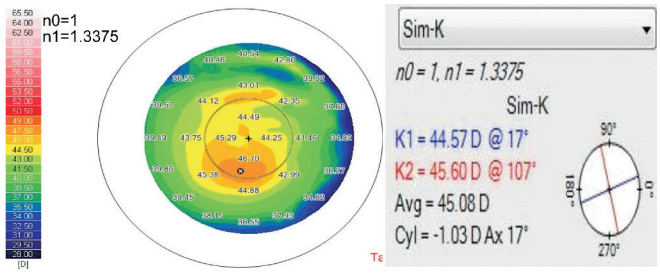

Figure 4 2-year post-operative tangential anterior topographic image and average topographic K value.

DISCUSSION

Spoerl *et al*[3] in 1998 first reported success by corneal collagen cross-linking and it is now often described as the most promising innovation in the treatment of progressive keratoconus. This article reports our 24-month results of prospective nonrandomized consecutive recruitment one arm cohort study of CXL for keratoconus without awaiting progression.

After CXL, uncorrected visual acuity (UCVA) has been reported to improve by 2.8 Snellen lines at 36mo[4]. Similarly, BCVA has been shown to improve by 2 Snellen lines[4] and −0.15 to −0.23 logMAR[5-6]. In our study, there was an improvement in the BCVA in the six month follow up. The average pre op logMAR BCVA was 0.58±0.40 which significantly improved to 0.44±0.32 after 6mo (P=0.002). Average 1y BCVA improved to 0.40±0.27 (P=0.005) and average 2y BCVA was same as observed at the end of 1y showing stability of vision. Visual improvement generally starts 3mo after treatment[7]. A temporary visual reduction, seen in the early postoperative phase due to stromal edema, was evident in 100% of eyes with confocal microscopy[8]. Average visual improvement has been between 1 and 2 Snellen lines from 1 to 4y after treatment[4-5]. The improved uncorrected visual acuity can be partially explained by reduction in the sphere and the spherical equivalent and the reduction in coma seen on aberrometry[9].

Raiskup-Wolf *et al*[5] reported improvement in vision after cross-linking attributable to decreased astigmatism (K readings reduction) and corneal curvature in a large cohort of patients followed up over 6y. Improvement in corneal symmetry indices and homogenization of the cornea as a result of the increased rigidity was also seen. In our study, the mean preoperative K value of 50.5±4.6 D significantly decreased to 49.0±4.6 D (P=0.004) in the first month and in the six month post-operative month it was 48.8±4.5 D (P=0.002). The first year follow up showed a mean K value of 47.9±4.0 D (P=0.005) and at the end of second year, the mean K value changed to 48.2±4.1 D (P=0.011).

In a study conducted by Caporossi *et al*[4], the mean K value was reduced by a mean of 2 diopters, the mean best spectacle-corrected visual acuity (BSCVA) improved by 1.9 Snellen lines, and the uncorrected visual acuity improved by 2.7 Snellen lines.

In a prospective non randomized study done by Maria Clara Arbelaez *et al*[10] comparative analysis of the pre-operative and 1-year post-operative evaluation showed a mean gain 1.65 lines of BCVA (P=0.002). The reduction in the average keratometry reading was 1.4 D (P=0.001) at the apex.

Arora *et al*[11] conducted a prospective contra lateral case control study and included 15 eyes of 15 keratoconus patients that underwent CXL. The criteria were not documented progressions, but the advanced keratoconus status in the fellow eye. At 1y after CXL, significant improvements were noted in logMAR BSCVA and apical keratometry.

We noted a significant increase in the IOP during the post-op period as compared to the preoperative IOP. Pre-operative IOP was 12.9±2.5 which changed to 14.4±3.4 (P=0.008), in the first post-operative month and in the six post-operative months it was 15.2±2.6 (P=0.001). The mean IOP after 1y was 14.8±3.3 (P=0.049) and after 2y it was 15.1±3.0 (P=0.035).

Kymionis *et al*[12] study showed that there was a statistically significant increase in the measured IOP 6mo after CXL (both P<0.001) that was probably caused by an increase in corneal rigidity. The mean measured was 9.95mmHg±3.01 (SD) before CXL, 11.40±2.89 mmHg at 6mo. The change in IOP measurements at postoperative examinations was not correlated with patient's age, preoperative pachymetry, or preoperative keratometry readings.

The relationship between corneal thickness and crosslinking has not been so far well explained. Thinning immediately after CXL has been thought to be the result of factors, post treatment stromal compaction, postoperative dehydration, and alterations in epithelial healing and distribution[13-14]. It also may represent a measurement artefact after treatment[15]. Studies report varying observations from no change in corneal thickness[16] to a decrease at 12mo[17] and an increase at 24mo[5]. In our study the pachymetry values showed significant reduction in the one month post CXL readings and thereafter follow up showed a lesser reduction, though pre-operative levels were not reached. Increase in corneal rigidity has been postulated as the reason for decrease in corneal pachymetry. Witting-Silva *et al*[18] reported a reduction in pachymetry after CXL in a three year follow up study.

Asri *et al*[19] also reported that age of more than 35y and female gender were further risk factors for postoperative progression. Vinciguerra *et al*[20] reported the most promising results in patients 18 to 39y of age. We did not observe any correlation between either age or gender with the change in

keratometry in our study group.

The importance of cross-linking lies in the fact that it is a low-invasive, outpatient procedure with high safety margin. It achieves a result so far not offered by any other modality of treatment[9].

A limitation of this study was the lack of control group. Control group could have helped us assess the progression and the results of early treatment and faster visual rehabilitation could have been documented. Moreover, aberrometry was not possible in any of the patients.

The decision to offer CXL to our patients was made as soon as diagnosis was evident on topography without waiting for progression to occur. Cross-linking was able to stop its progression in our series of cases. We believe this led to saving precious time. This aspect has not been much explored so far to the best of our knowledge, as all studies state usefulness of the procedure for cases of progressive keratoconus.

This study demonstrates that CXL can result in a significant reduction in corneal curvature and can stabilize keratoconus when treated on diagnosis. There is an improvement in the BCVA. The optimal timing of intervention remains debatable however;our encouraging results emphasize the need for early treatment in keratoconus patients without awaiting progression to enable faster visual stability and rehabilitation. The risks associated with the procedure seem to be minor relative to the morbidity of advanced disease.

In summary, based on the findings of this study, we conclude that CXL procedure is a safe treatment for mild to moderate Keratoconus, yields good visual results, and there is improvement and stabilization of Keratoconus and waiting for documentation of progression is not warranted.

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