Progression of Keratoconus after Corneal Collagen Cross-Linking Procedure

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ABSTRACT:

BACKGROUND:

Keratoconus is a non-inflammatory, usually bilateral disorder, that leads toabnormal thinning and steepening of the cornea duo to progressive corneal instability.

OBJECTIVE:

To estimate the progression of keratoconus after cross linking during 1 year duration.

PATIENTS AND METHODS:

This study is a prospective study carried out to estimate the progression of keratoconus after cross linking. It was conducted in Dar Al Salam eye hospital, Lasik center, Baghdad city, fromMarch, 2011 to the December, 2016. All patients with keratoconus included in this study were referred from private clinic.The surgery was done in Dar Al Salam hospital by one consultant ophthalmologist. The researcher followed up the keratoconus eyes for 1 year.

RESULTS:

Two hundred sixty six eyes of one hundred seventy two patients were completed follow up after Collagen cross-linking using UVA light and riboflavin. Mean age of patients was 18 ± 10 years and female to male ratio was nearly 2:1. Postoperatively, VA was unchanged in 206 eyes,improved in 50 eyes, and deteriorated in 10 eyes. No significant differences were observed in means of autorefraction, simulated keratometry and central corneal thickness postoperatively for all eyes ($p > 0.05$).

CONCLUSION:

Cross linking is a minimally invasive procedure. This method can halt or reduce keratoconus progression.

KEY WORDS: keratoconus and cross linking.

INTRODUCTION:

Cornea is the principal refractive surface of the human eye and along with sclera forms the outermost coat of the eyeball. It constitutes up to one-sixth of the entire eyeball. The corneal epithelium is derived from the surface ectoderm and the mesoderm give rise to Bowman's layer, stroma, Descemet's membrane and endothelium. The average diameters of the cornea vary from 11 to 12 mm horizontally and 9 to 11 mm vertically. Cornea accounts for approximately 48 diopters of the power. The posterior surface of the cornea is more spherical than the anterior surface and the central cornea is thinner (520 μm) than the peripheral cornea (650 μm or more). The tear film covers the anterior corneal surface and the posterior corneal surface is in contact with the aqueous [(1)].

Collagen I is the major macromolecular constituent of the corneal stroma, although collagen types III, V, and VI are also represented. The corneal stroma possesses the mechanical strength needed to form the anterior coat of the eye, whilst maintaining the high degree of transparency required for light transmission. Light transmission through the cornea is a result of a particular, cornea-specific arrangement of collagen fibrils. Corneal collagen uniquely forms small (32nm), uniformly spaced fibrils that are organized into larger bundles or fibers (termed corneal lamellae) of varying thickness (1-2μm) and width (5–100μm) that are arranged in interweaving orthogonal layers throughout the stroma. They are thinner and more interwoven in the anterior cornea [(2)].

Keratoconus is a non-inflammatory, usually bilateral disorder, which manifests as progressive corneal instability characterized by abnormal thinning and steepening of the cornea. This abnormal curvature of the cornea changes its refractive power, often resulting in irregular astigmatism and myopia and leading to mild to marked impairment in the quality of vision[(3)].

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The definitive cause underlying the development of keratoconus remains unclear. However, it appears to be a heterogeneous condition that may be produced by a variety of unrelated abnormalities of a metabolic and biochemical nature. The most common presentation of keratoconus is as a sporadic disorder, in which only a significant minority of patients exhibit a family history with autosomal dominant or recessive transmission[4].

The morphological signs of keratoconus include formation of Fleischer's ring—a pigmented ring that results from the accumulation of ferritin particles in the cytoplasm of epithelial cells and widened intercellular spaces—as shown by electron microscopy [5], breaks in Bowman's membrane, filled with cells, collagen, and PAS-positive material [6], stromal thinning and abnormal keratocyte morphology [6], and endothelial polymorphism [7]. In histopathological and biochemical studies, keratoconic corneas are characterized by increased levels of proteases and other catabolic enzymes, decreased levels of tissue inhibitors of metalloproteinases (TIMPs), increased collagenolytic activity, significantly increased expression of IL-4 receptors, apoptotic cell death of keratocytes, and dramatic changes in collagen orientation & distribution [8-9].

Corneal collagen cross-linking (CXL) with riboflavin and ultraviolet-A (UVA) is a new technique of corneal tissue strengthening by using riboflavin as a photosensitizer and UVA to increase the formation of intra and interfibrillar covalent bonds by photosensitized oxidation.[10]

Riboflavin (vitamin B2) is the precursor of flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), which are coenzymes that play a crucial role in the metabolism of proteins, fats, and carbohydrates. Riboflavin is an essential constituent of living cells and is non-cytotoxic. It acts as a photomediator, considerably increasing the absorption of UVA light on exposure to corneal stoma.[11-12]

The most common indications for cross linking includes:

1-corneal ecstatic disorders such as progressive Keratoconus and pellucid marginal degeneration.

2-post-LASIK ectasia.

3-infectious keratitis and corneal melting.

4-advanced corneal edema : CXL results in loss of water and compaction of corneal stroma , therefore it might be useful to improve the pathologic edema[13-14].

Several long-term and short-term complications of CXL have been documented which may be direct or primary due to incorrect technique application or incorrect patient's inclusion or indirect or secondary complications related to therapeutic soft contact lens, patient's poor hygiene, and undiagnosed concomitant ocular surface diseases (dry eye, blepharitis, etc.)[15].

The aim of this study is to estimate the progression of keratoconus after cross linking during 1year duration.

Patients and methods

This study is a prospective study carried out to estimate the progression of Keratoconus after cross linking. It was conducted in Dar Al Salam eye hospital, the LASIK Clinic, Baghdad, for a period from , March, 2011 to the December, 2016.

Inclusion criteria:

Documented evidence or reported progression in early to moderate keratoconus.

Exclusion criteria:

1. Corneal irregularity/scarring prevented acquisition of accurate refractive and topographic data.
2. K reading > 60D.
3. Central corneal thickness <400 μm.
4. Age > 40 years unless there is progressive keratoconus.
5. Pregnancy.
6. Other active ocular pathology.
7. Previous anterior segment surgery.
8. Diabetes.
9. Inability to remove rigid contact lenses for 3 weeks prior to examinations.
10. Patients not completed 1 year of follow up.

Data collection:

The data were collected through direct interview and fulfilling a prepared questionnaire. Keratoconus eyes were diagnosed by the same ophthalmologist. Pre and Post-operative examination was done. Auto refraction measurement was done by auto refractometer (Topcon KR8900), K-reading and CCT was done by Topography(OCULUS Pentacam)and(Sirius for the last 2 years).

The questionnaire included the followings:

1. Demographic information: Age and gender.
2. Pre and post-operative BSCVA.
3. Pre and post-operative auto refraction.
4. Pre and post-operative simulated keratometry (K).
5. Pre and post-operative central corneal thickness (CCT).

Surgery:

The surgery was done in Dar-Al Salam Hospital, by the same ophthalmologist. Prior to surgery, frequent application of topical anesthesia (Tetracaine1%) was done. The patient was positioned beneath an operating microscope, the eyelid skin sterilized with povidone iodine 5% and a lid speculum inserted. A 9.00 mm area of

central epithelium was removed using a disposable corneal epithelial spatula . Riboflavin 0.1% were instilled onto the cornea every 5 min for 30 min before irradiation to allow sufficient saturation of the stroma. UVA exposure was for 30 min utilizing 370 nm UVA radiation, calibrated prior to surgery with a UV light meter at 3 mw/cm^2 with a beam diameter of 8.00 mm. During UVA exposure, riboflavin 0.1% eye drops were administered every 3–5 min. Following surgery, Tobramycin 0.3% was administered, and soft contact lens was inserted. Oral analgesics, Panadol night (500mg paracetamol & Diphenhydramine Hydrochloride 25mg) three times a day was prescribed. The contact lenses were removed for all the patients after 5 days.

Follow up:

We followed up the keratoconus eyes at the 1st postoperative day , 5 days , 1 month , 3 months , 6 months, and 1 year. Most patients were lost their follow up after 1 year, for this reason no regular longer follow up can be done.

Statistical analysis:

By using computerized statistical software, All patients data entered; version 17 of Statistical Package for Social Sciences (SPSS) was used. Descriptive statistics presented as mean ± standard deviation and frequencies as percentages. Normality of the data verified by Kolmogorov Smirnov analysis. Multiple contingency tables conducted and appropriate statistical tests performed, Paired t-test was used to compare between means. In all statistical analysis, level of significance (p value) set at ≤ 0.05 and the result presented as tables.

RESULTS:

A total of 266 eyes with keratoconus were enrolled in this study, all the 172 patients were followed up after Collagen cross-linking using UVA light and riboflavin. Mean age of patients with studied eyes was 18±10 years with predominance of patients with age <20 years. Females were more than males with ratio nearly 2:1. All these findings were shown in table 1.

Table 1: Demographic characteristics of studied patients.

Variable	No. of Patients	%
Age mean ± SD (18±10 years)		
< 20 years	68	39.5
20-29 years	56	32.5
≥ 30 years	48	28
Total	172	100.0
Gender		
Male	58	33.7
Female	114	66.3
Total	172	100.0

Postoperatively, VA was unchanged in 206 eyes, improved in 50 eyes, and deteriorated in 10 eyes duo to progression of the diseaseand there were no long-term significant complications. The degree of improvement was one line for 34 eyes, two lines for 12 eyes and three lines for 4 eyes, table 2.

Table 2: Visual acuity and improvementdegree for studied eyes after 1 year.

Variable	No. of eyes	%
Visual acuity (VA)		
Unchanged	206	77.44
Deteriorated	10	3.76
Improved	50	18.80
Total	266	100.0
Improvement degree		
One line	34	68
Two lines	12	24
Three lines	4	8
Total	50	100.0

The mean cylinder of studied eyes preoperatively was -3.8 ± 2.2 and 1 year postoperatively the mean cylinder was -4.0 ± 2.5, the mean difference was 0.34 ± 1.3 with no significant difference between two readings (p=0.1), table 3.
The mean sphere of studied eyes preoperatively was -2.8 ± 2.5 and 1 year postoperatively the mean sphere was -2.7 ± 2.5, the mean difference was -0.06 ± 0.8 with no significant difference between two readings (p=0.7), table 3.
Mean K of studied eyes preoperatively was 48.8 ± 2.2 and postoperatively was 48.6 ± 3.1 with mean difference as -0.05 ± 0.9, no significant difference between K readings pre and postoperatively (p=0.8), table 3.
Mean CCT of studied eyes preoperatively was 493.9 ± 46.8 and postoperatively CCT mean was 495.1 ± 50.8 with mean difference as -1.5 ± 16.11. No significant difference was observed in CCT pre and postoperatively (p=0.5), table 3.

Table 3: Pre and 1 year postoperative results for studied eyes.

Parameter	Pre operative	1 year post operative	Difference	P
	Mean±SD	Mean±SD	Mean±SD	
Auto-refraction				
Cylinder	-3.8±2.2	-4.0±2.5	0.34±1.3	0.1
Sphere	-2.8±2.5	-2.7±2.5	-0.06±0.8	0.7
Simulated Keratometry (D)				
K (D)	48.8±2.2	48.6±3.1	-0.05±0.9	0.8
Central Corneal Thickness				
CCT	493.9±46.8	495.1±50.8	-1.5±16.11	0.5

Mean cylinder preoperatively for eyes with unchanged VA as final outcome was -3.7 ± 2.5and mean cylinder of them 1 year postoperatively was -3.5 ± 2.8 with mean difference as 0.5 ± 1.2, there was a statistically significant difference between pre and post-operative cylinder readings (p=0.01), table 4.
Mean sphere preoperatively for eyes with unchanged VA as final outcome was -2.8 ± 2.0 and mean sphere of them 1 year postoperatively was -2.7 ± 2.9 with mean difference as 0.07 ± 1.0, no statistically significant difference was observed in sphere readings pre and post operatively (p=0.7), table 4.
Mean K preoperatively of eyes with unchanged VA as final outcome was 47.9 ± 1.6 and postoperatively was 47.6 ± 2.5 with mean difference was -0.13±0.8. There was no significant difference in K means pre and post operatively (p=0.6), table 4.
Mean CCT preoperatively for eyes with unchanged VA was 485.1 ± 46.9 and postoperatively was 485 ± 47.6 with mean difference as -2.1 ± 13.9. There was no significant difference in CCT pre and post operatively (p=0.5), table 4.

Table 4: Pre and 1 year postoperative results for eyes with unchanged VA.

Parameter	Pre operative	1 year post operative	Difference	P
	Mean±SD	Mean±SD	Mean±SD	
Auto-refraction				
Cylinder	-3.7±2.5	-3.5±2.8	0.5±1.2	0.01
Sphere	-2.8±2.0	-2.7±2.9	0.07±1.0	0.7
Simulated Keratometry (D)				
K (D)	47.9±1.6	47.6±2.5	-0.13±0.8	0.6
Central Corneal Thickness				
CCT	485.1±46.9	485±47.6	-2.1±13.9	0.5

The mean cylinder preoperatively for eyes with improved VA as final outcome was -4.8 ± 1.6 and mean cylinder of them 1 year postoperatively was -4.4 ± 1.6 with mean difference as -0.5 ± 0.9, no significant difference was observed in cylinder readings pre and post operatively (p=0.5), table 5.

The mean sphere preoperatively for eyes with improved VA as final outcome was -2.1 ± 3.0 and mean sphere of them 1 year postoperatively was -1.2 ± 2.6 with mean difference as -0.6 ± 0.6, no significant difference was observed in sphere readings pre and post operatively (p=0.06), table 5.

Mean K preoperatively of eyes with improved VA as final outcome was 47.3 ± 1.4 and postoperatively was 47.5 ± 0.9 with mean difference was 0.2 ± 0.6. There was no significant difference in K means pre and post operatively (p=0.1), table 5.

Mean CCT preoperatively for eyes with improved VA was 520.1 ± 49.5 and postoperatively was 525.2 ± 52 with mean difference as -4.9 ± 14.1. No significant difference was observed in CCT pre and post operatively (p=0.3), table 5.

Table 5: Pre and 1 year postoperative results for eyes with improved VA.

Parameter	Pre operative	1 yearpost operative	Difference	P
	Mean±SD	Mean±SD	Mean±SD	
Auto-refraction				
Cylinder	-4.8±1.6	-4.4±1.6	-0.5±0.9	0.5
Sphere	-2.1±3.0	-1.2±2.6	-0.6±0.6	0.06
Simulated Keratometry (D)				
K (D)	47.3±1.4	47.5±0.9	0.2±0.6	0.1
Central Corneal Thickness				
CCT	520.1±49.5	525.2±52	-4.9±14.1	0.3

DISCUSSION:

Mean age of patients with studied eyes was 18 ±10 years with prevalent younger age groups. This finding is similar to results of Mohd-Ali B, et al study in Malaysia (2012) that reported high incidence of keratoconus among younger age [16]. Georgiou et al, whose study population mostly comprised people from the Indian continent found lower incidence of atopy among Asians compared Caucasians [17]. Furthermore, there were reports stating that the Asian keratoconus patients were generally younger when the condition first presented and required corneal grafting at earlier age. According to Pierson et al majority of Asian keratoconus patients reaches the advanced stage by the second decade of their life [18].

Females with keratoconus in present study were more than males. This finding is consistent with Fink BA, et al study in USA (2005) [19]. In a multicenter Collaborative Longitudinal Evaluation of Keratoconus (CLEK) study, Fink et al reported that gender differences exist in the history, vision and ocular symptoms of keratoconus patients [19]. Shneor E, et al study in UK (2013) reported prevalent male gender for development of keratoconus than females [20]. In performed study in New Zealand, men were reported to have earlier onset and experienced a more rapid disease course [21].

In another study conducted at a specialist contact lens clinic in United Kingdom, approximately 60% of the 130 keratoconic patients were men[22].This inconsistency from our findings might be due to racial difference and different sample size.

This study is similar to Wollensak G (2010) and Raiskup-Wolf F, et al (2008) studies in Germany shows that CXL with riboflavin is effective in halting the progression of keratoconus [23,24]. One year post-operatively, VA was improved for 30% of studied eyes with deterioration in 3.3%. This finding is close to results of Shalchi Z, et al review study in UK (2015) [25] and Stojanovic A, et al study in Norway (2014)[26] that reported VA improvement in about one third of studied eyes with absence or low VA deterioration. About two thirds of studied eyes had unchanged VA which is consistent with results of O' Brat DPS, et al study in UK (2011) which reported no significant difference in VA postoperatively [27]. Most of

eyes with improved VA gained 1-2 lines. This finding is similar to results of Stojanovic A, et al study in Norway (2014)[26].

Regarding auto-refraction, there was no statistically significant difference 1 year postoperatively in means of cylinder and sphere for all eyes (changed and unchanged VA). These findings are similar to results of Gore DM, et al study in UK (2013) [28] and Razmjoo H, et al study in Iran (2013) [29]. The only exception was for cylinder measurement done for eyes with unchanged VA, as there was statistically significant decrease in cylinder mean postoperatively (p=0.01). This finding is consistent with results of Saffarian L, et al study in Iran (2010) that found significant drop in cylinder after one year treatment of keratoconus with CXL [30].

Regarding simulated keratometry (K reading), no statistically significant differences were observed for K means pre and postoperatively for all eyes (changed and unchanged VA). Padmanaphan P, et al study in India (2015) [31] found no significant changes in K after CXL treatment with riboflavin for keratoconus.

Regarding central corneal thickness, there was no statistically significant difference in CCT of studied eyes pre and post operatively that is similar to results of Stojanovic A, et al study in Norway (2014) [26] and O' Brat DPS, et al study in UK (2011)[27].

Adverse events in this study were minimal and transient. All eyes exhibitedanterior corneal haze to some degree in the early postoperative period which cleared by 6 months. Ten eyes had deteriorated VA duo to continuous progression of the disease. There were no long-term complications associated with loss of corneal (or lenticular) transparency. There were no episodes of corneal infection, infiltration or scarring.

limitations in this study including, loss to follow up , selection bias and difference in corneal thickness.

CONCLUSION:

Cross linking is a minimally invasive procedure with no significant complications, that can halt or reduce keratoconus progression.

Recommendation:

Is to encouraging application of cross linking with riboflavin as a treatment choice for keratoconus in ophthalmological centers in Iraq.

Collagen Cross-Linking for the cornea can greatly decrease the need forcorneal transplant as an invasive procedure.Further large national sample studies should be supported.

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