Visual Outcome after Corneal Crosslinking in Patients with Progressive Keratoconus at the Royal Medical Services of Jordan

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ABSTRACT

Objectives: This study was designed to retrospectively evaluate the visual and topographic outcome after corneal crosslinking in patients with progressive keratoconus at the Royal Medical Services of Jordan.

Methods: The study is a retrospective, non-controlled, non-comparative study that was conducted in the LASIK and Refractive Surgery center at King Hussein military hospital, Royal Medical Services of Jordan between November 2015 and February 2018. All patients with progressive keratoconus who underwent corneal crosslinking (CXL) during that period were enrolled. Progression of keratoconus was defined as a recent change in the mean keratometry (Km) and/or manifest refraction during the last six months. An increase of 1.00 diopter (D) in the mean keratometry and/or an increase in manifest refraction (0.5 D spherical equivalent) were considered as a progression. Km value and corneal thickness were measured topographically by using pentacam. The extracted data included: age, gender, preoperative unaided vision, preoperative manifest refraction, type of crosslinking (epithelium off-iso CXL, epithelium on- Trans CXL), unaided vision 1 and 6 months after CXL, best corrected visual acuity preoperatively and six months after CXL, manifest refraction six months after CXL, mean keratometry (Km) pre operatively and six months post operatively, corneal thickness before cxl and six months after cxl, anterior and posterior segment examination, associated ocular diseases , complications, and follow up period. Patients with incomplete data or patients who had other types of keratectasia were excluded.

Results: During 28 months, a total of 46 patients were enrolled in the study, of whom 85 eyes underwent corneal crosslinking (39 patients had both eyes cross-linked, 7 patients had one eye cross-linked). Twenty-four (52.17%) patients were females and 22(47.83%) patients were males with a male: female ratio of (1: 1.01). The average age of females at time of surgery was (21.83± 4.32, range from 12 - 28) years which was close to males' average age (21.95±5.83, range from 12 - 31) years. The mean follow-up period was 6 months. Seventy (82.35%) eyes underwent standard corneal crosslinking (iso- CXL), while 15(17.65%) eyes underwent trans-epithelium corneal crosslinking. At 6 months after iso crosslinking, unaided visual acuity improved one Snellen line or more in 47(67.14%) eyes, and best corrected visual acuity improved one snellen line or more in 48(68.57%) eyes. Six months after Trans Cxl, unaided visual acuity improved one Snellen line or more in 8(53.3%) eyes, and best corrected visual acuity, improved one snellen line or more in 9(60%) eyes. Km value showed regression in 55 (78.57%) eyes six months after Iso Cxl and in 11 (73.33%) eyes six months after Trans CXL, none showed progression.

Conclusion: Crosslinking can improve unaided vision and best corrected visual acuity, arrest and even reverse progression of keratoconus in the studied population.

Keywords: Corneal Cross-linking, Keratoconus, Photosensitizer, Riboflavin, Ultraviolet light A,photosensitizer

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Introduction

Keratoconus is a non- inflammatory, progressive ectasia of the corneal stroma that can lead to high myopia,

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irregular astigmatism, acute hydrops, corneal thinning, protrusion, and scarring with eventual need to corneal transplantation in 10% to 20% of cases with progressive keratoconus. [1, 2] Traditionally, dealing with keratoconus impact on vision was the only available method to manage this condition by using spectacles, hard contact lenses, intrastromal corneal rings implant and corneal transplantation without attempting to alter the disease progression by itself.[3]

Corneal crosslinking was first developed in Germany in 1997 by Eberhard Spoerl at the Dresden University of Technology, [4] which works on altering the corneal mechanical and biochemical characteristics. It is a procedure in which a photo-sensitizer, riboflavin (vitamin B2), is applied to the cornea combined with ultraviolet light A (370 nm) enhance more covalent bonds between collagen fibers which makes cornea stiffer, flatter, and halting or may slowdown the progression of keratoconus.[6, 7, 8]

Rigid, stable cornea providing high quality of vision is the main aim of this technique. This study was designed to retrospectively evaluate the visual and topographic outcome after corneal crosslinking in patients with progressive keratoconus at the Royal Medical Services of Jordan.

Methods

The study is a retrospective, non-controlled, non-comparative study that was conducted in the LASIK and refractive surgery center at King Hussein military hospital, Royal Medical Services of Jordan between November 2015 and February 2018. All patients with progressive keratoconus who underwent corneal crosslinking (CXL) during that period were enrolled. Progression of keratoconus was defined as a recent change in the mean keratometry (Km) and/or manifest refraction during the last six month, an increase of 1.00 diopter (D) in the mean keratometry and/or an increase in manifest refraction (0.5 D spherical equivalent) were considered as a progression. Km value and corneal thickness were measured topographically by using pentacam, manifest refraction was done to all patients (no cycloplegic refraction was performed), patients who were using rigid contact lenses discontinued them one month before CXL. The extracted data included: age, gender, preoperative unaided vision, preoperative manifest refraction, type of crosslinking (epithelium off-iso CXL, epithelium on-Trans CXL), unaided vision 1 and 6 months post operatively, best corrected visual acuity preoperatively and six months after CXL, manifest refraction six months after CXL, mean keratometry (Km) preoperatively and six months post operatively, anterior and posterior segment examination, associated ocular diseases, complications, and follow up period. Pregnant patients, Patients with incomplete data or those who had other types of keratectasia were excluded.

The study and data collection complied with the tenets of the Declaration of Helsinki, and the ethical committee of the royal medical services approved the study.

Simple statistical analysis was used such as range, mean, standard deviation, and percentage.

Surgical Technique

The standard protocol of such case in the king Hussein Military hospital is as follow: Patients with corneal thickness more than 450 micrometer undergo epi-off (standard protocol, iso) crosslinking, while those with corneal thickness between 450 and 400 micrometer undergo epi-on (trans-epithelium) crosslinking. In standard protocol, one drop of pilocarpine 2% was applied to the eye followed by three drops of topical anesthesia (Tetracaine) five minutes apart. The eye was then scrubbed and draped and lid speculum inserted. By using beaver a 9 mm circle of epithelium free zone is created to enhance corneal absorption of vitamin B2 (Riboflavin 0.1% solution). One drop of Riboflavin 0.1% solution was applied to the cornea every two to three minutes for 15 minutes. After that, the cornea is irradiated by ultraviolet light type A (UV-A 370 nm) for 30 minutes, at an irradiance of 3 mW/cm^2 and 5 cm working distant from the eye, during irradiation drops of Riboflavin 0.1% solution and balanced saline solution were instilled on the cornea to prevent dryness; UV-A acted as a sensitizer that stimulated Riboflavin to form more covalent bonds between stromal collagen fibers, which, theoretically, should increase corneal rigidity, stability and halting progression of keratoconus. At the end of the procedure, insertion of soft bandage contact lens helped to relieve pain and to protect the growing epithelium, topical antibiotic (Ofloxacin^R 0.3% eye drops) were used five times a day, and preservative-free artificial tears eye drops are applied 6 times a day for one week. After one week, the soft bandage contact lens is removed, fluorometholone 0.1% eye drop prescribed 3 times a day, and all eye drops are tapered slowly over 1 month period except the use of artificial tears, which should be continued for more than 3 months particularly in patients with dry eye.

In trans–epithelium crosslinking, the epithelium is not removed, and One drop of Riboflavin 0.1% solution was applied to the cornea every 2 to 3 minutes for 30 minutes followed by UV-A irradiation for 30 minutes which eliminated the need for contact lens. Fluorometholone 0.1% was used from day one.

Each patient was seen and examined after one week, one, three, and six months intervals.

Results

A total of 46 patients were enrolled in the study, of whom 85 eyes underwent corneal crosslinking (39 patients had both eyes cross-linked, 7 patients had one eye cross-linked). Twenty-four (52.17%) patients were females, while 22 (47.83%) patients were males with a female to male ratio of (1.01:1). The average females' age at time of surgery was (21.83± 4.32; range 12 - 28) years which was close to males' average age (21.95±5.83; range 12 - 31) years. The follow-up period was 6 months. Seventy (82.35%) eyes underwent standard corneal crosslinking (iso- CXL), while 15 (17.65%) eyes underwent trans- epithelium corneal crosslinking. At one month after Iso crosslinking, unaided visual acuity remained the same in 40(57.14%) eyes, improved one Snellen line or more in 22(31.43%) eyes, and deteriorated one Snellen line or more in 8 (11.43%) eyes. At 6 months after iso crosslinking, unaided visual acuity improved one Snellen line or more in 47(67.14%) eyes, remained same as before crosslinking vision in 21(30%) eyes, and dropped one Snellen line or more, in 2(2.86%) eyes, (Table I).at six months after iso Cxl, best corrected visual acuity improved one Snellen line or more in 48(68.57%) eyes, remained the same as before Iso Cxl in 20 (28.57%)eyes, and deteriorated one Snellen line or more in 2(2.86%)eyes,(Table II)

One month after Trans Cxl, unaided visual acuity improved one Snellen line or more in 4(26.7%) eyes, 9(60%) eyes remained the same as before Cxl vision, and 2(13.3%) eyes lost one Snellen line or more. While, six months after Trans Cxl, unaided visual acuity improved one Snellen line or more in 8(53.3%) eyes, 6(40%) eyes maintained same as before Cxl vision, and one eye (6.7%) lost one Snellen line or more, **(**Table III). Best corrected visual acuity, six months after trans Cxl, improved one snellen line or more in 9(60%) eyes, 5(33.3%) eyes maintained same as before cxl vision, and one eye (6.7%) lost one Snellen line or more, (Table IV).

The Km values six months after Iso Cxl, Comparing to before Iso Cxl values, were as follow: In 55(78.57%) eyes Km regressed on average by 0.63 (D), remained the same value in 15 (21.43%) eyes, and showed no progression, (Table V).Meanwhile, the change of Km values six months after trans Cxl was as follows : Km regressed on average by 0.52 (D) in 11(73.33%)eyes, maintained same as before Cxl value in 4(26.67%) eyes, and progression wasn't observed**, (**Table VI).

The change of manifest refraction in spherical equivalent, six months after Iso Cxl , was as follows: 47(67.14%) eyes improved and showed regression in refractive error by 0.7 D (range from 0.13 to 2.25 D), 17(24.29%) eyes maintained same as before Cxl refraction, and 6(8.57%) eyes showed increase of refractive error by 0.49 D(range from 0.25 to 0.75 D), (Table VII).The average change of manifest refraction six months after Trans Cxl in spherical equivalent was as follow: 9(60%) eyes improved and manifested regression in refractive error by 0.68 D (range from 0.5 to 2.0 D), 4(26.67%) eyes maintained same as before Cxl refraction, and refractive error increase by 0.48 D (range from 0.25 to 0.8 D) in 2(13.33%) eyes**,** (Table VIII).

Nine patients had history of vernal keratoconjunctivitis, one patient had bilateral lens opacity, seven eyes developed complications; five had corneal haze and two had dry eye, all treated with topical eye drops.

Table I: The change of unaided visual acuity in one and six months (M) after Iso Cxl

Unaided visual acuity	Number of eyes after one month	Number of eyes after six months
1 Snellen line loss or more	8 (11.43%)	2 (2.86%)
Same as before crosslinking vision	40 (57.14%)	21 (30%)
1 Snellen line gain or more	22 (31.43%)	47 (67.14%)

Table II: The change of best corrected visual acuity six months (M) after iso Cxl

Best corrected visual acuity	Number of eyes after six months
1 Snellen line loss or more	2 (2.86%)
Same as before crosslinking vision	20 (28.57%)
1 Snellen line gain or more	48 (68.57%)

Table III: The change of unaided visual acuity in 1 and 6 months (M) after Trans Cxl

Unaided visual acuity	Number of eyes after one month	Number of eyes after six months
1 Snellen line loss or more	2 (13.3%)	1 (6.7%)
Same as before crosslinking vision	9 (60%)	6 (40%)
1 Snellen line gain or more	4 (26.7%)	8 (53.3%)

Table IV: The change of best corrected visual acuity 6 months (M) after Trans Cxl

Best corrected visual acuity	Number of eyes after six months
1 Snellen line loss or more	1 (6.7%)
Same as before crosslinking vision	5 (33.3%)
1 Snellen line gain or more	9 (60%)

Table V: The change in mean keratometry (Km) 6 months after Iso Cxl

Keratometry (Km) 6 months after Iso CXL	Number of eyes (%)	Average change in km (D)
Progression	0	0
No change	15 (21.43%)	0
Regression	55 (78.57%)	0.63

Table VI: The change in mean keratometry (Km) 6 months after Trans Cxl

Keratometry (Km) 6 months after trans CXL	Number of eyes (%)	Average change in km(D)
Progression	0	0
No change	4 (26.67%)	0
Regression	11 (73.33%)	0.52

Table VII: The change in manifest refraction 6 months after Iso CXL (spherical equivalent) in D

	Number of eyes (%)	Average change in refraction (D)
Worsening (Increase in spherical equivalent)	6 (8.57%)	+0.49 (0.25----0.75)
Same refraction	17 (24.29%)	----
Improving(decrease in spherical equivalent)	47 (67.14%)	-0.7 (-0.13---- -2.25)

Table VIII: The change in manifest refraction 6 months after Trans CXL (spherical equivalent) in D

	Number of eyes (%)	Average change in refraction (D)
Worsening (Increase in spherical equivalent)	2 (13.33%)	+0.48 (0.25---- 0.8)
Same refraction	4 (26.67%)	----------
Improving(decrease in spherical equivalent)	9 (60%)	-0.68 (-0.5----- -2.0)

Discussion

Crosslinking is a time dependent process that initiates new covalent bonds between corneal collagen fibers which lead to a change in the mechanical and biochemical characteristics of the cornea; ultraviolet light type A activates Riboflavin (vitamin B2) to initiate these changes which result in rigid, optically regular cornea,[9,10] which would enhance the unaided vision. In 2006, a study conducted in Italy by Caporossi et al, [11] showed significant improvement in unaided vision (3.6 line gain) post crosslinking in patients with progressive keratoconus. In this study, the percentage of eyes which gained one Snellen line and more was in line with Caporossi's result. Two patients (three eyes) lost one snellen line or more; both of them were young (12 and 13

years old, one eye underwent Trans Cxl and had corneal haze, and two eyes underwent iso Cxl and complicated by dry eye).

The natural course of the keratoconus never shows regression[5] ,increased corneal stiffness and stability after absorption of ultraviolet light –A and Riboflavin, which is maximum at the anterior part of the cornea[10,12,13], theoretically, should restore the cornea back to the normality. Caporossi et al [11], addressed reduction in the mean K of 2.1 ± 0.13 diopter (D) in the central 3.0 mm after follow up period of 3 months, in this study, the average mean keratometry (Km) scored regression in 66 eyes (Iso and Trans) and the average decrement was 0.63 D, and 0.52 D 6 months after Iso, and Trans Cxl respectively. Similar results have been reported from Iran [14], and India [15]. The difference in the average change of the km can be attributed to the variability of the follow up periods, and hence, the question should be, how durable these topographic changes are; a Middle East study conducted by El-Raggal, 2009 [13] showed significant reduction in the spherical refractive error (mean spherical error was -3.20 ± 1.46 D and changed to -2.73 ± 1.56 D) and transient stability of topographic changes post crosslinking in keratoconus patients; the regression of the Km value became insignificant at six months post crosslinking. However, no progression of corneal steepening was observed in any of the treated eyes. In this study, manifest refraction in spherical equivalent regressed by 0.7 D after Iso Cxl, and by 0.68 D after Trans Cxl which confirmed by the reduction in mean curvature (Km) detected topographically. A total of 56 (Iso and Trans) eyes showed reduction in refractive error, 55 (Iso and Trans) eyes showed improvement in unaided vision, and 57(Iso and Trans) eyes showed improvement in best corrected visual acuity. It seems logical that reduction in refractive error is associated with a significant increase in unaided vision [11]. Eight eyes showed progression of refractive error despite the stability, even regression, of Km values; one possible explanation is that seven eyes of those developed complications (five eyes had corneal haze, and two had dry eye).

Seven eyes developed minor complications in the form of corneal haze and dry eye; and they were treated topically, No serious complications such as microbial keratitis [16] were reported.

Crosslinking is the only reported treatment that halt or slowdown keratoconus progression [17, 18], and that eventually would decrease the need for keratoplasty [19] in this young age group and positively affect the quality of their life.

Despite the short follow up period (six months), this study agreed with other studies' results and showed dramatic impact of crosslinking on the cornea in terms of physiology (improvement of vision) and anatomy (decrease steepening; regression of km value) through simple , minimally invasive , and cost effective procedure which carried low risk of complications . Crosslinking would reduce the need for penetrating keratoplasty and improve the functionality of patients own cornea.

Conclusion

Crosslinking can improve unaided vision and best corrected visual acuity, arrest and even reverse progression of keratoconus in the studied population.We recommend future prospective study that involves larger population sample and follows patients for longer period to ensure the durability of this clinical changes.

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