Accelerated versus conventional corneal collagen crosslinking: Short-term clinical outcomes in stabilizing keratoconus

Walaa Aldairi, Reham AlQahtani, Salem Alzaid, Ahmed Mousa, Rajiv Khandekar, Samar A. Al-Swailem

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Abstract:

PURPOSE: The purpose of the study is to compare the short-term outcomes of corneal collagen crosslinking (CXL) using the conventional (Dresden) protocol and an accelerated CXL (ACXL) protocol to stop keratoconus (KC) progression.

METHODS: A chart review was performed for all the patients with KC who underwent CXL in the last 7 years. Data were compared at baseline and at all follow-up examinations for uncorrected visual acuity (UCVA), best spectacle corrected visual acuity (BCVA), keratometry (K), central corneal thickness, and complications of CXL. Pre- and post-intervention values were compared for each group. $P < 0.05$ was statistically significant.

RESULTS: After the treatment, there was a statistically greater improvement in UCVA in the conventional CXL (CCXL) group (49%) compared to the ACXL group (34%) ($P = 0.028$). The improvement in BCVA was similar between the groups ($P = 0.060$). Gain of two lines of UCVA and stability were comparable between groups ($P = 0.078$ and $P = 0.060$, respectively). The average flat K and steep K values fluctuated remarkably across different follow-up assessments in both the groups. At 3 months of follow-up, there was a statistically significantly faster return to baseline levels of flat and steep Ks in the CCXL group ($P = 0.028$ and $P = 0.002$, respectively).

CONCLUSION: The findings of the current study confirm the efficacy and safety of accelerated high-fluence CXL compared to CCXL. Both protocols were effective in stabilizing KC at 9th-month and the last follow-up visit. Larger prospective randomized controlled trials and longer follow-up are required to confirm our findings.

Keywords:

Corneal collagen crosslinking, keratoconus, maximum keratometry, riboflavin

Introduction

Keratoconus (KC) is a bilateral progressive corneal ectasia that can lead to significant visual morbidity. Several studies have investigated the underlying pathology to halt the progression of the ectasia, decrease irregular astigmatism, and preserve vision.[1] Over the last two decades, corneal collagen crosslinking (CXL) has been increasingly used as an effective modality for halting KC.

Over time, many accelerated protocols have been proposed that claim similar safety and efficacy as the conventional (Dresden) CXL (CCXL) protocol.[2,3]

In this retrospective study, we compare the conventional (Dresden) protocol to an accelerated protocol with a total energy of 7.20 J/cm^2 with 8 min irradiation time for progressive KC. To our knowledge, this is the largest reported series from this region. Its value will not be limited to Saudi Arabia (SA), but the benefit will extend to the international ophthalmic community, especially the Middle East region.

Methods

The Institutional Review Board/Ethics Committee at the King Khaled Eye Specialist Hospital (KKESH, RP 1209), Riyadh, SA, approved this study. This study adhered to the tenets of the Declaration of Helsinki of 1975, as revised in 2003. This retrospective cohort study

Department of Research, King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia

Address for correspondence:
Dr. Samar A. Al-Swailem, Department of Research, King Khaled Eye Specialist Hospital, P.O. Box 7191, Riyadh 11462, Saudi Arabia.
E-mail: angelofsa@yahoo.com

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compared patients who underwent accelerated CXL (ACXL) or CCXL for KC.

The sample size was calculated considering a 95% confidence interval, α error of 0.05, two-tailed proposed comparison with an effect size of 0.5, and estimated power of 90% where the total sample size was estimated at 210 eyes. The sample was then distributed into both study arms; however, minor changes were made according to data availability.

Patients were selected if they were diagnosed with progressive KC and underwent either the ACXL protocol or CCXL protocol from January 2010 to June 2016. All patients or their guardians (if <18 years old) consented to the procedure. Progressive KC was defined as changes in one or more of the following parameters over 6 months: increase in spherical equivalent ≥0.75 D, increase in maximum keratometry (Kmax) ≥1.0 D, and decrease in central corneal thickness (CCT) of 20 μm or more. The inclusion criteria were eyes with progressive KC, corneal thickness >400 μm, and a minimum of 9 months of follow-up after CXL. Patients with evidence of herpetic keratitis, corneal scarring, Vogt's striae, severe dry eye disease, concomitant autoimmune disease, guttata, pregnancy/lactation, and corneal ectasias other than KC were excluded from the current study.

Data were collected on patient demographics (age and gender), and clinical indicators collected were the involved eye, preoperative and postoperative uncorrected visual acuity (UCVA), best spectacle-corrected visual acuity (BCVA), manifesting refraction (if available), CCT as assessed by Pentacam (Oculus GmbH, Wetzlar, Germany), keratometry (K) including mean K on topography, flat K (K1), steep K (K2), Kmax (maximum anterior sagittal curvature), Kmean (defined as the simulated keratometry or Sim K and is determined as the average keratometry), tonometry, corneal clarity, fundoscopy, additional procedures either preoperatively or postoperatively such as intrastromal corneal ring segments implantation, need for keratoplasty after CXL, and postoperative complications of CXL. Postoperative data were collected at 3, 6, and 9 months in addition to the last follow-up visit to a maximum of 1.5 years.

The study sample was divided into Group 1 that underwent ACXL protocol and Group 2 that underwent conventional (Dresden) protocol (CCXL).

Corneal collagen crosslinking procedure

Written, informed consent was obtained from each participant. Parental consent was obtained if the patient was <18 years old. The procedure was performed in sterile condition first, topical anesthesia drops (oxybuprocaine hydrochloride 0.4%) were instilled in the operative eye, and the central 8–10 mm of epithelium was removed. To loosen the epithelium from the stroma, 8.0 mm retention ring was filled with an ethylic alcohol 20% solution and a 30-s soak was performed. The loosened epithelium was then removed using a spare. Corneal thickness (central and peripheral) was measured using ultrasonography (Sonogage Corneo-Gage™ Plus; Cleveland, OH, USA) before and after epithelial removal.

Group 1 (ACXL) underwent CXL as follows: riboflavin solution (VibeX Rapid; Isotonic 0.1% riboflavin with HPMC) was applied to the corneal surface at intervals of 1–5 min for 20 min. However, if CCT was between 399 and 375 μm and then hypotonic riboflavin was used. Subsequently, 8 min of irradiation (370 nm ultraviolet A [UVA]; Peschke crosslinking system [Peschke GmbH, Huenenberg, Switzerland] or Avedro crosslinking system [Glaukos Corp, San Clemente, California, United States]) was delivered in a pulse mode with an irradiance of 15 mW/cm^2 and a total energy of 7.20 J/cm^2.

Group 2 underwent CCXL as follows: riboflavin solution (VibeX; Isotonic 0.1% riboflavin with 20.0% dextran T500) was applied on the corneal surface at intervals of 1–5 min for 30 min or until riboflavin was seen in the anterior chamber. However, if CCT was between 399 and 375 μm, then a hypotonic riboflavin (without dextran) was applied. Subsequently, 30 min of irradiation (370 nm UVA, Peschke cross-linking system or Avedro cross-linking system) was delivered with an irradiance of 3 mW/cm^2 and a total energy of 5.4 J/cm^2.

In both groups, at the end of the procedure, a soft contact lens bandage was placed on the eye. The postoperative regimen included topical ofloxacin 0.3% or moxifloxacin 0.5% QID (Vigamox; Alcon Inc., Fort Worth, TX, USA) for 1–2 weeks. Topical prednisolone acetate 1% (Pred Forte, Allergan Inc., Dublin, Ireland) was prescribed for 2–4 weeks and then changed to topical fluorometholone 0.1% (Allergan Inc., Dublin, Ireland) for 4–8 weeks. Postoperatively, most patients were evaluated at 1 day, 1 week, 1 month, and every 3 months for 2 years and yearly thereafter.

Data management and analysis

Data were collected, verified, and coded using Microsoft Access (Microsoft Corp., Redmond, WA, USA). Data were then analyzed using SPSS for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). In patients who underwent bilateral surgery, each eye was analyzed separately. Categorical data were presented as frequency and percentages. The Chi-square test was used to test the association between categorical variables (Fisher's exact test when indicated). Student's *t*-test (Mann–Whitney *U*-test when indicated) was used to compare the mean of continuous variables between groups. $P < 0.05$ was considered statistically significant.

Results

The study sample comprised 211 eyes of 182 patients with progressive KC. There were 100 (52.13%) patients (110 eyes) in the ACXL group and 82 (47.87%) patients (101 eyes) in the CCXL group. The mean age of the patients was 22.2 ± 5.4 years (range, 9.0–37.3 years). There were 140 (66.4%) males and 71 (33.6%) females. There were 108 (51.2%) right eyes and 103 (48.8%) left eyes. The

average duration of follow-up was 15.5 ± 4.1 months (range, 9–25 months).

The mean age was 20.7 ± 5.3 years (range, 9.0–35.2 years) in Group 1 (ACXL group) and 23.84 ± 4.97 years (range, 18.87–28.8 years) in Group 2 (CCXL group). There was a statistically significant difference in the mean age between the two groups ($P = 0.001$). There were 74 (67.3%) males and 36 (32.7%) females in Group 1 and 66 (65.3%) males and 35 (34.7%) females in Group 2 ($P = 0.088$). Laterality was comparable between groups ($P = 0.308$). Table 1 presents the demographic and clinical characteristics of patients in both groups. Group 1 had more advanced KC based on corneal thickness and steep K readings. The CXL procedure was successful from the first time in all patients in both groups.

Visual outcome

The mean LogMAR UCVA was 0.65 ± 0.49 in Group 1 (ACXL) and 0.55 ± 0.45 in Group 2 (CCXL group) ($P = 0.132$). At the 3-month follow-up visit, UCVA had improved in both groups. The difference between the groups was not statistically significant ($P = 0.357$). At 6th-month follow-up, the vision began reaching the baseline assessment values. There was a statistically significant difference in UCVA between groups ($P = 0.034$) at 6th-month follow-up but not at 9th-month follow-up ($P = 0.133$). At last visit, UCVA improved significantly in both groups compared to baseline UCVA. There was statistically significantly greater improvement in Group 2 by 0.08 LogMAR (final LogMAR of 0.47 ± 0.45) compared to 0.07 LogMAR in Group 1 (final LogMAR of 0.58 ± 0.46) ($P = 0.030$).

A statistically significantly greater number of eyes (49%) in Group 2 experienced an increase in UCVA compared to Group 1 (34%) ($P = 0.028$). A gain of 2 or more lines of UCVA occurred in 22.8% of the eyes in Group 1, compared to 34.7% in Group 2 ($P = 0.078$). By the last visit, UCVA remained stable in 34.5% of Group 1 eyes compared to 19.8% of Group 2 eyes ($P = 0.06$). UCVA decreased in 24.5% of eyes in Group 1 compared to 22.8% in Group 2 ($P = 0.41$).

At baseline visit, BCVA was 0.19 ± 0.17 in Group 1 and 0.16 ± 0.16 in Group 2 ($P = 0.262$. At 3 months, BCVA decreased by an average of 2 lines in Group 1 and by 1 line in Group 2 ($P = 0.18$). However, both groups regained the baseline BCVA at the 6th-month follow-up visit and BCVA stabilized out at the last visit ($P = 0.44$).

BCVA improved in 30% of the eyes in Group 1 and in 32.7% of eyes in Group 2 ($P = 0.673$). A gain of 2 or more lines in BCVA was noted in 10.9% of eyes in both groups. BCVA remained stable in 41.8% of Group 1 eyes compared to 36.6% of Group 2 eyes ($P = 0.44$). A decrease of 2 lines or more of BCVA was noted in 7.2% of eyes in Group 1 and 9.9% of eyes in Group 2 ($P = 0.25$) [Table 2].

Central corneal thickness (topography)

At baseline, the mean CCT measured by tomography was statistically significantly lower in Group 1 (466.11 ± 42.35 μm) compared to Group 2 (481.68 ± 40.69 μm) ($P = 0.006$). During different follow-up visits, a marked reduction in CCT was noted in both groups; however, the differences between groups were statistically insignificant (at 3, 6, and 9 months of follow-up: $P = 0.111$, $P = 0.545$, $P = 0.305$, respectively). At last follow-up, Group 2 (CCXL) regained corneal thickness that was closer to baseline, yet Group 1 (ACXL) did not show a similar change. This difference was statistically significant ($P = 0.007$).

Table 1: Demographic and clinical characteristics of both groups at baseline

Characteristic	Category	Group 1: ACXL (n=110), n (%)	Group 2: CCXL (n=101), n (%)	P
Age (years)	Mean±SD	20.7±5.3	23.8±4.9	0.001
Gender	Male	74 (67.3)	66 (65.3)	0.088
	Female	36 (32.7)	35 (34.7)	
Eye	OD	60 (54.5)	48 (47.5)	0.308
	OS	50 (45.5)	53 (52.5)	
LogMAR UCVA	Mean±SD	0.65±0.49	0.55±0.45	0.132
LogMAR BCVA	Mean±SD	0.19±0.17	0.16±0.16	0.262
CCT (μm)		466.1 (42.4)	481.7 (40.7)	0.006
Flat keratometry (diopter)		46.2 (4.8)	43.9 (3.3)	0.001
Steep keratometry (diopter)		50.3 (5.9)	47.6 (4.5)	0.001

ACXL: Accelerated corneal collagen crosslinking, CCXL: Conventional corneal collagen crosslinking, SD: Standard deviation, UCVA: Uncorrected visual acuity, BCVA: Best-corrected visual acuity, CCT: Central corneal thickness, OS: Oculus sinister, OD: Oculus dextrus

Table 2: Changes in visual acuity across the two groups at last follow-up

Index	Category	Group 1: ACXL (n=110), n (%)	Group 2: CCXL (n=101), n (%)	P
UCVA	Improvement	37 (34)	49 (49)	0.028
	Gain of 2 lines	25 (22.8)	35 (34.7)	0.078
	Stability	38 (34.5)	20 (19.8)	0.060
	Reduction in 2 lines	27 (24.5)	23 (22.8)	0.410
BCVA	Improvement	33 (30)	33 (32.7)	0.060
	Gain of 2 lines	12 (10.9)	11 (10.9)	0.998
	Stability	46 (41.8)	37 (36.6)	0.673
	Reduction in 2 lines	8 (97.2)	10 (9.9)	0.250

ACXL: Accelerated corneal collagen crosslinking, CCXL: Conventional corneal collagen crosslinking, UCVA: Uncorrected visual acuity, BCVA: Best-corrected visual acuity

Keratometry results

Corneal astigmatism was measured using Scheimpflug simulated keratometry. At baseline, Group 1 had a statistically higher flat K at 46.17 ± 4.79 D compared to 43.92 ± 3.25 D in Group 2 ($P = 0.001$). A significant flattening effect was noted at the 9th-month visit and at the last follow-up in Group 1. In Group 2, a similar flattening effect was noted earlier, at the 3rd-month and 6th-month follow-up visits. In Group 2, the flat K values returned to baseline by the last follow-up visit which was statistically significantly different compared to Group 1 ($P = 0.028$).

The average steep Ks were statistically significantly higher in Group 1 (50.25 ± 5.95 D) compared to Group 2 (47.61 ± 4.49 D) ($P = 0.001$). A flattening effect was noted at the 3rd-, 6th-, and 9th-month visits in Group q but was statistically insignificant compared to baseline values; ($P = 0.87$, $P = 0.94$, and $P = 0.34$, respectively). The steep K values returned to average baseline values at the last follow-up. In Group 2, flattening was noted early at the 3 months follow-up visit, continued at the 6th- and 9th-month visits, and returned closer to baseline values by the last follow-up visit. The difference in the progression of steep K values was statistically significant between groups ($P = 0.002$). Figure 1 confirms that mean keratometry returned to baseline by the last follow-up visit which was statistically significantly between groups ($P = 0.01$). Although the initial flattening of mean keratometry was lost gradually with time, it maintained, at last follow-up, closer to the baseline.

Corneal astigmatism

Corneal astigmatism was assessed with simulated keratometry readings using Scheimpflug tomography. In both groups, the amount of corneal astigmatism decreased compared to baseline at the 3rd-, 6th-, and 9th-month follow-up visits. There was no statistical difference in the mean between-group difference between these three follow-up visits ($P = 0.09$, $P = 0.90$, $P = 0.081$, respectively). At the last follow-up visit, the decrease in Group 2 was statistically significant ($P = 0.01$) but not for Group 1 ($P = 0.80$).

Complications

The most common postoperative complications were corneal haze in both groups ($P = 0.295$). Three cases of sterile corneal infiltrate resolved without any sequelae.

Discussion

KC is highly prevalent in our region and is the leading indication for keratoplasty in the country.[4] Keratoplasty is one of the main options for visual rehabilitation for progressive KC with poor vision where all other treatments have been exhausted. However, keratoplasty requires good patient adherence for follow-up, compliance to treatment, especially

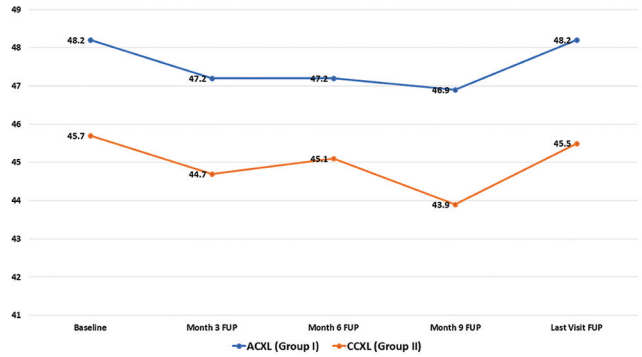

Figure 1: Changes in mean keratometry over follow-up visits in both groups. ACXL: Accelerated corneal collagen crosslinking, CCXL: Conventional corneal collagen crosslinking, FUP: Follow-up

equipped practice, and possibility of additional vision rehabilitation procedures. Several studies have documented a significant decline in the volume of keratoplasty procedures for KC after the introduction of CXL.[5]

The safety and efficacy of conventional CXL (Dresden protocol) are well established in the literature, and this procedure has been recently approved by the food and drug administration (FDA).[5,6] The favorable ectasia-stabilizing results with CXL have spurred clinical efforts at optimizing different aspects of the procedure such as the treatment time, intraoperative and postoperative comfort, and efficacy.

Several accelerated protocols have been proposed in the literature and compared to each other.[6-12] However, there are very few studies comparing the standard procedure (CCXL) to accelerated protocols.[6-12]

In this study, we compared the standard conventional protocol to the accelerated protocol with a total radiance of 7.2 J/cm^2. We analyzed a larger sample size than other comparative studies.[6-12] In addition, we had younger age patients than the other studies comparing the CCXL and the ACXL protocols.[6-12]

Yildırim *et al*. reported comparable results of two ACXL protocols in a randomized controlled trial.[7] They enrolled 74 eyes treated with intended UVA radiance of 5.4 J/cm^2 and 72 eyes treated with a radiance of 7.2 J/cm^2 and found comparable refractive and topographic outcomes in both groups.[6-12]

A recent prospective study included three protocols where 35 eyes were treated with the Dresden protocol, and two groups underwent accelerated treatment with different protocols (29 eyes received a total irradiance of 5.4 J/cm^2 and another 29 eyes received a total irradiance of 7.2 J/cm^2). Despite similar outcomes for keratometry measurements, BCVA, and other parameters, the study reported a significant improvement in KC indices with the conventional protocol.[11]

Tomita *et al*. compared prospectively the results of ACXL (15 min riboflavin, 3 min 30 mw/cm UVA light) to CCXL in 48 eyes with 1-year follow-up. They reported that both procedures were equally safe and effective, but ACXL was a faster procedure.[8] We compared ACXL (15 mW/cm^2 for 8 min) to CCXL (Dresden protocol), and our findings concur with the data found in the literature. Hence, to ensure the safety and efficacy of ACXL procedure compared to CCXL, we compared the visual outcomes as well as the keratometric parameters in addition to postoperative complications.

Stabilizing vision by halting the progression of KC is the main goal of CXL.[9,13-18] Vinciguerra *et al*. reported improved corneal and total wavefront aberrations and UCVA and BCVA at 12 months after CXL, in a prospective study.[13] In our study, vision stabilized in both groups in a similar manner which concurs with previous literature. However, we found a gain of 2 or more lines in 34% and 49% of eyes in the ACXL and CCXL groups, respectively ($P = 0.028$). This is a favorable

result although it is not the aim of this procedure. Theoretically, this improvement in UCVA and BCVA can be explained by corneal remodeling and improved corneal biomechanics along with a decrease in wavefront aberrations after CXL. These outcomes have been reported by several studies, especially with CCXL.[8,10,12,13,19]

We found that final BCVA was comparable in both groups. The baseline BCVA was regained in one-third of the treated eyes by the 6th-month visit ($P = 0.67$). The final BCVA was preserved in 41.8% of ACXL and 36.6% of CCXL cases with no statistically significant difference between groups ($P = 0.44$). This result supports the findings of previous studies.[8,18,19]

UCVA and BCVA in the early postoperative visits fluctuated in both groups, followed by a return to baseline values and/or an improvement over the duration of follow-up. A progressive improvement in vision and corneal topographic indices was reported in several studies with long-term follow-up (3–6 years), suggesting possible changes in our study population over time.[18,19]

Published data confirm that the cornea flattens after CXL.[8-10,13-22] Previous prospective, randomized, and retrospective studies of the standard (conventional) CXL protocol reported statistically significant flattening of the steepest simulated K value.[9,21] In their prospective clinical trial of the conventional protocol, Hersh *et al*. reported an improvement in visual acuity and Kmax in patients with progressive KC.[14] In addition, a prospective comparison of ACXL versus VCXL by Tomita *et al*. found no statistical significant difference in Kmean or Kmax values in both groups at 1 year postoperatively.[8] However, Tomita *et al*. reported a statistically significant difference in Kmean steepening in the accelerated group at both the 3rd-month and 6th-month visits, which regressed over time.[8]

In our study, the Kmean values of both groups regressed as early as 3 months. Furthermore, despite the fact that the ACXL group had steeper keratometry values, regression of Kmean, flat and steep K values exceeded those of CCXL at the last visit ($P = 0.01$, $P = 0.28$, $P = 0.002$, respectively). In addition, the decrease in corneal astigmatism was not significant in the ACXL group and was significant in the CCXL group compared to baseline values.

Transient thinning of the central cornea has been reported with a recovery to baseline values at the 6th-month visit.[11,21] However, in this study, ACXL showed statistically significant thinning compared to baseline. This can likely be attributed to the corneal haze in the early postoperative period after CXL, which leads to an underestimation of the pachymetry measurements obtained with tomography.

The demarcation line represents the depth of treatment and the associated impact on corneal biomechanical features after crosslinking. Although the retrospective nature of the current study precluded collection of data on this feature, the literature reports that an accelerated protocol produces a demarcation line up to 350 mm in depth.[8] When the duration is reduced and the irradiation energy is increased, a demarcation line can be incomplete and patchy different accelerated protocols. Some have reported that pulsed accelerated protocol (7.2 J/cm^2 instead of 5.4 J/cm^2) may facilitate more oxygen reuptake while prolonging treatment time at 8 min may influence a deeper penetration of oxidative damage.[8,9,20]

This study may be limited by its retrospective nature, lack of refraction data, and dropout of some follow-up visits. Our analysis was limited to the 9th-month and the last follow-up visit outcomes out to a maximum of 18 months, even though the CCXL group had a longer duration of postoperative follow-up. As suggested in the literature, long-term follow-up data may show further changes.[18,19] In addition, Group 1 (ACXL) had a slightly more advanced cases at baseline, which may have introduced a selection bias. At last, we evaluated KC cases regardless of the causes of ectasia particularly, the postlaser *in situ* keratomileusis ectasia, which may warrant further investigation.

Conclusion

Our study adds to the evidence on the efficacy and safety of accelerated high-fluence CXL compared to CCXL. Both protocols were effective in stabilizing KC at 9 months and out to 18 months. Given the simplicity, minimal cost, and likelihood of reducing the need for keratoplasty, CXL might also be well suited for developing countries. Larger prospective, randomized controlled trials with longer duration of follow-up are necessary to confirm the long-term safety and efficacy of accelerated crosslinking.

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Conflicts of interest

There are no conflicts of interest.

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