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Research Article

A Comparative Study: 36 Months Follow up Results of Accelerated Versus Conventional Corneal Collagen Cross-linking in Progressive Keratoconus Patients

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Abstract

Purpose: To compare the 36-month visual acuity, refraction, corneal topography, and corneal pachymetry outcomes of the conventional and accelerated corneal collagen crosslinking in progressive keratoconic eyes.

Methods: A prospective cohort study of 191 eyes of 76 patients. 91 eyes were treated with conventional crosslinking (C-CXL; 3mW/cm^2 for 30 minutes), while 100 eyes were treated with accelerated crosslinking (A-CXL; 30mW/cm^2 for 3 minutes). Preoperative and post-operative uncorrected (UCVA) and best corrected visual acuity (BCVA), spherical equivalent (SE), manifest refraction and corneal topography were evaluated and compared at different intervals of 3, 6, 12, 24 and 36 months.

Results: Both groups show significant improvement from baseline at final follow up in terms of uncorrected visual acuity. But the conventional method shows more improvement at final follow up (C-CXL; LogMAR 0.22, A-CXL; LogMAR 0.54, p = 0.03). There was no significant difference in terms of best corrected visual acuity. Both groups show insignificant improvement in spherical equivalent (SE) and cylinder. K1, K2 show comparable improvement in both groups, Kmean and Kmax show insignificant improvement from baseline in both groups. Central corneal thickness shows minimal change from baseline, with significant improvement by C-CXL (416.38 µm) over A-CXL (462.75 µm) (p = 0.028). No complications were detected in both groups.

Conclusion: Both conventional and accelerated CXL improved UCVA with more improvement at long-term follow up with the C-CXL. Entirely, C-CXL, as well as A-CXL, offers productive results in the strengthening of corneal tissue and disease stabilization.

Keywords: Cross Linking; CXL; Keratoconus; Conventional; Accelerated; Visual; Topographic; Refractive Outcomes

Introduction

Keratoconus is a relatively common eye disease [1]. It is usually bilateral, asymmetrical, noninflammatory corneal ectasia [2] characterized by progressive central and paracentral corneal thinning which leads to corneal protrusion and fibrosis, progressive irregular astigmatism, and refractive function deterioration which can

lead to high myopia [3]. The prevalence of keratoconus worldwide was 1.38 per 1000 [4]. Keratoconus commonly appears at teenage years. This early onset of the disease is a bad prognostic factor due to disease progression, which increase the rate of the need of corneal transplantation. Therefore, it is importantly to halt or slow down disease progression [5].

Numerous methods of treatment have been identified for keratoconus such as intracorneal ring implantation, gas-permeable contact lenses and lamellar or penetrating keratoplasty. None of the above-mentioned techniques can prevent the progression of the disease [6]. Corneal cross linking (CXL), which was developed in the 1990s, is a relatively new para- surgical technique that became the preferred treatment modality for corneal ectatic diseases because the primary goal of this therapy is to stabilize corneal ectasia and with proven efficacy in preventing disease progression by increasing corneal stiffness [7,8]. CXL is not a refractive procedure. By using riboflavin (vitamin B2) as a photosensitizer, followed by ultraviolet-A (UV-A) irradiation, together they induce covalent cross-links between collagen fibers, thereby increasing corneal strength and stability [9].

This traditional procedure already known as conventional CXL [10]. Recently, accelerated CXL was developed to shortens the exposure time by increasing the UVA power [11].

According to the literature, clinical studies comparing both treatment protocols showed comparable effect with parallel safety profiles [11-14], however, due to the lack of standard protocols of the treatment make these studies results limited. More evidence is needed to investigate the effectiveness of both CXL modalities. For that our study was conducted to compare the visual, refractive, topographic, and pachymetric outcomes in patients with progressive keratoconus who were treated with either conventional or accelerated crosslinking.

Methods

Study design and setting

A Prospective cohort study was done to follow up patients after corneal collagen cross-linking via conventional and accelerated treatment protocols for progressive keratoconus. The study was approved by Institutional Review Board (IRB) at An-najah national university, and the guidelines of the Declaration of Helsinki were followed. The study was conducted from January 2014 to December 2018 at two different centers in Nablus- Palestine. Center A was referred to the ophthalmology department at An-Najah national university hospital (NNUH) where the conventional treatment protocol was used, while An-Noor eye center at specialized Arab hospital was defined as Center B, where the accelerated treatment protocol was used. Informed consent was obtained from all patients.

Study population and sampling technique

The study applied conventional sampling method and included 191 eyes from 76 patients, where 91 eyes were treated by using the conventional crosslinking, while 100 eyes were treated by using the accelerated cross linking. All Patients were included according to the following criteria: patients with grade (I-III) keratoconus according to Amsler–Krumeich classification [15] and have a corneal thickness of 400 microns or more with at least one indication for CXL. Rise of 1.00 dioptre (D) in maximum keratometry (Kmax) in 1 year, drop of visual acuity (VA) (after excluding other probable non-cornearelated causes) and the necessity for fitting new contact lens more than one time in two years were accounted as indications for CXL [2]. On the other hand, patients with advanced keratoconus associated with stromal scarring in need for corneal grafting, corneal thickness less than 400 microns, corneal infections, corneal hydrops, severe dry eye, previous ocular surgery, or pregnancy and breast-feeding at time of presentation or at follow up were excluded.

Data collection and pre-operative assessment

Patients' relevant sociodemographic were extracted from patients' medical files, including age and sex. Pre-operatively, the participants underwent complete ophthalmic examination, including slit lamp examination, dilated fundoscopic examination, visual acuity (both uncorrected (UCVA) and best corrected (BCVA)), subjective refraction and corneal topography with central corneal thickness (CCT). For assessment of corneal topography and CCT, Pentacam Conventional Scheimpflug System was used (Oculus PentacamHR, OCULUS Optikgeräte GmbH, Wetzlar Germany). These baseline measures were also repeated at each visit of follow up and in both centers.

Surgical techniques

All cross-linking procedures were performed under sterile conditions in the operating room using local anesthesia. In both treatment protocols, 8-mm central corneal epithelium was scraped off using a scraper. In center A, Isotonic Riboflavin 0.1% solution without Dextran (Peschke Meditrade GmbH, Huenenberg, Switzerland) was applied every 2 minutes for 30 minutes as a photosensitizer. Then, UV-llumination was applied using the (VEGA CBM X-Linker,

Costruzione Strumenti Oftalmmici, ScandicciFirenze, Italy), with wavelength of 370 nm, and 3 mW/cm^2 irradiations for 30 minutes (total energy of 5.4J/cm^2). In center B, Isotonic Riboflavin 0.1% solution without dextran ((Peschke Meditrade GmbH, Huenenberg, Switzerland) was applied every 2 minutes for 10 minutes. UV-illumination was applied using the device (UV-X 2000, IROC Innocross AG,Zug, Switzerland), with wavelength of 370 nm, and 30 mW/cm^2 irradiation for 3 minutes (with similar total energy of 5.4J/cm^2). Caution was taken to avoid limbal area during illumination in both procedures.

Key differences between the 2 treatment protocols been summarized in table 1. Bandage contact lens was then applied after both procedures. Patients were prescribed antibiotic (ofloxacin ophthalmic solution 0.3%), steroid (prednisolone acetate 1% suspension) starting from the first day after operation and tapered over one month with complete wound healing, Refresh tears were also added to the prescription after steroid has been stopped. Follow up of patients started on day 1, week 1, then at 3, 6, 12, 24, 36 months after the procedure.

Conventional	Protocol	Accelerated
Yes	Removal of epithelium	Yes
Isotonic Riboflavin 0.1% without Dextran	Riboflavin	Isotonic Riboflavin 0.1% without Dextran
Every 2 mins for 30 mins	Duration of Soak	Every 2 mins for 10 mins
VEGA CBM X-Linker, Costruzione Strumenti Oftalmmici, Scandicci Firenze, Italy	UV-illumination Device	UV-X 2000, IROC Innocross AG, Zug, Switzerland
3mW/cm^2 for 30 minutes (total energy: 5.4J/cm^2)	Illumination protocol	30 mW/cm^2 continuously for 3 minutes (total energy: 5.4J/cm^2)

Table 1: Difference between Conventional vs Accelerated Treatment Protocols.

Statistical analysis

All data was analyzed using the SPSS software Version 20. All continuous data were presented as means and standard deviations. To compare the preoperative and postoperative measures between the two groups, two samples independent T-test and paired T-tests were performed for normally distributed variables, and nonparametric tests were used if variables are not normally distributed. A probability of equal or less than 5% ($p \leq 0.05$) was considered statistically significant.

Results

Baseline characteristics

We studied 191 eyes from 76 patients, where 91 eyes were treated by using the conventional crosslinking, while 100 eyes were treated by using the accelerated cross linking. In the A-CXL group, there mean age was 21.06 ± 5.220 whereas in the C-CXL group was 18.77 ± 5. 825. The male/female ratio in the C-CXL and group A-CXL group where similar to each other measuring 0.57 and 0.47 respectively. In general, there was no statistical difference between the ACXL and CXL groups in the measures of demographics, preoperative visual acuity, refraction, topography, except in Cylinder (D) there was a statistical significance of p-value 0.017 between the two groups. Please refer to Table 2 for the baseline characteristics of both CXL groups.

	C-CXL (91)	A-CXL (100)	P-value
Age	18.77 ± 5.82	21.06 ± 5.22	≤0.01
Gender (M: F)	0.57	0.47	0.18
UCVA	0.65 ± 0.55	0.72 ± 0.52	0.42
BCVA	0.23 ± 0.27	0.28 ± 0.22	0.22
Spherical	-3.01 ± 3.4	-2.79 ± 2.68	0.64
Cylinder (D)	-1.42 ± 3.11	-2.53 ± 3.07	0.017
K1 (D)	46.66 ± 4.72	46.33 ± 3.55	0.57
K2 (D)	50.7 ± 6.13	50.12 ± 4.45	0.46
K-mean (D)	48.46 ± 4.7	48.2 ± 3.9	0.69
CCT	455.4 ± 47	446.25 ± 36.6	0.14

Table 2: Comparison of baseline characteristics between C-CXL and A-CXL group.

Abbreviations and Units: C-CXL: Conventional Corneal Crosslinking, A-CXL: Accelerated Corneal Cross Linking, M: F: Male/Female Ratio, UCVA: Uncorrected Visual Acuity, BCVA: Best Corrected Visual Acuity, D: Diopter, K: Keratometry, CCT: Central Corneal Thickness.

Visual acuity measurements

In terms of visual acuity measurements within the C-CXL group, there was significant improvement in UCVA (LogMAR) of 0.16 ($p = 0.02$), 0.18 ($P \leq 0.01$) and 0.29 ($P \leq 0.01$) from the baseline at 3,

6 and 12 months, respectively. This was compared to the A-CXL that showed no significant change of UCVA in any visit, except at 6 months (-0.23, P ≤ 0.01). For BCVA, the C-CXL group showed significant change of -0.11 (p = 0.04) and -0.06 (P ≤ 0.01) at 6 and 12 months, respectively. There was no significant change at other visits. The A-CXL group, also showed significant changes at 2 visits, - 0.11 (p = 0.08) and -0.12 (p = 0.08) at 12 and 36 months, respectively. Please refer to Table 3 for Visual Acuity measurements at baseline and post-cxl.

Comparing both groups, there was no statistically significant difference in the UCVA change from baseline throughout follow up except at 36 months in the favor for C-CXL (C-CXL -0.44, A-CXL -0.19, P ≤ 0.01.

			Baseline	3 months	6 months	12 months	24 months	36 months
UCVA	C-CXL	Mean ± SD	0.66 ± 0.55	0.5 ± 0.45	0.48 ± 0.42	0.37 ± 0.35	0.4 ± 0.5	0.22 ± 0.12
		P-value [a]		0.02	≤0.01	≤0.01	0.43	0.12
	A-CXL	Mean ± SD	0.73 ± 0.52	0.63 ± 0.35	0.5 ± 0.39	0.55	0.67 ± 0.33	0.54 ± 0.17
		P-value		0.43	≤0.01	0.34	0.25	0.25
	P-value [b]		0.42	0.09	0.9	0.32	0.13	0.03
BCVA	C-CXL	Mean ± SD	0.23 ± 0.28	0.24 ± 0.3	0.12 ± 0.38	0.17 ± 0.23	0.07 ± 0.09	0.13 ± 0.09
		P-value		0.74	0.04	≤0.01	0.11	0.18
	A-CXL	Mean ± SD	0.28 ± 0.22	0.25 ± 0.14	0.28 ± 0.25	0.17 ± 0.13	0.21 ± 0.13	0.16 ± 0.11
		P-value		0.23	0.55	0.08	0.17	0.08
	P-value		0.22	0.86	0.36	0.12	0.09	0.48

Table 3: Comparison of visual Acuity outcomes at baseline and follow-up periods between C-CXL and A-CXL.

Abbreviations: C-CXL: Conventional Corneal Crosslinking, A-CXL: Accelerated Corneal Cross Linking, UCVA: Uncorrected Visual Acuity, BCVA: Best Corrected Visual Acuity, SD: Standard Deviation.

[a] indicates if the difference between the visual acuity values at baseline and follow-up periods are statistically significant

[b] indicates if the mean of the visual acuity between both groups are statistically significant.

Refractive changes

In the C-CXL group there was no statistically significant improvement in spherical equivalent (D) over 3, 6, 12-, 24- and 36-months period, comparable to A-CXL group that showed also no statistically significant improvement over 3, 6, 12 and 36 months except in the24months period (0.760 ± 1.07, p = 0.03). Regarding cylinder (D) measurements, in the C-CXL group at 3 months measurement there was statistically significant improvement from baseline -.96 ± 2.34 (P ≤ 0.01) and statistically insignificant improvement over the 6, 12, 24, 36 measurements. Whereas subjects in the A-CXL group had a statistically insignificant improvement in cylinder correction except the measurement at 12 months there was statistically insignificant worsening -.04 ± 4.45 (p = 0.95). There was no significant difference in the change in spherical equivalent and cylinder between the 2 groups throughout the follow visits.

Topographic changes

There was a significant decrease in K1 from baseline measures in the C-CXL group of 0.11D (p = 0.02), 2.14D (P ≤ 0.01), 1.92D (p = 0.02) at 12, 24, 36 months, respectively. For K2, there was no significant reduction except at 36 months (1.1D, ≤0.01). There was no significant change in K-mean throughout the visits except at 12 months 0.27D (p = 0.03). On the other hand, A-CXL group had no significant change from baseline measures in K1, K2, K-mean throughout the visits. Figure 1 shows the changes between K-mean in both groups, there is more reduction in K-mean of -1.65D in A-CXL group compared to 0.21D in C-CXL group.

In the C-CXL group there was a statistically insignificant reduction in K-max except at the 12 months measurement which was statistically significant 54.63 ± 6.66 (P ≤ 0.01). In the A-CXL group

Variable			Baseline	3 months	6 months	12 months	24 months	36 months
Spherical Equivalent	C-CXL	Mean ± SD	-3.02 ± 3.41	-0.33 ± 1.58	-0.2 ± 3.4	-0.74 ± 9.2	-0.75 ± 7.8	-0.71 ± 4.1
		P-value [a]		0.13	0.66	0.28	0.21	0.46
	A-CXL	Mean ± SD	-2.78 ± 2.68	-0.22 ± 1.49	1.01 ± 3.31	0.3 ± 2.35	0.76 ± 1.07	0.54 ± 3.58
		P-value		0.21	0.08	0.48	0.03	0.59
	P-value [b]		0.64	0.32	0.49	0.5	0.45	0.95
Cylinder	C-CXL	Mean ± SD	-1.43 ± 3.12	-0.96 ± 2.34	-0.59 ± 3.2	1.07 ± 3.4	1.44 ± 3.6	3.3 ± 5.02
		P-value		≤0.01	0.18	0.07	0.12	0.27
	A-CXL	Mean ± SD	-2.54 ± 3.08	-0.72 ± 2.4	0.22 ± 2.8	-0.04 ± 4.4	1.08 ± 2.3	2.08 ± 3.8
		P-value		0.09	0.43	0.95	0.10	0.05
	P-value		≤0.01	0.97	0.27	0.32	0.48	0.77

Table 4: Comparison of refractive changes at baseline and follow-up periods between C-CXL and A-CXL.

Abbreviations: C-CXL: Conventional Corneal Crosslinking, A-CXL: Accelerated Corneal Cross Linking, SD: Standard Deviation.

[a] indicates if the difference between the values of each variable at baseline and the follow-up periods are statistically significant

[b] indicates if the mean of each variable between both groups are statistically significant.

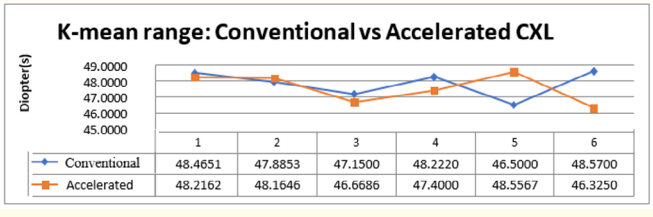

Figure 1: Shows the changes of K-mean at different points through follow up periods.

also there was a statistically insignificant reduction in K-max in all measurements There was no significant difference between each measurement when compared to the other group.

Pachymetric changes

There was a significant reduction in central corneal thickness in the C-CXL group from baseline of -38.5 µm (P ≤ 0.01), -26.08 µm (P ≤ 0.01), -12.88 µm, P ≤ 0.01) at3, 12, 24 months, respectively. Whereas in the A-CXL group, a significant reduction was noted at 3 months (5.8µm, P ≤ 0.01), but no significant improvement beyond 3 months.

Comparing both groups, there is a significant reduction in central corneal thickness between 3 months P ≤ 0.01. There was no significant difference in the reduction of central corneal thickness with time between the two groups except the measurements at 3 months, in which the C-CXL showed greater reduction than the A-CXL group. (C-CXL; -38.5, A-CXL -5.86; P ≤ 0.01).

Discussion

Conventional corneal collagen cross-linking has been established as the most effective treatment modality for progressive keratoconus. In the last few years, accelerated cross-linking protocol has emerged as a comparable timesaving treatment. Since then, the literature has been putting effort to study its comparability to the conventional method. Although the non-inferiority of the A-CXL has been verified by comparative studies [16]. There are controversies about the outcomes and effectiveness for the A-CXL to achieve the best efficacy and safety profile compared to the C-CXL. This paper studied and compared the visual, refractive, and topographic outcomes of cross-linking in its accelerated and conventional protocols at different time points after CXL.

In this study, both C-CXL and A-CXL groups showed significant improvement in UCVA in terms of LogMAR units until 12 months, 6 months, respectively. This result consistent with Woo., *et al.* [11]

Variable			Baseline	3 months	6 months	12 months	24 months	36 months
K1	C-CXL	Mean ± SD	46.7	46.1	45.3	46.6	44.6	44.8
		P-value [a]		0.38	0.06	0.02	≤0.01	0.02
	A-CXL	Mean ± SD	45.9	46.3	45.1	45.6	46.7	44
		P-value		0.09	50	0.34	0.83	0.2
K2	C-CXL	Mean ± SD	51	49.9	49.1	50.1	48.4	49.9
		P-value		0.21	0.11	0.07	0.06	≤0.01
	A-CXL	Mean ± SD	49.9	50	48.3	49.3	50.4	48.7
		P-value		0.59	0.62	0.34	0.60	0.35
K-mean	C-CXL	Mean ± SD	48.6	47.9	47.1	48.3	46.5	48.8
		P-value		0.35	0.07	0.03	0.05	0.90
	A-CXL	Mean ± SD	47.9	48.2	26.6	47.4	48.5	46.3
		P-value		0.36	0.47	0.28	0.82	0.60
K-max	C-CXL	Mean ± SD	55.3	54.8	53.2	54.6	54.2	53.7
		P-value		0.59	0.14	≤0.01	0.17	0.11
	A-CXL	Mean ± SD	55.0	54.9	52.6	54.9	55.5	53.2
		P-value		0.85	0.41	0.65	0.31	0.49
	P-value [b]		0.66	0.88	0.76	0.75	0.15	0.95

Table 5: K1, K2, K-max and K-mean at baseline and follow-up periods.

Abbreviations: C-CXL: Conventional Corneal Crosslinking, A-CXL: Accelerated Corneal Cross Linking, SD: Standard Deviation, K: Keratometry.

[a] indicates if the difference between the values of each variable at baseline and the follow-up periods are statistically significant

[b] indicates if the mean of K-max between both groups are statistically significant.

Variable			Baseline	3 months	6 months	12 months	24 months	36 months
CCT	C-CXL	Mean ± SD	453.1 ± 40	414.6 ± 0.0	549.6 ± 54	427.3 ± 52	440.2 ± 51	416.3 ± 58
		P-value [a]		≤0.01	0.44	≤0.01	≤0.01	0.06
	A-CXL	Mean ± SD	449 ± 33	443.2 ± 35	438.6 ± 86	429.7 ± 74	452.7 ± 35	462.7 ± 30
		P-value		≤0.01	0.76	0.09	0.72	0.89
	P-value [b]		0.14	≤0.01	0.41	0.84	0.21	0.02

Table 6: Comparison of central corneal thickness (CCT) at baseline and follow-up periods between C-CXL and A-CXL.

Abbreviations: CCT: Central Corneal Thickness, C-CXL: Conventional Corneal Crosslinking, A-CXL: Accelerated Corneal Cross Linking, SD: Standard Deviation.

[a] indicates if the difference between the values of the CCT at baseline and the follow-up periods are statistically significant

[b] indicates if the mean of CCT between both groups are statistically significant at different time points.

who had significant improvement in the UCVA from baseline in C-CXL group at 3 months and in A- CXL at 6 months. The current study shows significant improvement in BCVA in both C-CXL and A-CXL groups at first 12 months. Improvement continues in subsequent visits, but it was not significant at final follow up. Viswanathan., *et al.* [2] has conducted long-term study comparing accelerated (UVA irradiance 9 mW/cm^2) and conventional CXL groups with mean follow-up of 2 years. He showed improvement in BCVA in C-CXL and A-CXL at final visit, which was not statistically significant, but there was significant improvement between two groups. Shetty., *et al.* [17], in his prospective randomized interventional study, showed that group IV with radiation intensity of 30 mW/cm^2 for 3 minutes had no significant improvement from baseline at final follow up. That showed significant improvement compared to conventional CXL.

In spherical equivalent, our study shows no significant improvement from baseline through follow up periods in C-CXL group, and similarly in A-CXL except at 24 months. Furthermore, it finds no significant difference in the change in spherical equivalent and cylinder between the 2 groups throughout the follow visits. This was also noted by previous authors. Spherical equivalent and cylinder error reduction were noticed in both accelerated and conventional crosslinking, but with no significant difference between the 2 groups [12,13].

According to Sadoughi M., *et al.* study [18] it corresponds with our study that there was no change in K-mean in C-CXL throughout the visits except at 12 months. In A-CXL group, there was no change from baseline measures in K-mean throughout the visits. There is more reduction in K-mean in A-CXL group compared to C-CXL group, which were not significant compared with preoperative variables. In the C-CXL group there was insignificant reduction in K-max except at the 12 months measurement which was significant. In the A-CXL group also there was insignificant reduction in K-max in all measurements. There was no significant difference between each measurement when compared to the other group. According to Woo M., *et al.* study [11], there was no changes between the C-CXL and CA-CXL groups in the change of postoperative K-mean values at 12 months, which corresponds with our stud.

Although our study has the strength of having large sample size with a long postoperative follow up period of 3 years in comparison with other similar studies, the main limitation is patients' non-compliance with follow up, this may be due to multiple factors which include place of residency, pregnancy status, and financial issues. Furthermore, lack of data regarding the demarcation line and biochemical changes which would be necessary to differentiate between both groups was considered another limitation to this study.

Conclusion

In conclusion, this study strengthened the preexisting evidence on the safety and efficacy of crosslinking as a treatment of progressive keratoconus. Conventional CXL was comparable with accelerated CXL at 4 time points in 3 years and showed better outcomes in visual acuity. Larger and longer-termed prospective interventional studies are needed to further evaluate efficacy in both methods.

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