Efficacy of accelerated corneal cross-linking for the treatment of progressive keratoconus: Two-year's outcomes.

Abdulmoghni O. Al-Barrag*, Ahmed M. Al-Asbahi

Department of Ophthalmology, Sana'a University, Sanaa, Yemen

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Abstract

Purpose: To evaluate the long-term results of accelerated Corneal Cross-Linking (CXL) in Yemeni patients with progressive keratoconus, between January 2016 and January 2018.

Methods: Fifty eyes of 32 patients were record complete follow up for 2 years, underwent accelerated CXL at 18 mW/cm^2 for 5 minutes in one eye. The follow-up visits were scheduled on second day, 5th day, 12th, 18th, and 24 months after the treatment.

Results: There were highly significant improvement in Kmax, and Kmean preoperative and two years postoperative, (P=0.006) and (P=0.000). We noted a significant flattening of keratometry, Kmax flattened by 0.5 diopter, and Kmean, by 0.33 diopter, of the cornea. Pachymetry apex decreased during two years follow up with (p=0.001), (p=0.009), but was stable after CXL follow up (p=0.38). In terms of thinnest corneal thickness there was decrease in the corneal thickens after CXL two years later (P=0.006), while after the treatment it was stable during the study period with (P=0.156). The best spectacle-corrected visual acuity showed improvement over the entire two year's follow-up with (p=0.027).

Conclusion: Accelerated CXL is an effective treatment method to prevent progression in young patients with progressive keratoconus without the occurrence of serious complications or side effects.

Keywords: Accelerated, Corneal cross linking, Progressive keratoconus, Keratometry.

Abbreviations: Corneal Cross-Linking (CXL), Ultraviolet Light (UV), Central Corneal Thickness (CCT), Thinnest Corneal Thickness (TCT), Spherical Equivalent (SEQ), Dioptric Sphere (DS), Uncorrected Mean Visual Acuity (UVA), Best Corrected Visual Acuity (BCVA), Best Spectacle-Corrected Visual Acuity (BSCVA), Standard Deviation (SD), Right (Rt), Left (Lt), Progressive Index (PI), Dioptric Cylinder (DC).

Introduction

Corneal cross-linking is a special treatment that combines eye drop medication and Ultraviolet Light (UV) to strengthen the tissues of the cornea. It is a low-invasive procedure designed to strengthen the corneal structure and stop the progression of keratoconus. Various advances have highlighted the opportunity to optimize the procedure improving efficacy and refractive outcomes [1,2]. These include new riboflavin formulations, higher Ultra Violet A (UV-A) irradiance sources, and programmable UV-A patterns. The method was applied for the first time at Dresden University of Technology (Germany) in 1998 [3]. The efficacy and safety of the procedure were confirmed in numerous clinical trials [4,5]. From the times of "Dresden Protocol" until now, several accelerated CXL protocols were introduced with the purpose of reducing illumination time by increasing intensity while maintaining the fluence at 5.4 J/cm^2.

Keratoconus is a degenerative non-inflammatory corneal disorder. It leads to decreased vision by distorting the anterior corneal surface, and inducing apical thinning, high irregular astigmatism, and central scarring of the cornea [6]. Several modalities such as hard contact lens, intracorneal stromal ring implantation, and penetrating keratoplasty are used to treat keratoconus [7]. All these techniques only correct the refractive error of the cornea with no effect on the progression of keratoconus [8]. The only treatment that is believed to have the ability to stop or decrease the progression of keratoconus is Collagen Cross-Linking (CXL) [9]. It increases stiffness and rigidity of the anterior corneal stroma [9,10], and enhances corneal resistance to proteolytic enzymes by inducing photochemical crosslinking and covalent bindings between individual collagen fibers [9,10]. Early signs of keratoconus, is a good candidate for corneal crosslinking. It halts the progression of keratoconus, and help to avoid major surgery, such as a corneal transplant with a failure rate of approximately 3% and a complication rate of ≤ 1% [11].

Methodology

This is prospective unmasked, randomized observational conducted study, with two years follow up on patients with progressive keratoconus underwent accelerated CXL. The treatments were performed unilaterally and on an outpatient basis. The ethics committee approved the study protocol following the tenets of the declaration of Helsinki. Since January 2016 with duration of two years, 570 of consecutive

patients who were diagnosed progressive keratoconus, according to Amsler-Krumeich's classification measured by corneal tomography (Pentacam Typ 70700, OCULUS Optikgeräte GmbH, Wetzlar, Germany), were received accelerated CXL with an irradiance of 18 mW/cm^2 at total doe of 5.4 J/cm^2, for five minutes. Only 50 eyes of 32 patients were record complete follow up for 2 years. Inclusion criteria included patients aged between 10 and 35 years were included in the study with confirmed progressive keratoconus who had a clear cornea without opacity, and Central Corneal Thickness (CCT) >390 μm were included. The upper age limit of 35 years was chosen because progressive keratoconus typically is observed as in younger patients. Exclusion criteria included a minimum corneal thickness less than 390 nm, axial corneal scarring, previous refractive or other corneal surgery, a history of chemical burns, severe infections, herpes simplex keratitis, and other corneal or ocular surface disorders. Patients who were pregnant or breastfeeding at the time of enrolment also were excluded, because may have a severe impact on the progression of keratoconus. Furthermore, legally we do not have the permission to use UV light for pregnant patients in our center because of its side effects. Patients with kmax more than 58.5 D seen from pentacam, has been excluded from this study, and those who were not cooperative enough for 2-year follow-up were also excluded.

Patients were visited preoperatively, and in the early postoperative period (until epithelial healing), then 12, 18, and 24 months after CXL. Every follow-up visit, ophthalmic examinations included determining (UCVA), and Best Spectacle-Corrected Visual Acuity (BSCVA), expressed in logarithm of the Minimum Angle of Resolution (log MAR) units, using subjective refraction for distant vision with assessment of the anterior and posterior segment of the eye in by the slit lamp using Volk 90 D lens. Intraocular pressure measurement depends on Goldmann applanation tonometer (Haag-Streit AG, Koeniz, Switzerland). Elevation-based topography was analyzed like the flattest (K_{flat}) and steepest (K_{steep}), mean keratometry (K_{mean}), K_{max}, Central Corneal Thickness (CCT), Thinnest Corneal Thickness (TCT), anterior and posterior elevations at the apex preoperatively, and after accelerated CXL.

The cross-linking procedure was performed in operating theatre using a standard technique condition. Corneal anesthesia was achieved using lidocaine 2% taken form vial 30 ml given as eye drops. The central 8 mm corneal epithelium was debrided using a small piece of isopropyl alcohol swab applied onto the central part of the cornea, to help riboflavin absorption and make the treatment more effective, end with irrigation of the cornea by balance salt solution to clear alcohol from the cornea. Topical Peschke® M Standard Riboflavin Solution without Dextran for epi-off procedure solution,(PESCHKE Trade GmbH Boesch 73·6331 Huenenberg· Switzerland) was instilled every 2 min for 30 minutes, for all patients. Those patient's (21 eyes) with thinnest cornea between 390 and 455 microns was added Hypotonic Riboflavin Solution Peschke® (HRSP) for corneal swelling, after isotonic solution to increase the corneal hydration and thickness intraoperatively, given as one drop every two minutes for 10 minutes more. After the installation of the riboflavin as a photosensitizer, the CCL-365-18 device (CCL-365-18 MLase AG industriestr. 17, 82110 Germening Germany) was used to deliver Ultraviolet A radiation of 370 nm wavelength with an aperture of 8 mm at 50 mm from the apex of the cornea. With corneal exposure to UV-A 365 nm light for five minutes at an irradiance of 18 mW/cm^2, of total dose 5.4 J/cm^2. Whenever treatment was fished the eye surface was washed with 20 mL of a balanced salt solution, antibiotic eye drops (moxifloxacin 0.5%, Vigamox[a]; Alcon Co., Inc.) install to the eye, and inserted a bandage soft contact lens (Freshkon; HEMA, USA) of negligible power, until the closure of epithelial defect between 3-5 days postoperatively. Topical antibiotic eye drops continue four times per day to fit any bacterial infection for one week more, tears natural free of preservative (Alcon), also was given four times per day for a month. Postoperatively, all patients received oral analgesia in the form of (Diclofenac sodium 100 mg tab). Eye examinations done in every second day for a week, and one month after accelerated CXL to document corneal healing, and exclude any possible early postoperative complications, while the follow-up visits were scheduled on, one year, then every six months up to two years. Fluoromethalon (FML Allergan) eye drops was given three times per day, after epithelial healing, with tapering weekly postoperatively in some few cases, those patients having corneal haziness, and oedema. The corneal haze stage was scored according to Hanna's 5-item scale (Stage 0: Clear cornea without any haze; Stage 1: Minimal, focal haze of stroma; stage 2: scattered, well-visible stromal haze; Stage 3: Diffuse stromal haze, partially obscuring iris details; Stage 4: Focal and diffuse haze obscuring iris details).

Statistical analysis

All data were collected in an Excel spreadsheet (Microsoft Office Professional Plus 2019). Statistical package for the social sciences, version 21 (IBM SPSS Statistics 21.0, IL, USA), was used to analyze the data. The Kolmogorov-Smirnov test was performed to test distribution of the sample means. Friedman Test was used to compare the quantitative variables using the χ^2 test. Additional analyses of the change in the primary outcome parameter e.g., (K_{max}) from baseline to 24 months and the repeated measure analysis to investigate the relationship between the change in K_{max} at different times with baseline parameters was assessed using same Friedman analysis where a significant relationship was observed. P value less than 0.05 was considered statistically significant.

Results

Only, 50 eyes of 32 patients from 570 of consecutive patients underwent CXL with two years follow up. Other patients had no good facilities for follow up due to a lack of compliance, poverty, and ware in Yemen given difficulties to collect the data from all patients. Mean age of the patients was 20.48 ± 5.23 years (range from 12 to 32 years), also 26 (52%) were females, and 24 (48%) males, were treated with 18 mW/cm^2 of total dose 5.4 J/cm^2, accelerated CXL for five minutes (Table 1).

Table 1: *Age and gender.*

		The baseline characters of the study	
Age Mean ± SD		20.48 ± 5.23	
Eye		No.	%
	Rt	28	56
	Lt	22	44
Gender	Female	26	52
	Male	24	48

K_{max} and K_{mean}, showed maximum keratometry flattened by 0.5 diopter, and mean keratometry flattened by 0.33 diopter, with high significant improvement over the entire follow-up period with significant changes (p=0.009), (p=0.000),respectively (Table 2). Corneal topographic astigmatism, there was no significant difference between the preoperative and all postoperative values (P more than 0.05), (Table 2).

Pachymetry apex, and Thinnest Corneal Thickness (TCT) decreased during first year follow up with (p=0.004), (p=0.003), seen in (Table 2), but stability of the corneal thickness was seen compare with the base line of treatment and after 2 years follow up (p=0.38), (p=0.156) respectively (Table 3).

Progressive index was statically significant increased during the period of the study in all tables. Refractive error preoperatively as Spherical Equivalent (SEQ), the mean rank before treatment was 2.73 at one year, 2.46 one and half year, 2.28 and 2.53 after 2 years, comparison of the differences between baseline, 12, 18, and 24 months. SEQ was stable during the study with statistical significance (p=0.299) (Table 4), and (p=0.46) (Table 5).

Table 2: *Comparison keratometry reading and corneal thickness before and after corneal cross linking.*

Methods	**The time**						
	B c3r	**1 year**	**p**	**18 months**	**p**	**2 years**	**p**
K max	52.47 ± 3.8	51.96 ± 3.48	0.01	51.98 ± 3.5	0.007	51.97 ± 3.4	0.009
K mean	47.03 ± 2.42	46.74 ± 2.3	0	46.8 ± 2.3	0	46.7 ± 2.3	0
Cortopoastig	4.04 ± 1.8	3.98 ± 1.7	0.46	3.9 ± 1.7	0.88	3.9 ± 1.7	0.24
Pachyapex	470.14 ± 35.2	462 ± 42.9	0.004	464 ± 38.6	0.001	465 ± 39.5	0.009
TCT	460.9 ± 34.3	453 ± 43.23	0.003	455 ± 39.4	0.03	455.3 ± 40.3	0.1
PI	1.66 ± 0.4	1.8 ± 0.5	0.004	1.8 ± 0.4	0.002	1.8 ± 0.5	0

Table 3: *Comparison of corneal parameters after corneal cross linking.*

Methods	**The Time**						**Friedman test χ^2**	**P**
	1 year		**18 months**		**2 years**			
	n=50		**n=50**		**n=50**			
	Mean	**St deviation**	**Mean**	**St deviation**	**Mean**	**St deviation**		
K max	51.96	3.48	51.98	3.47	51.97	3.4	0.211	0.9
K mean	46.74	2.304	46.748	2.3199	46.74	2.315	1.727	0.422
Cortopoastig	3.98	1.664	3.924	1.647	3.864	1.719	7.96	0.019
Pachyapex	462.2	42.94	464.22	38.6	464.98	39.46	1.91	0.38
TCT	452.7	43.13	455.3	39.38	455.34	40.31	3.71	0.156
PI	1.85	0.53	1.77	0.44	1.83	0.48	7.83	0.02

Table 4: *Results of accelerated corneal cross linking before and after treatments.*

Methods	The Time					Friedman test χ2	p
		B c3r	1 year	1.5 Year	2 years		
		n=50	n=50	n=50	n=50		
SEQ	Median (interquartile)	-2.3 (-13-3)	-2.75(-13-3.25)	-2.5 (-13.5-4.75)	-2.38 (-13-4)	3.67	0.299
	Mean Rank	2.73	2.46	2.28	2.53		
DC	Median (interquartile)	-4 (-9.5 -0.75)	-4.4 (-10 - -1)	-4.25 (-10 - -1)	-4.5 (-9.75-0.5)	8.215	0.042
	Mean Rank	2.88	2.3	2.54	2.28		
UVA	Median (interquartile)	0.16 (0.03-1)	0.10 (0.03-0.63)	0.20 (0.02-0.63)	0.20 (0.03-0.5)	2.14	0.55
	Mean Rank	2.58	2.39	2.38	2.65		
BCVA	Median (interquartile)	0.50 (0.10-1.0)	0.57 (0.02-1.0)	0.50 (0.05-1.0)	0.63 (0.20-1.0)	9.16	0.027
	Mean rank	2.56	2.72	2.14	2.58		

Table 5: *Results of accelerated corneal cross linking after treatments.*

Methods	The time			Friedman test χ2	P
	1 year	18 months	2 years		
	n=50	n=50	n=50		
	Mean ± SD	Mean ± SD	Mean ± SD		
SEQ	-2.88 ± 3.12	-2.62 ± 3.3	-2.56 ± 3.17	1.56	0.46
DC	-4.53 ± 2.1	-4.48 ± 2.15	-4.58 ± 2.095	1.59	0.45
UVA	0.19 ± 0.155	0.189 ± 0.129	0.19 ± 0.10	3.39	0.18
BCVA	0.67 ± 0.32	0.58 ± 0.31	0.64 ± 0.31	10.44	0.005

Refractive cylindrical correction preoperatively, the median cylindrical error was -4.0 Dioptric Cylinder (DC), and after treatments was -4.4 DC, -4.25 DC, and -4.5 DC, at 12, 18, and 24 months respectively, with mild progression leading to statistical significance (p=0.042), (Table 4), while after 2 years of treatment the cylindrical refractive error was stable not reach to statistical significance of progression (p=0.45), (Table 5). Uncorrected Visual Acuity (UVA) was improved during the period of the study. Preoperatively, the median was 0.16, at 12 and 18 months, changed to 0.10 go back to 0.20 after 2 years with statically significant (p=0.55) (Table 4), comparing the differences between preoperative UVA and 2 years follow up reach no statistical significance of improvement with (p=0.18), (Table 5). Best Corrected Visual Acuity (BCVA) showed significant improvement over the entire two years' follow-up period with statically significant (p=0.027) (Table 4), and (p=0.005) (Table 5) respectively.

Discussion

Accelerated CXL protocols have been replaced in recent years in ophthalmic practice [12-15]. In this difficult situation in Yemen accelerated CXL method, applied with 18 mW/cm^2 radiation for 5 minutes, of surface dose of 5.4 J/cm^2, where the epithelium was extracted. The Bunsen and Roscoe law of reciprocity states that the effect of a photochemical or photobiological reaction is directly proportional to the total irradiation dose, irrespective of the time span over which the dose is administered [16]. Irradiance with 18 mW/cm^2 for 5 min demonstrated efficacy in halting disease progression; however, the topographic flattening was lower as compared to conventional CXL [17,18]. Current studies have stated that treatments performed for 10 minutes with 9 mW/cm^2 radiation and 5 minutes with 18 mW/cm^2 radiation are safe, decrease the risk of progression of keratoconus, and have clinical results like the standard Dresden Protocol. [18,19].

Topographic results

In this study, K_{max} was 52.47 ± 3.8 preoperatively and 51.97 ± 3.4 at the second year. At the second year, an average flattening of k_{max} 0.5 D and k_{mean} 0.3 D was detected, with clinically significant (p=0.009), (p=0.000), (Table 2). Accelerated CXL treatment can thus be considered to provide a partial regression in k_{max} and k_{mean} as well as to reduce the risk of progression [20]. Reported the stability of K_{mean} and K_{max} over 5-years with a non-significant reduction of 0.11 D and 0.24 D, respectively [21], reported that the K_{max} value was the most important criterion in the follow-up of the progression of keratoconus. K_{max} measured using the Pentacam is objective, quantitative, repeatable, and well represents the severity of the topographic distortion in keratoconus [22], found a decrease of 1.4 D in K_{max} at the 6-month follow-up of treatment with accelerated CXL (9 mW/cm^2, 10 min) [22] indicated a decrease of 0.62 D in K_{max} at the 1-year follow-up of an accelerated CXL procedure (30 mW/cm^2, 3 min) [23].

The mean Pachymetry apex preoperatively was 470 ± 35.2 and two years post operatively was 46 5 ± 39.5 with clinically significant of progression (p=0.009), (Table 2), while for two year's follow up almost stable pachymetry apex with (p=0.38), (Table 3). Thinnest Cornea Thickness (TCT) had measured throughout 2 years of follow-up was significantly lower than the baseline, preoperatively was 461 ± 34.3, and two years post operatively was 455 ± 40.3 with no clinical significant of progression (p=0.1), (Table 2), while during two years follow up almost stable corneal thickness with (p=0.156), (Table 3). This corroborates with previous studies reporting a decrease in (CCT) or (TCT) following standard CXL [24]. The inter-method difference was the decrease in CCT, which was greater in the standard group than in the accelerated group [25]. Significant reduction in TCT has also been observed following transepithelial accelerated CXL [26,27]. Keratocyte apoptosis, changes in corneal hydration, collagen fibril, and extracellular matrix remodeling may explain the small; however, persistent corneal thinning that is observed after conventional CXL [24], but conceivably, could account for the similar corneal thinning observation in accelerated and transepithelial CXL. These results are like our finding in this study [28], reported that the riboflavin/UVA treatment leads to a dose-dependent keratocyte damage that can be expected in human corneas down to a depth of 300 µm using a surface UVA dose of 5.4 J/cm^2. They reported that a standard surface UVA dose of 3 mW/cm^2 has a toxic effect on the endothelial cells of corneas thinner than 400 µm.

Some few cases in this study developed cornel haze 3 cases (1.5%), and 3 cases (1.5%) early of sterile infiltrates keratitis, with good response to florumethalon (FML, ALLERGAN) and moxifloxacin 0.5%, eye drops the other one eye was punctate keratitis response well to tears natural (Tears Natural Free, Alcon) eye drops. One patient under contraceptive pills received CXL advise her to change to intravaginal devices to avoid any pathological stress to the cornea by the hormonal changes. Complications of CXL corneal haziness persistent corneal haze is one of the most frequently reported complications of CXL that can affect visual acuity [29]. It is postulated that repopulation of activated keratocytes after the immediate loss of keratocytes following CXL is responsible for haze formation [30]. Endothelial cell damage and corneal oedema, thin corneas are at increased risk of endothelial cell damage after CXL, thus CXL is not recommended in corneas with a CCT less than 400 microns [31]. Postoperative Infectious keratitis and corneal ulcers are possible complications of CXL [32,33].

Spherical Equivalent (SEQ) was stable during the period of the study with no improvement compared to the baseline (p=0.299), (Table 4), and, (p=0.46), table (Table 5), Dioptric Sphere (DS) suggests that even with the standard CXL protocol, there is less improvement in patients with DS [34]. While the Cylindrical Equivalent show progression from base line before treatment, (p=0.042) (Table 4), then become stable during the 2 years of the study (p=0.45), (Table 5), comparing from other studies show no significant changes in spherical equivalent, visual and topographic results [35]. The improvement of DC was rapid in the first year following the CXL and stabilized thereafter until the end of follow-up [36].

Uncorrected Mean Visual Acuity (UVA) and Best Corrected Visual Acuity (BCVA) deteriorated significantly within the first 2 weeks after the CXL, while after 2 years follow up there is highly significant improvement in UVA, was improved from 0.16 (0.03-1) log MAR preoperatively to 0.20 (0.03-.50) log MAR at 2 years follow up, with no clinically significant (p=0.55) (Table 4), while BCVA was improved from 0.50 (0.10-1.0) log MAR preoperatively to 0.63 (0.20-1.0) log MAR at 2 years follow up, with clinically significant with (p=0.027), (Table 4), and (p=0.005), (Table 5). We assume that the improvement in visual acuity is because of the flattening effect of the anterior keratometry and decrease in corneal aberrations following the treatment. Given these results, accelerated CXL treatment has positive results in visual acuity in keratoconus patients. Many other studies have shown that BCVA may improve after treatment [22,37,38] compared the standard procedure with an accelerated CXL procedure (18 mW/cm^2, 5 min), and found no considerable difference in BCVA [37].

Keratoconus progression, especially at younger ages, is aggressive and may not stop on its own. Accelerated crosslinking allows a shorter treatment time by delivering the same energy more quickly, compared to the standard crosslinking procedure [38].

Conclusion

Collagen cross linking is an effective technique to stabilize or improve visual acuity, refraction, and keratometric values. Cornea assumes a more regular shape as a result of CXL procedure without inducing adverse effect on corneal endothelium and biomechanical parameters such as corneal resistance factor and corneal hysteresis. One of the shortcomings of our study was short follow-up. Corneal collagen cross-linking is often described as the most promising innovation in the treatment of progressive keratoconus in recent years.

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Conflict of interest

There are no conflicts of interest.

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*Correspondence to

Dr. Abdulmoghni O. Al-Barrag

Department of Ophthalmology

Sana'a University,

Sanaa, Yemen

E-mail: al_barrag@yahoo.com