Accelerated (18 mW/cm^2) Corneal Collagen Cross-Linking for Progressive Keratoconus

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Purpose: The aim of this study was to determine the efficacy of accelerated riboflavin–ultraviolet A–induced corneal collagen cross-linking (CXL) (irradiance of 18 mW/cm^2 for 5 minutes).

Methods: In this study, we retrospectively reviewed the charts and anterior segment data of patients after accelerated CXL. Visual, topographic, pachymetry, and densitometry data were extracted and analyzed before surgery and at follow-up (minimum 12 months) after treatment.

Results: A total of 28 eyes of 20 patients (mean age, 28.1 ± 8.1 years) were included in this study. The mean follow-up time was 21.7 ± 7.2 months (range, 12–34 months). No statistically significant changes were found in the mean corrected distance visual acuity, corneal astigmatism, Kmean, Kflat, Ksteep, corneal pachymetry (at the apex and at the thinnest point), and corneal densitometry at follow-up. A significant reduction of Kmax, index of surface variance, index of vertical asymmetry, and Km of the posterior corneal surface (Km^B) was observed (Kmax: $P = 0.018$; index of surface variance: $P = 0.016$; index of vertical asymmetry: $P = 0.038$; Km^B: $P = 0.008$). No complications were reported during the postoperative follow-up period in this study.

Conclusions: Based on a mean follow-up time of 21.7 months, accelerated CXL (18 mW/cm; 5 minutes) is effective in stopping the progression of keratoconus without raising any safety concerns. Improvement in Kmax and stabilization of corrected distance visual acuity were noted after treatment. However, prospective studies with longer follow-up using different accelerated CXL settings are needed to validate these findings.

Key Words: keratoconus, accelerated corneal cross-linking, corneal densitometry

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Treatment options for progressive keratoconus are glasses, contact lenses, intracorneal ring segments, or a combination of these at further stages. However, these treatment options cannot stop disease progression, and corneal transplantation remains the only option to achieve visual recovery in advanced stages. With the introduction of corneal collagen cross-linking (CXL) with riboflavin and ultraviolet A (UV-A) light in 1997 by Spöerl et al,[1] a treatment became available that would stop the progression of keratoconus and reduce the need for keratoplasty.[2–4]

Different variations of the standard Dresden protocol[5] have been developed to optimize the outcome after CXL. These modifications include the use of hypoosmolar riboflavin to treat thin corneas, use of transepithelial corneal CXL, inclusion of combined CXL and refractive surgery, and use of accelerated CXL. In accordance with the photochemical law of reciprocity (Bunsen–Roscoe law), the same photochemical effect is achieved with a reduced irradiation time and a corresponding increase in irradiation intensity, such that the total dose remains the same. This principle shortens the treatment duration while maintaining the total radiant exposure (5.4 J/cm^2). However, there is a paucity of clinical data concerning the efficacy and safety of the different protocols for accelerated CXL.[3–6]

This study aims to evaluate the long-term clinical outcomes (minimum follow-up period of 1 year) of accelerated CXL at 18 mW/cm^2 for 5 minutes in patients with progressive keratoconus. We prove the effectivity of accelerated CXL in halting the progression of keratoconus using topographical parameters and different keratoconus-specific indices. This is also the first investigation of the long-term effect of accelerated CXL on corneal transparency using the Pentacam densitometry module.

METHODS

In this study, we retrospectively reviewed the charts and anterior segment data acquired by the Scheimpflug-based Oculus Pentacam of 20 patients who had undergone accelerated CXL for progressive keratoconus at the Department of Ophthalmology, University of Muenster Medical Center, between March 2012 and January 2014. CXL was performed with the Peschke CCL-365-18 unit (Peschke Meditrade GmbH, Huenenberg, Switzerland).

Corrected distance visual acuity (CDVA) and corneal topography data including steep K (Ksteep), flat K (Kflat), average keratometry reading (Km), average keratometry reading of the posterior corneal surface (Km^B), corneal astigmatism, maximal corneal curvature reading at the corneal apex (Kmax),

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corneal densitometry, and corneal pachymetry were extracted and analyzed before CXL and on follow-up visits. Tomography, pachymetry, and densitometry data were recorded using rotating Scheimpflug corneal and anterior segment tomography (Pentacam HR; Oculus GmbH, Wetzlar, Germany).

We also analyzed changes in different Pentacam topographic indices that are usually used to evaluate patients with keratoconus: keratoconus index (KI), central keratoconus index (CKI), index of surface variance (ISV), index of vertical asymmetry (IVA), index of height asymmetry (IHA), and index of height decentration (IHD).[7] The ISV and IHD are reported to be the most sensitive and specific criteria for diagnosis, progression classification, and surgical follow-up of keratoconus.[7]

A new Pentacam software module enables corneal densitometry to be analyzed.[8,9] Corneal densitometry can be measured in 4 annular zones of the cornea. The zones are centered on the apex of the cornea, the first zone being 2 mm in diameter, the second zone 2 to 6 mm, the third zone 6 to 10 mm, and the fourth zone 10 to 12 mm. The densitometry measurement can be provided for the anterior (first 120 μm), central (from the first 120 μm to the posterior 60 μm), and posterior parts (60 μm) of the cornea. Densitometry is expressed in grayscale units, ranging from a minimum light scatter of 0 (maximum transparency) to a maximum light scatter of 100 (minimum transparency).[8,9]

Standard epithelium-off accelerated CXL was performed under sterile conditions. Ultrasound corneal thickness was measured before and after epithelial removal. Riboflavin 0.1% was instilled after epithelial removal every 2 minutes for 30 minutes. UV-A irradiation was performed for 5 minutes at 18 mW/cm^2. During the period of UV-A exposure, riboflavin solution was also applied every 2 minutes to saturate the stroma with riboflavin.

Patients were instructed to discontinue the use of hard contact lenses at least 3 weeks before any assessment and CXL treatment. All patients reported in this study underwent a minimum follow-up of 12 months. Patients with preoperative extensive corneal scarring, history of previous eye surgery, any other eye disease(s), or contact lens wear within 3 weeks of measurement were excluded.

Statistical Analyses

Data management was performed with Microsoft Excel 2010. IBM SPSS Statistics 22 for Windows (IBM Corporation, Somers, NY) was used for statistical analyses. Changes at follow-up compared with baseline were assessed using 2-sided Wilcoxon signed-rank tests, assuming the left and right eyes of the same patient as independent. All data are reported as mean ± SD. The level of statistical significance was set at $P \leq 0.05$. Inferential statistics are intended to be exploratory, not confirmatory, and were interpreted accordingly. The comparisonwise type I error rate was controlled instead of the experimentwise error rate.

RESULTS

A total of 28 eyes of 20 patients (6 women and 14 men) with progressive keratoconus who had undergone riboflavin–UV-A accelerated CXL were included in this retrospective study. The mean patient age was 28.1 ± 8.1 years, and the mean follow-up time was 21.7 ± 7.2 months (range, 12–34 months). The mean CDVA did not significantly improve (before: 0.41 ± 0.3 logMAR, after: 0.36 ± 0.32 logMAR; $P = 0.097$) (Table 1). No complications such as chronic epithelial defects, corneal decompensation, or infectious keratitis were reported during the postoperative follow-up period in this study.

The improvement of Kmax at the follow-up visit was statistically significant (before: 59.0 ± 8.0 D, after: 57.4 ± 7.1 D; $P = 0.018$); changes in all other topographical parameters of the anterior corneal surface were not significant (Table 1). Average keratometry reading of the posterior corneal surface (Km^B) improved significantly after treatment ($P = 0.008$).

ISV and IVA decreased significantly after treatment (ISV: $P = 0.016$; IVA: $P = 0.038$). Changes in other keratoconus indices were not significant (KI: $P = 0.903$; CKI: $P = 0.275$; IHA: $P = 0.066$; IHD: $P = 0.134$) (Table 2).

There were no statistically significant differences in the corneal thickness at the apex (before: 458.8 ± 41.9 μm, after: 449.7 ± 45.2 μm; $P = 0.11$) or at the thinnest point (before: 437.6 ± 47.3 μm, after: 431.3 ± 45.5 μm; $P = 0.213$) (Table 1).

Corneal Densitometry

The change in total corneal light backscatter at total corneal thickness and at total diameter after accelerated CXL was not significant (before: 17.1 ± 1.9, after: 17.0 ± 3.3; $P = 0.156$). Furthermore, there were no statistically significant differences in any layer or annulus (Table 3). The total corneal light backscatter at total corneal thickness and at total diameter decreased significantly in patients with a minimum follow-up period of 24 months (before: 17.09 ± 1.6, after: 15.9 ± 1.5; $P = 0.013$). The differences are also significant in both central annuli in all layers and at total thickness (Tables 3 and 4).

DISCUSSION

The standard protocol (Dresden protocol) for CXL has been described in a number of long-term studies as an effective and safe method to stop keratoconus progression and to minimize the need for keratoplasty.[2,4,10–12] This procedure uses UV-A light application of 3 mW/cm^2 for 30 minutes for a given treatment.[5] Technological advances and modern CXL devices reduce the duration of the procedure by using higher-energy power settings.

In preclinical studies, Schumacher et al[13] described how accelerated CXL (10 mW/cm^2, 9 minutes) can be regarded as equivalent to the standard procedure in terms of an increase in corneal stiffness in porcine corneas. Other accelerated CXL protocols resulted in comparable findings.[14] However, accelerated CXL protocols applying the same amount of energy will necessarily neither be effective in stopping keratoconus progression nor have the same clinical outcome and safety profile.

At present, several CXL devices with different CXL protocols and settings are in clinical use. With their time- and cost-saving benefits, accelerated CXL protocols enjoy a high degree of acceptance among patients and surgeons.

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TABLE 1. Visual Refractive and Topographical Parameters on Preoperative Assessment and at Follow-up

n = 28	Mean Before CXL	Mean After CXL	Difference	*P*
CDVA, logMAR	0.4 ± 0.3	0.4 ± 0.3	0.1 ± 0.2	0.097
Km, D	48.2 ± 4.3	48.3 ± 4.4	−0.05 ± 1.4	0.962
Kmax, D	59.0 ± 8.0	57.4 ± 7.1	1.5 ± 2.8	**0.018**
Kflat, D	46.4 ± 4.4	46.5 ± 4.5	−0.1 ± 1.6	0.764
Ksteep, D	50.3 ± 4.2	50.2 ± 4.4	0.05 ± 1.8	0.419
Corneal astigmatism, D	3.9 ± 1.8	3.7 ± 1.8	0.2 ± 1.8	0.415
Pachymetry apex, μm	458.8 ± 41.9	449.7 ± 45.2	9.1 ± 22.4	0.112
Pachymetry minimum, μm	437.6 ± 47.2	431.3 ± 45.5	6.3 ± 25.0	0.213
Km^B, mm	−6.9 ± 0.9	−7.2 ± 0.8	0.2 ± 0.4	**0.008**

Bold: statistically significant results.

However, there is a paucity of clinical studies determining the safety and long-term efficacy of higher-energy accelerated CXL settings. Different clinical studies present considerably long-term results for standard CXL in halting the progression of keratoconus and/or achieving regression of disease.[2,4,12] The Siena eye cross-study described corneal flattening (Kmean decrease) and an improvement in uncorrected visual acuity and CDVA.[4] Hashemi et al[2] were able to show stabilization in the Kmean, Kmax, uncorrected distance visual acuity, and refractive astigmatism over a 5-year follow-up period. Another study by Raiskup et al presented the results of 34 eyes after CXL, including a mean follow-up period of 131.9 ± 20.1 months. This long-term study described a significant improvement in CDVA and long-term stabilization of keratoconus.[12]

Some studies of accelerated CXL with a follow-up period of 6 to 12 months have been published in the last few years. Elbaz et al showed stabilization of topographic parameters after 12 months of follow-up after accelerated CXL (10 minutes, 9 mW/cm^2).[6,15] Cinar et al showed that refractive and visual results of the accelerated CXL method and the conventional CXL method for the treatment of keratoconus were similar over a shorter period (6 months).[16,17]

Based on preclinical data and other clinical studies with different accelerated CXL settings (irradiance of 9 mW/cm^2 for 10 minutes, 7 mW/cm^2 for 15 minutes),[13–17] stabilization or halting of keratoconus progression was expected in our study. The presented data suggest that 5-minute accelerated CXL (irradiance of 18 mW/cm^2) is effective for halting the progression of keratoconus over a mean follow-up time of 21.7 months. We were able to show a significant improvement in Kmax and the keratoconus indices (ISV and IVA). This study also shows stabilization of the CDVA, pachymetry, Kflat, Ksteep, corneal astigmatism, and the keratoconus indices (CKI, KI, IHA, and IHD). The ISV and IHD are reported to be the most sensitive and specific criteria for progression classification, and surgical follow-up of keratoconus.[7] This study revealed an ISV improvement together with unchanged IHD after accelerated CXL. These results are consistent with recent findings after standard CXL in patients with progressive keratoconus.[18,19] In a study with 12 months of follow-up, Kolozsvári et al[18] described a significant improvement of the ISV and KI and stabilization of IHA and CKI. In a further study with the same duration of follow-up, Greenstein et al[19] described a significant improvement in ISV and IVA after CXL and a significant improvement in KI.

TABLE 2. Different Keratoconus-Specific Indices on Preoperative Assessment and at Follow-up

n = 28	Mean Before CXL	Mean After CXL	Difference	*P*
ISV	112.7 ± 39.5	103.0 ± 36.3	9.7 ± 16.6	**0.016**
IVA, mm	1.3 ± 0.4	1.2 ± 0.4	0.1 ± 0.2	**0.038**
KI	1.3 ± 0.1	1.3 ± 0.1	0.003 ± 0.01	0.903
CKI	1.1 ± 0.1	1.1 ± 0.1	0.006 ± 0.03	0.275
IHA, μm	35.1 ± 25.3	41.5 ± 26.8	−6.5 ± 27.9	0.066
IHD, μm	0.2 ± 0.1	0.2 ± 0.1	−0.01 ± 0.037	0.134

Bold: statistically significant results.

In this retrospective study, we did not follow endothelial cell density. However, none of the patients in this study developed any postoperative complications such as corneal decompensation due endothelial cell loss, cataract, or chronic epithelial defects over the follow-up period despite the accelerated CXL setting with higher energy.

The analysis of corneal densitometry has attracted increasing interest over the last few years. It has been described in infectious keratitis, corneal dystrophies, corneal graft surgery, after refractive surgery, in different stages of keratoconus, and after cross-linking in patients with keratoconus.[8,20–28] The time course of corneal densitometry after CXL over 1 year has been described by Greenstein et al and Gutierrez et al. These studies describe how corneal densitometry peaks in the first months after CXL and achieves preoperative values again approximately 1 year after CXL.[26,27] We recently described the long-term course of corneal densitometry after standard CXL (3 mW/cm^2; 30 minutes).[28] Densitometry values are still found to be improving 1 year after standard CXL. Two years after CXL, corneal densitometry values are significantly lower than preoperative values.[28]

To our knowledge, this study is the first to provide long-term densitometry data after accelerated CXL. Table 3 summarizes the densitometry data of all patients; no

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TABLE 3. Corneal Light Backscatter in Grayscale Units After Accelerated CXL

n = 28		Mean Before CXL	Mean After CXL	Difference	*P*
Anterior layer	An. 0.0–2.0 mm	30.0 ± 6.2	29.5 ± 7.0	0.4 ± 6.9	0.449
	An. 2.0–6.0 mm	24.6 ± 4.1	23.3 ± 4.5	1.3 ± 5.2	0.064
	An. 6.0–10.0 mm	19.3 ± 2.6	18.5 ± 3.5	0.8 ± 2.6	0.058
	An. 10.0–12.0 mm	23.5 ± 8.2	26.1 ± 7.8	−2.6 ± 8.0	0.107
	Total diameter	23.7 ± 3.1	23.2 ± 4.1	0.5 ± 3.9	0.174
Central layer	An. 0.0–2.0 mm	16.9 ± 2.3	16.9 ± 3.6	0.0 ± 3.7	0.485
	An. 2.0–6.0 mm	14.4 ± 1.7	14.1 ± 2.5	0.3 ± 2.6	0.163
	An. 6.0–10.0 mm	13.6 ± 2.2	13.4 ± 3.2	0.1 ± 2.0	0.208
	An. 10.0–12.0 mm	17.3 ± 4.6	18.7 ± 5.9	−1.4 ± 4.6	0.207
	Total diameter	15.0 ± 1.7	15.1 ± 3.0	−0.1 ± 2.5	0.435
Posterior layer	An. 0.0–2.0 mm	12.5 ± 1.8	12.1 ± 2.7	0.4 ± 2.5	0.234
	An. 2.0–6.0 mm	12.1 ± 1.1	12.0 ± 2.1	0.1 ± 1.9	0.374
	An. 6.0–10.0 mm	12.2 ± 2.5	12.4 ± 3.4	−0.1 ± 1.8	0.622
	An. 10.0–12.0 mm	15.7 ± 4.4	16.6 ± 6.6	−1.0 ± 4.2	0.471
	Total diameter	12.7 ± 1.6	12.9 ± 2.9	−0.2 ± 2.1	0.510
Total thickness	An. 0.0–2.0 mm	19.8 ± 3.3	19.5 ± 4.3	0.3 ± 4.2	0.274
	An. 2.0–6.0 mm	17.0 ± 2.2	16.4 ± 3.0	0.6 ± 3.1	0.112
	An. 6.0–10.0 mm	15.1 ± 2.4	14.8 ± 3.3	0.3 ± 2.1	0.121
	An. 10.0–12.0 mm	18.8 ± 5.2	20.5 ± 6.2	−1.7 ± 5.1	0.118
	Total diameter	17.1 ± 1.9	17.0 ± 3.3	0.04 ± 2.8	0.156

significant differences could be seen in relation to baseline. In the group with longer follow-up (minimum follow-up period of 24 months), corneal densitometry at total corneal thickness and at total diameter is significantly lower than at baseline (Table 4). A comparable phenomenon has been described after standard CXL (3 mW/cm^2; 30 minutes).[28]

In conclusion, based on a mean follow-up time of 21.7 months, accelerated CXL (18 mW/cm^2) is effective in halting the progression of keratoconus and seems to have similar effects on corneal stiffness, corneal topography, and corneal transparency compared with the standard protocol. More studies with longer follow-up are needed to validate these findings.

TABLE 4. Corneal Light Backscatter in Grayscale Units in Patients With Minimum Follow-up of 24 Months After Accelerated CXL

n = 14		Mean Before CXL	Mean After CXL	Difference	*P*
Anterior layer	An. 0.0–2.0 mm	31.4 ± 7.0	26.9 ± 4.0	4.5 ± 5.1	**0.005**
	An. 2.0–6.0 mm	25.7 ± 4.8	21.6 ± 2.7	4.0 ± 4.5	**0.003**
	An. 6.0–10.0 mm	19.0 ± 2.0	16.8 ± 1.7	2.2 ± 1.8	**0.004**
	An. 10.0–12.0 mm	22.4 ± 6.6	27.3 ± 7.5	−5.0 ± 6.8	**0.022**
	Total diameter	24.0 ± 2.7	21.8 ± 2.1	2.2 ± 2.8	**0.013**
Central layer	An. 0.0–2.0 mm	17.3 ± 2.6	15.4 ± 1.9	1.9 ± 2.5	**0.008**
	An. 2.0–6.0 mm	14.7 ± 2.0	13.0 ± 1.5	1.6 ± 1.9	**0.006**
	An. 6.0–10.0 mm	12.9 ± 1.5	11.9 ± 0.9	1.0 ± 1.1	**0.021**
	An. 10.0–12.0 mm	16.8 ± 4.8	18.5 ± 5.6	−1.7 ± 3.8	0.124
	Total diameter	14.8 ± 1.4	13.9 ± 1.4	0.9 ± 1.4	**0.03**
Posterior layer	An. 0.0–2.0 mm	13.0 ± 1.9	11.5 ± 1.9	1.5 ± 2.0	**0.017**
	An. 2.0–6.0 mm	12.1 ± 1.1	11.2 ± 0.9	0.9 ± 1.2	**0.023**
	An. 6.0–10.0 mm	11.4 ± 1.6	10.9 ± 1.1	0.5 ± 1.0	0.096
	An. 10.0–12.0 mm	15.5 ± 5.5	15.9 ± 6.7	−0.4 ± 3.0	0.551
	Total diameter	12.5 ± 1.4	11.9 ± 1.6	0.6 ± 1.0	**0.05**
Total thickness	An. 0.0–2.0 mm	20.5 ± 3.6	17.9 ± 2.2	2.6 ± 3.0	**0.004**
	An. 2.0–6.0 mm	17.5 ± 2.5	15.3 ± 1.7	2.2 ± 2.4	**0.006**
	An. 6.0–10.0 mm	14.4 ± 1.6	13.2 ± 1.1	1.2 ± 1.3	**0.006**
	An. 10.0–12.0 mm	18.2 ± 5.2	20.6 ± 5.8	−2.4 ± 4.0	**0.033**
	Total diameter	17.1 ± 1.6	15.9 ± 1.5	1.2 ± 1.7	**0.013**

Bold: statistically significant results.

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