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CORNEAL CROSS-LINKING IN PATIENTS AFFECTED BY KERATOCONUS: SAFETY AND EFFECTIVENESS

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ABSTRACT

Objective: To conduct a thorough retrospective review of clinical outcomes and complications in order to assess the safety and effectiveness of corneal cross-linking (CXL) in patients with keratoconus (KCN). **Methods:** Retrospective analysis was performed on 1168 eyes from 886 individuals with diagnosed KCN who had CXL. Patients having at least a year of follow-up were included in the study, which was authorized by the ethics committee. Clinical and topographical markers were used to make the diagnosis, and ultraviolet A (UVA) and riboflavin were used for CXL. Following surgery, patients were observed at predetermined intervals, with an emphasis on safety results, corneal topography, and visual acuity. **Results:** The participants' average age was 22.48 ± 6.72 years, and the male-to-female ratio was 3.3:1. The cornea's thickness prior to surgery was 472.67 ± 38.21 µm. After three years, there was a substantial improvement in both uncorrected distance visual acuity (UDVA) and corrected distance visual acuity (CDVA) ($p = 0.03$ and $p = 0.007$, respectively). The maximum keratometry, or Kmax, dropped ($p < 0.001$) from 56.28 ± 6.11 to 54.98 ± 6.18. Visual acuity and Kmax decrease showed stability across a five- and ten-year follow-up period. The depth of the demarcation line and corneal thickness stayed constant, with 99.2% of eyes exhibiting no advancement. Mild corneal haze, persistent corneal flattening in 1.97% of eyes, and peripheral sterile corneal infiltrates in 1.13% of instances were among the tolerable complications that had no appreciable effect on the final results. **Conclusions:** During long-term follow-up, CXL has shown to be a safe and effective treatment for progressive keratoconus, with notable improvements in corneal curvature and visual acuity. The technique is a good substitute for corneal transplantation since it has low risks and a high rate of stability in the progression of keratoconus.

KEYWORDS: CXL, KCN, CDVA, UDVA.

INTRODUCTION

As a result of rising myopia and irregular astigmatism, keratoconus (KCN), a progressive, usually bilateral, asymmetric corneal ectasia, can cause considerable visual impairment. Prior to the development of corneal collagen cross-linking (CXL), the only ways to treat KCN were to control the refractive errors using glasses, speciality contact lenses, and intrastromal ring segments; these methods had no effect on the course or prognosis of the underlying disease. When KCN reaches an advanced stage, corneal scarring or contact lens intolerance may cause a loss of best-corrected vision, frequently requiring corneal transplantation. In fact, KCN is still the most common reason for penetrating keratoplasty in the world. In addition, a side effect of laser refractive surgery is corneal ectasia resembling KCN (Larkin et al., 2021).

Through the formation of stronger chemical linkages between collagen fibrils, CXL, a minimally invasive technique, aims to reinforce the corneal structure and stop the progression of corneal ectasia. Using ultraviolet A (UV-A, 365 nm) light and riboflavin (vitamin B2), a photochemical reaction is triggered, forming covalent connections between collagen molecules and between collagen molecules and proteoglycans through oxidative stress. Potential advantages of CXL include preventing or delaying corneal ectasia from progressing further, protecting both best-corrected and uncorrected vision, and lowering the need for corneal transplantation and the related hazards to one's vision (Asri et al., 2011).

However, there are certain well-known hazards associated with CXL, including infection, stromal haze, photophobia, delayed epithelial repair, discomfort, and treatment failure. Corneal perforation, severe corneal flattening, noninfectious endotheliitis, and endothelial failure are less commonly reported consequences. Wollensak et al. published the first clinical research on CXL for treating individuals with progressing KCN. Subsequent research has validated the effectiveness of CXL, resulting in its extensive use for KCN and post-laser refractive surgery ectasia (Wollensak et al., 2003).

Wollensak described the conventional CXL procedure, sometimes known as the "Dresden protocol," which entails removing the corneal epithelium in the central 9-mm zone and applying 0.1% riboflavin in 20% dextran every two minutes for thirty minutes. The cornea is subsequently subjected to 30 minutes of UV-A light (370 nm) at an intensity of 3 mW/cm², providing 5.4 J/cm² of total energy. Before irradiation, a corneal thickness of at least 400 µm is usually necessary to prevent endothelial damage (Wollensak et al., 2003).

A number of changes have been made to the Dresden protocol, mostly to minimize the time needed for treatment (rapid CXL) and postoperative recovery (epithelium-on CXL), as well as to allow for corneas thinner than 400 µm (sub-400 protocol). While epithelium-on CXL may be safer but marginally less effective than epithelium-off procedures, evidence suggests that some expedited techniques offer efficacy comparable to the Dresden protocol. The type of riboflavin employed and its corneal penetration capacity play a major role in the outcome. Further investigation into novel methodologies and riboflavin compositions could potentially augment the efficaciousness of epithelium-on CXL. Since the Dresden protocol was the first widely used method, it is sometimes considered the gold standard; however, epithelium-off methods and certain expedited protocols are also equally successful (Caruso et al., 2020).

MATERIALS AND METHODS

In this work, data from 1168 eyes belonging to 886 consecutive individuals with keratoconus were retrospectively evaluated.All subjects provided informed consent, and the study was approved by the ethics committee. Parents gave their assent when their children were minors. The study complied with the specified ethical guidelines.

A number of clinical and topographical markers, including inferior-superior discrepancies, maximal keratometry (Kmax), simulated K values, and topography patterns of keratoconus, were used to make the diagnosis of the disorder. The course of the disease was indicated by a rise in Kmax of one or more diopters in a 12-month period. For children under the age of 14, topographic exams were performed every three months, and for those over that age, every six months, in addition to thorough ophthalmological tests and refraction. Patients who had undergone at least a year of follow-up were excluded. Other forms of ectasia, corneal scars, corneal thickness less than 400 µm, history of infectious keratitis, dry eye, corneal endothelial pathology, autoimmune illnesses, or prior ocular procedures were among the exclusion criteria. Three weeks prior to their tests, patients who wore contact lenses were urged to stop wearing them.

Every patient had a comprehensive ophthalmological examination, which included specular microscopy, preoperative and postoperative pachymetry, topographic assessment using the CSO-Eye Top Topographer and CSO-Sirius Topo-Tomography, and measures of uncorrected and corrected distance visual acuity (UDVA and CDVA). Snellen charts were utilized to record the UDVA and CDVA, which were then transformed to LogMAR (Logarithm of the Minimum Angle of Resolution) for statistical examination. For patients treated prior to 2012, the Eye-Top Topographer was utilized, and for those treated subsequent to 2012, the Sirius Topo-Tomography. The same device was used to measure each eye at various intervals. The day of operation saw the recording of baseline parameters. Three topographic measurements were made, and the best scan was chosen for analysis. Prior to 2011, preoperative pachymetry was carried out using an ultrasound probe for patients receiving treatment; subsequently, Visante optical coherence tomography (OCT) was used. The preoperative data were used in postoperative pachymetry. One month following CXL, the stromal demarcation line was evaluated using anterior segment OCT. Using the manufacturer's software, measurements were performed at a 180° orientation. One-day, five-day (to remove the contact lens), one-month, six-month, one-year, and yearly follow-up appointments were planned. Using a certain software package, one eye each subject was randomly picked for statistical analysis. 886 eyes were included in the safety analysis, and 610 eyes that had undergone postoperative follow-up for at least three years were included in the visual result study.

Surgical Technique

All eyes underwent CXL using riboflavin and ultraviolet A (UVA) light, adhering to a routine procedure. Shortly before the procedure, a topical anesthetic (oxybuprocaine hydrochloride, 0.2%) or lidocaine 4% was used. After removing the corneal epithelium from the center 9 mm, a 30-minute soaking phase was conducted using a 0.1% riboflavin-20% dextran solution (Ricrolin; Sooft, Montegiorgio, Italy). After that, the center 9 mm of the cornea was exposed to UVA radiation (370 nm) for 30 minutes (5.4 J/cm² total energy) using a solid-state device (Vega X-Linker; CSO, Florence, Italy) that delivered riboflavin every 150 seconds. If necessary, anesthetics were reapplied. Every patient had a successful procedure. In the surgery room, parents attended certain pediatric patients. The majority of patients just had topical anesthetic. Following surgery, a bandage contact lens was used for five days until full epithelial healing, and levofloxacin 0.5% drops were given. Following the removal of the bandage contact lens, patients were prescribed levofloxacin (0.5%) drops six times a day for five days, sodium hyaluronate lubricant drops 0.15% four times a day for thirty days, and fluorometholone 0.1% drops four times a day for three weeks.

Statistical Analysis

The Statistical Package for Social Sciences was used to evaluate the data once they were entered into Microsoft Excel (SPSS). To choose the right parametric or non-parametric tests, the normality of the data distributions was evaluated using the Shapiro-Wilk test. The Wilcoxon signed-rank test was utilized to compare vision characteristics, whereas a paired t-test was employed to compare keratometric results. The link between Kmax and the depth of the demarcation line was investigated using Spearman correlation. In order to account for repeated measurement mistakes, Bonferroni correction was used, with a significance level of $p < 0.05$ set.

RESULTS

1168 eyes from 886 participants were included in this retrospective analysis. The data were split into two groups: one for safety analysis and another for visual outcomes because of variations in follow-up completeness. Only one randomly chosen eye per patient was used for statistical analysis. 886 eyes were included in the safety study, and 610 eyes that had been followed up on for at least three years were included in the visual result analysis. The information is displayed as mean ± standard deviation. The patients had an average age of 22.48 ± 6.72 years, a male-to-female ratio of 3.3:1 (682 males and 204 females), and an adult-to-minor ratio of 5.76 since 131 patients (14.7%) were less than 18 years old. At the thinnest point, the average preoperative corneal thickness was 472.67 ± 38.21 µm (n = 886), with values larger than 400 µm in all patients. Nine eyes were placed under general anesthesia for the surgery, with the other eyes receiving merely topical anesthetic.

Table 1: Demographic and clinical characteristics of patients undergoing collagen cross-linking.

Number of eyes included	**886**
Age (years)	22.48 ± 6.72
Male Ratio	3.3:1
Adult Ratio	5.76
Preoperative minimum corneal thickness (µm)	472.67 ± 38.21
Maximum keratometry (diopters)	56.33 ± 5.99
Uncorrected distance visual acuity (LogMAR)	0.50 ± 0.34
Corrected distance visual acuity (LogMAR)	0.15 ± 0.14

The results showed that three years after the surgery, uncorrected distance visual acuity (UDVA) improved to 0.49 ± 0.36 LogMAR and corrected distance visual acuity (CDVA) to 0.14 ± 0.15 LogMAR (n = 610). With p-values of 0.03 and 0.007, respectively, these modifications were statistically significant. After three years of follow-up, there was a substantial decrease in maximal keratometry (Kmax), from 56.28 ± 6.11 to 54.98 ± 6.18 ($p < 0.001$, n = 610). There was no significant link (0.3%) between changes in spherical equivalent and corneal flattening, and there was only a negligible correlation (1%), between corneal flattening (change in Kmax) and CDVA improvement (change in LogMAR). At baseline, the thinnest corneal point measured 467.75 ± 37.38 µm (n = 610), and at the three-year follow-up, it measured 463.45 ± 40.44 µm ($p = 0.32$). Measuring one month after the surgery, the collagen cross-linking (CXL) treatment demarcation line had a mean depth of 254.24 ± 76.78 µm (n = 886). In the majority of cases (94.8 %, 840/886), it was easily visible, and in the less obvious cases, it was rather easy to trace. The possible measure of CXL efficacy, Kmax decrease, did not significantly correlate with the depth of the demarcation line (Spearman's Rho = 0.21, $p = 0.86$, n = 610).

Visual acuity did not change from the three-year follow-up in the 519 eyes with a full five-year follow-up and the 35 eyes with a ten-year follow-up; at five years, UDVA was 0.46 ± 0.36 LogMAR ($p = 0.22$) and CDVA was 0.14 ± 0.18 LogMAR ($p = 0.18$). Long-term outcomes demonstrate stability in visual acuity, with a notable five-year follow-up showing a notable improvement. Kmax drop relative to baseline persisted for the duration of the 10-year follow-up.

Table 2: Visual outcomes of 35 eyes with a full 10-year follow-up.

UDVA	**p-value**	**CDVA**	**p-value**	**Kmax**	**p-value**
Baseline (n = 35)	0.72 ± 0.34	NA	0.19 ± 0.14	NA	59.49 ± 5.86
1 year	0.66 ± 0.31	0.67	0.18 ± 0.12	0.63	58.32 ± 6.35
3 years	0.60 ± 0.29	0.22	0.15 ± 0.11	0.06	57.60 ± 5.99
5 years	0.60 ± 0.34	0.16	0.12 ± 0.12	<0.001	56.67 ± 6.11
10 years	0.61 ± 0.38	0.30	0.16 ± 0.13	0.14	57.11 ± 6.22

In 99.2% of the eyes with a three-year follow-up (n = 610), keratoconus remained stable and did not develop after CXL. After therapy, five eyes (0.82%) exhibited progression, which is defined as an increase in Kmax of

greater than one diopter. Due to corneal thinning, two patients with progression did not receive further treatment; instead, they were content with their visual acuity; one patient did not use spectacles, while the other used hard gas permeable contact lenses. Following at least five years of follow-up, three patients who had progressed were given the same regimen again and demonstrated both clinical and topographic stability. Table 3 provides a summary of these individuals' characteristics. The inadequate demarcation line depths of 153 µm and 174 µm were observed in two of these patients. Variations in the ocular surface, primarily from moderate dry eye, led to variations in Kmax values. After a week, topography was reassessed with lubricants applied.

Table 3: Patients with keratoconus progression after corneal collagen cross-linking.

Patient Number	Age	Sex	Demarcation Line Depth (µm)	Time of Onset of Progression (Years)	Retreatment
1	10	M	240	8	No
2	23	F	153	7	No
3	10	M	277	2	Yes
4	19	M	174	2	Yes
5	16	M	263	1	Yes

In terms of safety and side effects, keratoconus progressed in five patients after CXL. After acquiring a contact lens intolerance and not being content with their eyesight corrected by spectacles, six patients underwent successful deep anterior lamellar keratoplasty. This intolerance was not thought to be a direct consequence of CXL because it appeared at least three years after surgery. With the exception of nine instances with anterior stromal opacity, all cases had a mild form of corneal trace haze that disappeared within six to twelve months and had no effect on visual acuity. Due to anterior corneal stromal opacity and scarring, or ocular surface inflammation in two atopic patients, CDVA reduced in 11 eyes (1.24%). After three years of follow-up, twelve eyes continuously experienced corneal flattening (1.97%) more than three diopters. After one week of surgery, ten patients (1.13%) experienced peripheral sterile corneal infiltrates, which disappeared with the removal of their contact lenses and topical steroid treatment. Ten eyes (1.13%) had mild dry eye symptoms, which were resolved with lubricants. Both epithelial hypertrophy and chronic abnormalities were not observed in any of the patients. A overview of the observed problems is given in Table 4.

Table 4: Postoperative complications.

Complication	Number (Percentage)
Treatment failure (progression)	5/610 (0.82%)
Mild trace haze	886/886 (100%)
Anterior stromal opacity (scarring)	9/886 (1.02%)
Reduction in best corrected visual acuity (one or two lines)	11/886 (1.24%)
Continuous corneal flattening	12/610 (1.97%)
Sterile infiltrates	10/886 (1.13%)
Temporary dry eye	10/886 (1.13%)

DISCUSSION

Corneal cross-linking (CXL) has significantly transformed the management of keratoconus, demonstrating efficacy across both adult and pediatric populations. Standard protocols such as the Dresden protocol, alongside accelerated methods, have shown promising results in these groups. Recently developed approaches, like the Custom Fast protocol, utilize mathematical models based on the Lambert-Beer law and riboflavin consumption rates to optimize the treatment (Ostacolo et al., 2013) (Caruso et al., 2017) (Rubinfeld et al., 2019). This study presents long-term outcomes from a substantial cohort of keratoconus patients. Due to heterogeneity in follow-up data, patients were categorized into two groups: one with at least one year of follow-up for safety analysis (886 eyes), and another with at least three years for evaluating visual outcomes (610 eyes).

The average age of participants was 22.48 ± 6.72 years, with a predominance of males (682) compared to females (204), resulting in a male-to-female ratio of 3.3:1, consistent with existing literature (Magli et al., 2015). While both uncorrected and corrected visual acuity showed minimal improvement after three years of CXL, this change had limited clinical significance. However, the mean Kmax significantly decreased by 1.30 ± 1.49 diopters ($p < 0.001$, $n = 610$), reflecting flattening of the corneal cone, which aligns with previous studies. The pachymetry at the thinnest corneal point showed a decrease from 467.75 ± 37.38 µm to 463.45 ± 40.44 µm after three years ($p = 0.32$, $n = 610$). This slight reduction, observed in studies using different measurement tools, may be attributed to collagen fiber compaction and epithelial remodeling post-surgery. The variability in pachymetric measurements due to the use

of different instruments limits the significance of these results (Caruso et al., 2020).

The depth of the demarcation line was comparable to previous findings but did not significantly correlate with the reduction in Kmax (Spearman's Rho = 0.21, p = 0.86), as noted in other studies. This study observed lower-than-average demarcation line depths, potentially indicating excessive riboflavin absorption during CXL (Knutsson et al., 2017).

Long-term follow-up data was available for only 35 patients, spanning a decade, revealing stable topographic parameters and mean visual acuity. Out of these, three patients (8.6%) showed signs of progression, a finding that will be further discussed. These results are consistent with other studies with similar long-term follow-ups, supporting the sustained effectiveness of CXL. Future research will provide additional evidence on the long-term success of CXL in halting progressive keratoconus (Vinciguerra et al., 2020).

Infectious keratitis, a rare complication reported in previous studies at rates of 0.17% to 1.3%, was not observed in this cohort. This could be attributed to the temperate climate, absence of immunosuppressive therapies among patients, and stringent postoperative care instructions. Prior to surgery, a short course of steroids was sometimes used to mitigate ocular surface inflammation. No short-term surgical complications other than sterile infiltrates and temporary dry eye were noted. Sterile infiltrates occurred in 10 eyes (1.13%), a rate consistent with other studies. Corneal haze, which varied significantly across studies, was noted as mild and did not impact visual acuity. This haze typically resolves within 6 to 12 months post-treatment and may not affect vision substantially, though contrast sensitivity testing was not performed (Çakmak et al., 2020).

Eleven eyes (1.24%) experienced a reduction in corrected distance visual acuity (CDVA) by one or two lines, a lower rate compared to other reports. Most cases were associated with anterior corneal stromal opacity and scarring. Two cases of vision loss were related to inflammation and epithelial irregularities in atopic patients. No signs of keratoconus progression were evident in these cases (Çerman et al., 2017).

Five eyes (0.82%) exhibited keratoconus progression, defined as an increase in Kmax by more than one diopter post-treatment. Two of these patients, who had corneal pachymetry values below 400 µm, were not retreated. Three patients with progression underwent retreatment using the Dresden protocol and showed clinical and topographic stability after a minimum of five years. Risk factors for progression included younger age and suboptimal demarcation line depths. Although the progression rate in our series was relatively low compared to other studies, the possibility of underestimation exists, particularly as longer follow-up data might reveal higher failure rates. The rate of progression increased to 8.6% in the 10-year follow-up group, although this rate may be inflated due to the younger age and lower adult-to-minor ratio in this subset (Achiron et al., 2021).

The study's primary limitations include incomplete follow-up data and variations in pachymetric measurements due to differing techniques used over time. Additionally, endothelial cell density was not measured, an important aspect for assessing potential endothelial damage (Padmanabhan et al., 2017).

In summary, this extensive retrospective cohort study validates the safety and effectiveness of CXL in treating progressive keratoconus and provides valuable insights into its long-term outcomes, contributing significantly to the current literature.

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