Corneal Cross-Linking for Pediatric Keratoconus: Long-Term Results

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Purpose: To assess the efficacy and safety of cross-linking in pediatric patients with keratoconus and to provide a systematic literature overview regarding this subject.

Methods: In this prospective cohort, 54 eyes of 36 pediatric patients with keratoconus underwent standard epithelium-off cross-linking. Follow-up measurements taken up to 5 years after treatment were compared with baseline values. Logistic regression was used to identify the underlying cause in case of progression despite treatment. Finally, a systematic search was performed in PubMed and Embase, and data were extracted and summarized.

Results: At all follow-up visits up to 5 years, maximum keratometry values improved significantly (mean change at 5 years −2.06 diopters (D), $P = 0.01$); moreover, average keratometry, uncorrected distance visual acuity, and corrected distance visual acuity improved at all follow-up times, though not always to the level of statistical significance. In 12 eyes (22%), keratoconus had progressed by ≥1.0 D by the last follow-up visit, despite corneal cross-linking. Cones that were more decentralized were identified as the underlying cause of disease progression. The systematic search yielded 17 unique articles: 10 articles on epithelium-off cross-linking, 2 on accelerated cross-linking, 2 on transepithelial cross-linking, 1 on both epithelium-off and transepithelial cross-linking, and 2 on transepithelial cross-linking with iontophoresis.

Conclusions: Our long-term follow-up reveals that epithelium-off cross-linking is both apparently safe and effective when used to prevent keratoconus progression in pediatric patients. However, disease progression occurred in 22% of the treated eyes; this progression was attributed to a more decentralized cone location.

Key Words: keratoconus, pediatric, corneal, cross-linking

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Keratoconus is a progressive corneal disease with onset typically occurring in adolescence or early adulthood,[1] although cases of severe keratoconus have been reported in children as young as 4 years of age.[2] Keratoconus causes visual impairment because of formation of irregular astigmatism; in most advanced cases, corneal scarring can also occur.[1] Progression of keratoconus usually stabilizes in the fourth decade of life, leaving patients in a relatively fixed disease stage for the remainder of their lives.[1] Interestingly, an inverse relationship has been found between patient age and disease severity; on average, pediatric cases are more severe and are more likely to develop progressive keratoconus.[3] In children, the progression of keratoconus can be both rapid and devastating; as a result, younger patients have a higher likelihood of requiring corneal grafting surgery.[4,5] In addition to the clear burden associated with corneal transplant surgery, the rate of graft survival in young patients is considerably lower than in adults.[6]

Corneal cross-linking (CXL) can prevent the progression of keratoconus by increasing rigidity of corneal collagen due to the chemical production of noncovalent bonds between collagen fibrils.[7,28] The beneficial effect of CXL with respect to preventing disease progression has been demonstrated convincingly in adults, and this has helped increase the popularity of CXL as the treatment of choice for progressive keratoconus in adults.[8–10] To date, however, no controlled trials have been performed to evaluate the efficacy or safety of CXL in children, although several cohort studies on cross-linking in pediatric populations have been published.[11–26]

In this study, we provide a systematic overview of the published literature regarding the outcome in children with progressive keratoconus who underwent CXL. In addition, we report the long-term outcome (ie, up to 5 yrs after undergoing CXL) of our own pediatric patient population, focusing on the efficacy and safety of CXL.

PATIENTS AND METHODS

Dataset and Study Design

The prospective cohort study included all consecutive pediatric patients (ie, under the age of 18 yrs) who underwent an epithelium-off CXL procedure for progressive keratoconus at the University Medical Center Utrecht, the Netherlands, from January 2010 through December 2013. The diagnosis of keratoconus was established in concordance with the global consensus on keratoconus and ectatic diseases report.[26] The

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following inclusion criteria were applied for CXL treatment: Kmax progression defined as a change of ≥1.0 diopter (D) within one year, a centrally clear cornea, and minimum corneal thickness of 400 μm before ultraviolet-A (UV-A) irradiation.

This study was approved by the Ethics Review Board of the University Medical Center Utrecht and was performed in accordance with local laws, the European guidelines for Good Clinical Practice, and the tenets established by the Declaration of Helsinki.

Surgical Procedure

After the corneal epithelium was removed using a blunt knife, cross-linking was performed in accordance with the Dresden protocol, using a 30-minute isotonic riboflavin soaking time and 30 minutes of UV-A irradiation with a perpendicular emission plane (370 nm at 3 mW/cm^2, UV-X 1000; Peschke Meditrade GmbH, Waldshut-Tiengen, Germany) as described previously.[7,27] All procedures were performed under topical anesthesia (oxybuprocaine 4 mg/mL and tetracaine 5 mg/mL). Postoperative medication included moxifloxacin hydrochloride (Vigamox 5 mg/mL), artificial tears (Duratears Free, dextran 1 mg/mL, hypromellose 3 mg/mL), nepafenac (Nevanac 1 mg/mL), and steroids (after epithelial healing) (FML Liquifilm 1 mg/mL), as well as oral medication for pain (tramadol) if needed. The dosage and frequency of the oral medication was based on age and body weight.

Measurements and Devices

Ophthalmic evaluations were performed before CXL and at all follow-up visits (1, 3, 6, 12, 24, 36, 48, and 60 mo after undergoing CXL). This evaluation included uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), manifest refraction, Scheimpflug corneal tomography (Pentacam HR type 70,900; Oculus GmbH, Wetzlar, Germany), and a slit-lamp evaluation with particular focus on atopic/allergic eye disease and eyelid abnormalities. UDVA and CDVA were measured in Snellen lines and used as outcome measures together with Kavg and Kmax. Progression was defined as a change in Kavg and/or Kmax of ≥1.0 D. Cone eccentricity was defined as the distance between the apex of the cone and the pupil center. Contact lens wearers were instructed to remove their lenses 2 weeks before all evaluations.

Statistical Analysis

Normality and homogeneity of residuals were checked visually using a Q-Q plot. A 2-tailed paired samples Student *t* test was used to compare each baseline measurement with the respective follow-up measurements. A logistic regression was performed with the presence or absence of progression (as defined above) at the last follow-up visit as a dependent parameter, with preoperative UDVA, CDVA, Kavg, Kmax, cone eccentricity, central corneal thickness, and age as independent parameters. Differences with $P < 0.05$ were considered significant. Data were collected and analyzed using SPSS 21.0 (IBM, Armonk, NY).

Systematic Literature Search

A systematic search was performed in the PubMed and Embase databases on January 6, 2016. The search terms were "keratoconus," "keratoconic," and "corneal ectasia" in the title and/or abstract. The initial search yielded 4831 articles in PubMed and 5223 articles in Embase. The identified articles were then screened based on their title and abstract. All clinical studies based on cross-linking in pediatric and/or adolescent patients were included. Case reports and case series were excluded. All included articles were then used for cross-referencing. Data regarding the following outcomes were extracted: UDVA, CDVA, keratometry in the flattest meridian (Kflat), keratometry in the steepest meridian (Ksteep), mean keratometry value (Kavg), maximum keratometry value (Kmax), and corneal thickness.

RESULTS

Baseline Characteristics

Our study comprised 54 eyes of 36 patients. Twenty-nine patients (81%) were male, and mean age at the time of treatment was 14.8 years (range: 11–17 yrs). The baseline characteristics of the study population are summarized in Table 1.

Visual Acuity Outcomes

The baseline and follow-up measurements of UDVA and CDVA are summarized in Table 2. Relative to baseline, UDVA had improved at all follow-up times, with the difference reaching significance at the 1-year ($P < 0.001$), 2-year ($P = 0.01$), and 3-year ($P = 0.02$) visits. Moreover, CDVA improved significantly after undergoing cross-linking at all follow-up visits, with the exception of

TABLE 1. Baseline Characteristics of 54 Eyes of 36 Patients With Pediatric Keratoconus (No Missing Values)

	Value	SD or %
Age (yrs), mean	14.8	±1.6
Male, n	29	81%
UDVA, mean	0.32	±0.31
CDVA, mean	0.59	±0.32
Kflat (D), mean	47.1	±4.4
Ksteep (D), mean	51.3	±5.4
Kavg (D), mean	49.1	±4.7
Kmax (D), mean	59.1	±9.0
Eccentricity (mm), mean	0.95	±0.69
Central thickness, mean	490	±39.7

Central thickness, corneal thickness at the pupil center; eccentricity, distance between the apex of the cone and the pupil center; Kavg, average keratometry; Kflat, keratometry in the flattest meridian; Kmax, maximum keratometry; Ksteep, keratometry in the steepest meridian; n, number of patients.

TABLE 2. Visual and Keratometry Outcomes in Pediatric Keratoconus Patients After Undergoing Cross-Linking

	UDVA	*P*	CDVA	*P*	Kmax (D)	*P*	Kavg (D)	*P*	n
Baseline, yr	0.33		0.61		59.0		59.0		54
Δ1	+0.13	<0.001*	+0.22	<0.001*	−1.65	0.001*	−0.27	0.16	54/54
Δ2	+0.07	0.01*	+0.19	<0.001*	−1.13	0.02*	−0.18	0.39	46/54
Δ3	+0.09	0.02*	+0.24	<0.001*	−1.94	0.001*	−0.60	0.001*	25/37
Δ4	+0.06	0.17	+0.19	0.01*	−2.14	0.01*	−1.38	0.03*	18/23
Δ5	+0.05	0.38	+0.08	0.18	−2.06	0.01*	−0.65	0.09	9/9

*Indicates statistical significance ($P < 0.05$).

Δ, change relative to the respective baseline value; CDVA, corrected distance visual acuity, decimals; Kavg, average keratometry; Kmax, maximum keratometry; n, number of eyes analyzed/number of eyes that had reached this follow-up moment at the time of analysis.

the 5-year follow-up visit, in which the improvement was not significant ($P = 0.18$).

Keratometry Outcomes

The baseline and follow-up measurements of Kmax and Kavg are summarized in Table 2. Compared with baseline, Kmax improved significantly 1 year after treatment, and this improvement remained significant throughout the entire follow-up period. Moreover, Kavg improved throughout the entire follow-up period, with improvement reaching significance at the 3-year and 4-year follow-up visits ($P = 0.001$ and $P = 0.03$, respectively).

Adverse Events

No postoperative infections or cases of endothelial cell failure were encountered during the follow-up period (data regarding endothelial cell density are not shown). One eye with preoperative CDVA of 1.2 deteriorated to 0.9 and 0.8 at the 1-year and 2-year follow-up visits, respectively; this decline in CDVA was due to persistent haze. None of the other eyes lost ≥2 Snellen lines. No other adverse events occurred.

In 12 eyes (22%) of 9 children (25%), keratoconus had progressed by ≥1.0 D at the last follow-up visit, despite CXL treatment (Kavg progression up to 4.2 D and Kmax progression up to 7.2 D). Progression was noted at 1 year after treatment in 10 eyes and 2 years after treatment in 2 eyes. If progression had not occurred within 2 years after treatment, it was not observed throughout the remaining study period. Interestingly, none of these patients showed a decline of one or more Snellen lines in either UDVA or CDVA. None of the 36 patients underwent any additional CXL treatment or corneal transplantation.

Cause of Progression

A multivariable logistic regression analysis revealed that cone eccentricity was the only independent factor significantly related to the progression of keratoconus ($P = 0.03$, $\beta = 2.11$). Specifically, eyes in which the cones were more decentralized were more likely to progress. None of the remaining factors were significantly associated with keratoconus progression, including preoperative UDVA ($P = 0.29$), CDVA ($P = 0.85$), Kavg ($P = 0.66$), Kmax ($P = 0.28$), central corneal thickness ($P = 0.95$), and age ($P = 0.81$).

Systematic Literature Overview

The systematic search yielded 16 unique articles on cross-linking for keratoconus in pediatric patients and/or adolescents. Cross-referencing did not yield any additional articles. Ten articles reported on epithelium-off cross-linking,[11–19] 2 on accelerated cross-linking,[20,21] 2 on transepithelial cross-linking,[22,23] 1 on both epithelium-off cross-linking and transepithelial cross-linking,[24] and 2 on transepithelial cross-linking with iontophoresis.[25,26] All 16 articles were cohort studies in which treatment outcomes were compared with baseline values. Caporossi et al[12] compared 2 groups with different corneal thicknesses; for our analysis, we used the combined corneal thickness data. The outcomes of the systematic search and a summary of the outcome parameters are presented in Table 3.

DISCUSSION

In our pediatric population, epithelium-off cross-linking can be considered both apparently safe and effective, achieving stable long-term results up to 5 years. However, 22% of the eyes had disease progression in terms of increased keratometry readings, although no additional CXL treatment or corneal transplantation was applied in any patient, as none of these eyes lost a Snellen line in either UDVA or CDVA.

Given the relentless progression of keratoconus often observed in pediatric patients, Chatzis and Hafezi[13] proposed that CXL should be performed as early as possible, before disease progression occurs. One of the principal advantages of CXL is that it minimizes the need for corneal transplantation. Indeed, the link between cross-linking and the reduced need for keratoplasty was reported recently by Sandvik et al.[30] Hersh et al performed a randomized trial and reported that only 10% of patients (5/49) had progressive keratoconic disease (ie, Kmax progression ≥1.0 D) despite treatment.[9] Furthermore, Wittig-Silva et al[10] reported that only 2% of patients (1/46) had disease progression after undergoing cross-linking; it is worth noting, however, that their definition of progression was ≥2.0 D. The prevalence of progression was much higher in our pediatric cohort than in the aforementioned studies in adults, which suggests

TABLE 3. Overview of Studies on Pediatric Keratoconus Patients Treated With Cross-Linking (Results of the Last Follow-up Visit Are Shown)

Author (yr)	Type of CXL	Patients (Eyes)	Age Range	Follow-up Time	UDVA	CDVA	Kflat	Ksteep	Kavg	Kmax	Corneal Thickness
Ozgurhan et al[21]	Accelerated	38 (44)	9–18	24	Better	Better	Better	Better	Better	NA	NA
Shetty et al[20]	Accelerated	18 (30)	11–14	24	Better	Better	Better	Better	NA	NA	NA
Arora et al[11]	Epi-off	15 (15)	10–15	12	Better	Better	—	—	—	Better	NA
Caporossi (2011)	Epi-off	NA (77)	10–18	36	Better	Better	Better	NA	Better	Better	Better
Chatzis and Hafezi[13]	Epi-off	NA (11)	9–19	36	NA	Better	NA	NA	NA	—	—
Kodavoor et al[19]	Epi-off	24 (35)	9–16	12	NA	Better	NA	NA	NA	Better	Worse
McAnena and O'Keefe[14]	Epi-off	14 (25)	13–18	12	—	Better	—	NA	—	—	—
Peyman et al[15]	Epi-off	37 (64)	NA	12	Better	Better	Better	Better	NA	Better	Worse
Soeters (2014)	Epi-off	NA (31)	12–17	12	Better	Better	—	—	Better	Better	Worse
Uçakhan et al[16]	Epi-off	40 (40)	10–18	48	Better	Better	Better	Better	Better	Better	Worse
Vinciguerra (2012)	Epi-off	40 (40)	9–18	24	Better	Better	Better	—	Better	NA	—
Viswananthan (2014)	Epi-off	18 (25)	8–17	20.1	NA	—	Better	Better	NA	NA	NA
Magli (2012)	Epi-off	19 (23)	12–18	12	—	—	Better	NA	Better	Better	NA
Magli (2012)	Transepithelial	10 (14)	12–18	12	—	—	Better	NA	Better	Better	NA
Buzzonetti and Petrocelli[23]	Transepithelial	13 (13)	8–18	18	NA	Better	Worse	Worse	Worse	NA	—
Salman[22]	Transepithelial	22 (22)	13–18	12	Better	—	NA	NA	—	Better	—
Buzzonetti et al[25]	Iontophoresis	14 (14)	10–18	15	NA	Better	—	—	—	—	—
Magli et al[26]	Iontophoresis	13 (13)	11–18	18	—	Better	NA	—	NA	Worse	Better

—, no significant change; Accelerated, accelerated cross-linking with epithelium removal; Better, significant improvement ($P < 0.05$); CDVA, corrected distance visual acuity; Epi-off, standard epithelium-off cross-linking; Follow-up time, (mean) follow-up time in months; Iontophoresis, transepithelial cross-linking with iontophoresis; Kavg, average keratometry; Kflat, keratometry in the flattest meridian; Kmax, maximum keratometry; Ksteep, keratometry in the steepest meridian; NA, data were not available; Patients (eyes), number of patients and number of eyes at the last follow-up visit; Transepithelial, transepithelial cross-linking; Worse, significant deterioration ($P < 0.05$); yr, year in which the study was published.

that cross-linking may have different effects in different age groups. Thus, in children, cross-linking may provide somewhat less protection against the future need for corneal transplantation.

Our analysis of the cause of progression revealed that decentralized cone location was the only independent underlying cause of keratoconus progression in this subset of patients. This finding is consistent with our previous results in which cone eccentricity was identified as a major predictor of the Kmax outcome.[31] Greenstein et al[32] previously hypothesized that this could be due to less homogenous UV light exposure and/or the distribution of irradiation over a larger area in the peripheral parts of the cornea. Riboflavin uptake and the depth of the stromal demarcation line were not routinely measured and were therefore not suitable for statistical analysis.[33,34]

Caporossi et al[12] performed the largest study on cross-linking in children to date; their study initially included 152 patients with keratoconus in which 77 eyes were available for analysis 3 years after treatment. Their results were analyzed by comparing patients with corneal thickness <450 μm and patients with corneal thickness >450 μm with their respective preoperative measurements. In both groups, both UDCA and CDVA improved significantly within 1 year. Moreover, topographic results showed significant improvement in keratometry readings, and these effects lasted at least 3 years after treatment (the last reported follow-up visit). This is in concordance with results of the study by Uçakhan et al,[16] who published an improvement in both visual and keratometry outcomes 4 years after treatment. Those findings are in contrast with the findings reported by Chatzis and Hafezi,[13] who concluded that the effect of cross-linking may not be long-lasting, as the initial Kmax improvement was no longer significant at 2-year follow-up and revealed a trend—albeit not significant—toward deterioration at the 3-year follow-up visit. However, the improvement in CDVA did remain significant.[13] In our study, the effect of cross-linking on Kmax did not decline over time; in fact, significant improvement was measured throughout the entire 5-year follow-up period.

In conclusion, our results support the notion that epithelium-off cross-linking is an apparently safe and effective method for preventing keratoconus progression in pediatric patients, providing clinical benefits for at least 5 years after treatment. However, disease progression occurred in 22% of the treated eyes; this progression was attributed to a more decentralized cone location.

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