Research Square

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Long Term Follow-up of Corneal Collagen Cross-Linking in Pediatric Keratoconus

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Abstract

Purpose:

To evaluate the long-term outcomes of epithelium-off corneal collagen cross-linking using the Dresden protocol in pediatric keratoconus patients.

Methods:

This retrospective case series included pediatric patients who underwent standard collagen corneal cross-linking at a single site. Clinical assessment comprised visual acuity, refraction, and Scheimpflug tomography. A minimum follow-up of 60 months was required. The protocol consisted of UVA irradiation at 3 mW/cm² for 30 minutes (total dose 5.4 J/cm²). Postoperative management included topical antibiotics until re-epithelialization and corticosteroids for 2 weeks.

Results:

Twenty-three eyes of 13 patients (mean age 15.35 years; range: 12–17.5) were analyzed with a mean follow-up of 12.18 ± 2.92 years. Uncorrected distance visual acuity improved from 0.70 ± 0.44 to 0.41 ± 0.40 logMAR ($p < 0.001$), while corrected distance visual acuity improved from 0.26 ± 0.22 to 0.09 ± 0.16 logMAR ($p < 0.001$). Mean flat and steep keratometry remained stable ($p > 0.05$), while maximum keratometry decreased significantly from 53.88 ± 8.05 D to 52.43 ± 6.97 D ($p = 0.009$). Only one eye (4.3%) progressed by > 1 D in maximum keratometry. No permanent corneal haze was observed

Conclusions:

Standard epithelium-off corneal cross-linking using the Dresden protocol is safe and effective in halting keratoconus progression in pediatric patients. Long-term follow-up demonstrated durable disease stabilization, significant visual improvement, and minimal complications, supporting early intervention as the standard of care in this high-risk population.

Introduction

Pediatric keratoconus (KC) represents a unique and particularly challenging subset of the disease, distinguished by its early onset, rapid progression, and significant impact on visual development. This corneal ectatic disorder, which often manifests during adolescence or even earlier, is characterized by progressive thinning and protrusion of the cornea, leading to irregular astigmatism and subsequent visual impairment.

Compared with adults, children with KC frequently present with more advanced disease at the time of diagnosis and show a higher likelihood of rapid progression. This aggressive course underscores the importance of early detection and timely management, given the profound implications on visual function, educational achievement, and overall quality of life in affected children (1–4). Left untreated or inadequately managed, pediatric KC can lead to severe corneal scarring or may necessitate corneal transplantation (5). In Early childhood, children are particularly susceptible to amblyopia, making disease control even more critical in the higher prevalence groups such as the vernal keratoconjunctivitis group (VKC) (6–9).

Over the past two decades, treatment strategies have evolved substantially, with corneal collagen cross-linking (CXL) emerging as the standard of care for halting disease progression (10). Studies have demonstrated its safety and efficacy

in pediatric cohorts, with authors advocating for earlier intervention compared with adults, given the aggressive nature of the disease in younger patients (11,12). Adjunctive approaches, such as customized contact lens fitting (13), continue to play an important role in visual rehabilitation, but CXL remains the cornerstone for preventing irreversible structural damage.

Methods

This retrospective case series included children under the age of 18 years with KC who underwent CXL under topical anesthesia. Treatment was administered following the original epithelium-off Dresden protocol at 3 mW/cm2 for 30 minutes, with a total dose of 5.4 J/cm2. The study was approved by the institutional review board and ethic committee at the Samson Assuta Ashdod University Hospital and adhered to the tenets of the Declaration of Helsinki – authorization number 0116-24-AAA.

At the end of the procedure, contact lens was applied and Ofloxacin 0.3% eye drops were prescribed 4 times a day until full epithelization and the lens then was removed. Fluorometholone 0.1 (FML) eye drops were prescribed 4 times a day for two weeks. Clinical evaluation comprised of visual acuities, refractive assessments, and Scheimpflug corneal tomography at each follow-up. The study included all patients with a minimum follow-up duration of 5 years.

Statistical analysis

Descriptive statistics were used to summarize patient demographics and baseline characteristics. Paired t-tests employed to compare pre- and postoperative outcomes, as appropriate. Statistical significance was set at $P < 0.05$. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA).

Results

Results Twenty-three eyes of 13 patients were included in the study. The mean age at the time of treatment was 15.35 years (range: 12 to 17.5 years). The mean follow-up was 12.18 ± 2.92 years (range 6 – 16). Uncorrected distance visual acuity significantly improved from 0.70 ± 0.44 to 0.41 ± 0.40 logMAR ($P < 0.0001$), and corrected distance visual acuity improved significantly from 0.26 ± 0.22 to 0.09 ± 0.16 logMAR ($P < 0.0001$). While mean flat and steep keratometry values were not significantly altered ($P > 0.05$ for both), the mean maximum keratometry value significantly decreased from 53.88 ± 8.05 D preoperatively to 52.43 ± 6.97 D at 12 years postoperatively ($P = 0.009$) (Table 1). Maximum keratometry had progressed by > 1 D in one eye (4.34%), yet visual acuity, refraction and corneal thickness remained unchanged. The patient experienced no subjective deterioration in vision therefore re CXL was not performed and patient continued close follow-up. No permanent corneal haze was observed in any patient.

Table 1. Visual and Tomographic parameters at baseline and postoperative

	Pre op (Mean ± SD)	Post op last follow-up (Mean ± SD)	*P value*
UDVA (LogMar)	0.70 ± 0.44	0.41 ± 0.40	< 0.001*
CDVA (LogMar)	0.26 ± 0.22	0.09 ± 0.16	< 0.001*
Cylinder (D)	-4.90 ± 4.18	-3.65 ± 4.53	= 0.389
K1 (D)	45.83 ± 3.61	45.26 ± 3.72	= 0.210
K2 (D)	50.26 ± 5.77	49.48 ± 5.09	= 0.0790
Kmax (D)	53.88 ± 8.05	52.43 ± 6.97	= P = 0.009*
TCT (µm)	464 ± 31.2	451 ± 32.1	< 0.0001*

*Statistical significance

logMAR, logarithm of the minimum angle resolution; UDVA, uncorrected distant visual acuity; CDVA, corrected distant visual acuity; CXL, Corneal collagen cross-linking

Discussion

As with KC in the adult population the frequency of KC in the pediatric population is higher than previously reported and the disease tends to be more aggressive. A hospital-based study reported an incidence of KC of 0.53% among pediatric patients and o those, two patients had an initial presentation with corneal hydrops (1). Léoni-Mesplié et al. reports on grade 4 KC in patients under 15 at the time of diagnosis in 27.8% versus 7.8 in adults and faster progression in this group (2). Gupta et al. (North India Childhood KC study) reports 46% progression in a pediatric group with age ranging from 8–18 years, 8% were under 10 years of age, 8% of children developed hydrops and 58.6% had VCK (3). Chatzis et al report on progression of KC in 88% of patients between 9–19 years old (4). In a cohort of 80 pediatric KC patients referred to Alexandria University Main Hospital between 2018 and 2019, 30 patients were younger than 14 years of age. Three patients presented with corneal hydrops, and 25% were classified as stage 4 disease (5). Patients with VKC are at increased risk of KC and exhibit a more severe disease (9).

As in the adult's group, CXL is indicated for arresting the progression of the disease and there is an emerging consensus in sceitific meetings that CXL should be offered immediately upon diagnosis in the pediatric group.

Vinciguerra et al. report on stability of pediatric KC after CXL with up to 14 years of follow-up. No patients were retreated by CXL (13). Arora et al. report on stabilization of KC in 15 eyes of 15 KC patients aged between 10–15 years with one year follow up (14). Similar results are reported by Rodolfo et al. in a group between 10–16 years with results comparable to the adult group in one, three and four years follow-up (15-17). Godefrooij et al. report on the efficacy and safety of epithelium-off CXL in pediatric KC patients over a 5-year period, although disease progression occurred in 22% of eyes, primarily in decentralized cones (18). Padmanabhan et al. report outcomes of 377 pediatric KC eyes that underwent epithelium-off CXL for

progressive KC, showing significant improvements in visual acuity, keratometry, and topography over a mean follow-up of up to 6.7 years. Corneal flattening was more pronounced in cases with moderately advanced disease and centrally located cones. Stabilization was achieved in 85% of eyes at 2 years and 76% at 4 years, though some loss of effect was reported beyond 4 years (19). Stabilization of KC was reported also in accelerated CXL (ACXL); in 49 eyes of 49 patients, with a mean age of 14.2 years (range: 9.5–17.3) and mean follow-up duration of 4.61 ± 1.9 years (20). Nicula et al report on halting KC progression in two groups of pediatric KC patients treated by the Dresden or Accelerated epi off CXL protocols with a follow up of 4 years (21). Henriques et al. report a 23% progression rate in 26 eyes of pediatric patients treated by the Dresden Protocol and followed up for 3 years (22). Mazzotta et al report progression rate of 24% in 10 years follow Up (23). The KERALINK randomized controlled trial in pediatric patients aged 10–16 years demonstrated KC progression in 2 patients (7%) treated with CXL compared with 12 patients (43%) who received standard care with 18 months of follow-up (24). Simantov et al. report a 7-year follow-up of 60 eyes in 30 patients, where one eye underwent CXL and the fellow eye was observed. During follow-up, eight untreated eyes (26.6%) showed progression and subsequently required CXL, whereas only one treated eye (3.3%) needed retreatment (25).

Our study demonstrated a reduction in Kmax, this is in line with other reported outcomes following CXL in pediatric age group. A retrospective analysis of 131 eyes from 110 children (mean age 16 ± 2 years) treated with CXL for keratoconus demonstrated significant improvement in Kmax (from 53.81 to 52.31). Greater corneal flattening was observed with non-accelerated protocols and in eyes with more advanced baseline disease. The study concluded that CXL is effective in pediatric KC, with non-accelerated protocols providing superior outcomes (26). Our group previously reported on 29 pediatric KC patients treated with the Dresden protocol and followed up for a mean period of over 2 years. KC arrest was documented, accompanied by improvements in visual acuity and a reduction in astigmatism (27). The results of our study, with a mean follow-up of 12 years, confirm the safety and efficacy of the epithelium-off Dresden protocol in pediatric patients. We observed significant improvement in both uncorrected and corrected distance visual acuity, in addition to statistically significant reduction in maximum keratometry. Disease progression was non-conclusive in one eye (4.3%) showing > 1 D of steepening. This patient had no change visual acuity, refraction or corneal thickness. Moreover, the patient did not experience subjective deterioration in vision, therefore re CXL was not performed and we opted for continued close follow-up.

No permanent corneal haze or other significant complications were noted highlighting the excellent safety profile of the procedure over a prolonged follow-up period.

The main strengths of our study are the very long follow-up period and the uniform use of the original Dresden protocol, which allows reliable comparison with historical data. The study also provides real-world evidence of both functional and structural improvement in a challenging pediatric population. Limitations include the small sample size, the retrospective

design, and the absence of a control group, which may restrict generalizability. Nevertheless, the stability of outcomes and the absence of complications strongly support the role of standard CXL as the cornerstone of pediatric KC management.

Declarations

The participate/patient/ or legal guardian consented to participate in the study.

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