*Original Research Article*

EJO European Journal of Ophthalmology

European Journal of Ophthalmology
1–4

DOI: 10.1177/1120672118760149
journals.sagepub.com/home/ejo
SAGE

# Long-term efficacy and safety after corneal collagen crosslinking in pediatric patients: Three-year follow-up

**Maria A Henriquez, Sandra Villegas, Mirel Rincon, Carmen Maldonado and Luis Izquierdo Jr**

**Abstract**

**Purpose:** To evaluate the effectiveness of standard corneal collagen crosslinking for children with progressive keratoconus.

**Methods:** Prospective study including 26 eyes of 26 patients younger than 18 years old with progressive keratoconus at Oftalmosalud Instituto de Ojos, Lima, Peru. Standard epi-off corneal crosslinking was performed in all eyes between January 2012 and January 2013. Pre- and postoperative evaluation (at 3 years) included uncorrected and best-corrected visual acuity and Scheimpflug analysis. Crosslinking failure was defined as an increase in maximum keratometry ($K_{max}$) of more than 1 diopter after 1 year or more.

**Results:** Mean uncorrected visual acuity improvement was 0.24 LogMAR ($p = 0.07$) and mean best-corrected visual acuity improvement was 0.18 LogMAR ($p = 0.01$). None of the eyes lost more than one line in the best-corrected visual acuity. Four eyes (15.38%) lost two lines in the uncorrected visual acuity at 3 years postoperative. Mean steeper keratometry improvement was 1.14 diopters ($p = 0.60$). Progression rate was 23.07%.

**Conclusion:** Standard epi-off corneal collagen crosslinking is safe and effective to halt the progression of the keratoconus with significant improvement in the best-corrected visual acuity at 3-year follow-up.

**Keywords**

Crosslinking, keratoconus, children

Date received: 14 September 2017; accepted: 30 January 2018

## Introduction

According to the United States bank and International Eye banking statistics, keratoconus represents the second most common reason for the necessity of corneal transplantation.[1] Keratoconus is generally first diagnosed in young people at puberty or their late teens; however, in a percentage of patients, it presents during pediatric ages and is more aggressive and has a higher progression risk than it does in older age groups.[2,3]

Because corneal collagen crosslinking (CXL) appears to be the only procedure able to halt the progression of keratoconus, the interest in its effectiveness in the pediatric population is increasing because it could result in the avoidance of a corneal transplant.[4–6] Although its effectiveness in adults is widely known, limits exist regarding the long-term results for pediatric groups. There are a few reports of the effects of CXL being lost after 2 years; however, other reports indicate stabilization of the disease in 90% of cases after 5 years. Progression rates range between 5% and 88% in different studies.[7–11] Different sample sizes, CXL procedures, and follow-up could explain the various results; however, more long-term studies involving a pediatric

Research Department, Oftalmosalud Institute of Eyes, Lima, Peru

**Corresponding author:**
Maria A Henriquez, Research Department, Oftalmosalud Institute of Eyes, Av. Javier Prado Este 1142, San Isidro, Lima 27, Peru.
Email: mariale_1610@hotmail.com

population are imperative and could contribute to the understanding of this subject.

In this study, we present visual results after corneal collagen CXL for patients younger than 18 years of age with long-term follow-up of 3 years.

## Methods

This prospective pre–post study design included patients diagnosed with progressive keratoconus who were found eligible for a CXL procedure at Instituto de Ojos, Oftalmosalud (Lima, Peru) from January 2012 to January 2013. The study complied with the Declaration of Helsinki, the ethics committee, and the Institutional Review Board (IRB) of the institution approved the study, and written informed consent was obtained from the parents or legal representative prior to the procedure. If the child was able to understand the nature of the study, then written informed consent was obtained from that child as well.

Inclusion criteria were younger than 18 years of age, keratoconus diagnosis, a clear central cornea, minimal pachymetry of 400 µm (at the thinnest point), and documented progression defined by an increase in steep keratometry by ≥1 diopter (D) during the previous 6–12 months. Exclusion criteria were amblyopia, retinal pathology, and history of ocular infection.

Patients were examined at baseline and 3 years after the corneal CXL. Manifest refraction, uncorrected visual acuity (UCVA), best-corrected visual acuity (BCVA), slit lamp examination, and Scheimpflug imaging analysis (Oculus Pentacam GmBH, Wetzlar, Germany) data were obtained at each follow-up time. All participants who wore contact lenses were instructed to discontinue their use at least 3 days before examinations (for scleral and soft contact lenses) or 2 weeks before examinations (for rigid permeable lenses).

### *Surgical procedure*

Local anesthetic eye drops containing proparacaine hydrochloride 0.5% (Alcaine; Alcon Laboratories) were administered. For standard epi-off CXL, epithelial removal (9 mm) was performed using a blunt spatula (Asico AE2766). Pachymetry was confirmed using a manual pachymeter (Ophthasonic A-Scan/Pachometer III; Accutome, Malvern, PA). Isotonic riboflavin 0.1% solution (B2 riboflavin) plus 20% Dextran 500 (Peschke, Huenenberg, Switzerland) was administered every 5 min for 30 min until complete corneal impregnation using a suction ring positioned on the cornea pooled with riboflavin. Then the cornea was rinsed with balanced salt solution and yellow tyndall was checked during the slit lamp examination. If tyndall was not observed, then 10 extra minutes of impregnation was indicated until tyndall was observed. Ultraviolet A (UVA) irradiation was performed using CCL-VARIO (Peschke Ltd, Borsigstrabe, Germany) for 30 min (3 mW/cm$^2$), and isotonic riboflavin 0.1% solution was re-administered to the cornea every 5 min.

The post-CXL medication consisted of antibiotic eye drops (Vigamox (moxifloxacin hydrochloride); Alcon Nederland) and non-steroidal anti-inflammatory drops (Nevanac (nepafenac) 0.1%; Alcon Nederland) for 1 week, preservative-free artificial tears for 4 weeks, and topical steroids (fluorometholone 0.1% drops; Allergan BV) three times per day for 3 weeks starting 1 week after CXL. A bandage contact lens (Purevision; Bausch & Lomb) was used and removed after 5 days.

### *Statistical analysis*

Statistical analyses were performed using SPSS version 22.0. Comparisons of means were performed using Student's t-test and the non-parametric Mann–Whitney test. Data were expressed as mean and standard deviation values. For any case, a p value of $<0.05$ was considered statistically significant.

## Results

A total of 26 eyes of 26 patients were included; 14 (53.84%) males and 12 (46.15%) females were involved in the study. The mean age was 13.69 (range: 10–17) years. Table 1 shows preoperative and postoperative data (3 years) for all parameters studied. The mean improvement in the UCVA and BCVA were 0.24 LogMAR and 0.18 LogMAR, respectively. The mean Steeper keratometry improvement was 1.14 D. Progression rate (described as CXL failure) was 23.07%. None of the eyes lost more than one line in the BCVA. Four eyes (15.38%) lost two lines in the UCVA at 3 years postoperative. Postoperative complications related to the procedure were observed in two eyes with stromal haze that lasted 1 month and resolved with topical corticosteroid treatment.

## Discussion

It was noted at 1-year follow-up that CXL is capable of halting the progression of keratoconus in children;[11–16] however, long-term results beyond 3 years are limited in the literature and may differ between authors. Chatzis and Hafezi[7] used standard epi-off CXL in a retrospective case series and reported follow-up of 36 months for 11 eyes. They found significant improvements in corrected distance visual acuity (CDVA) and no significant improvements in maximum keratometry ($K_{max}$); in fact, they referred that the improvements in $K_{max}$ found at up to 24 months lost significance at 36 months. Hashemi et al.[8] used standard epi-off and reported a pediatric subgroup analysis of 10 eyes. Significant improvements were found for BCVA, and no significant improvements were found for UCVA and maximum keratometry at 5-year follow-up. Caporossi et al.[10] used standard epi-off in a

**Table 1.** Pre- and postoperative changes at 3-year follow-up.

| | Preoperative | Postoperative | p value |
|---|---|---|---|
| UCVA | 0.71 (0.59) | 0.47 (0.43) | 0.07 |
| BCVA | 0.26 (0.27) | 0.08 (0.09) | 0.01 |
| Steeper keratometry | 51.19 (3.68) | 50.94 (2.88) | 0.60 |
| Flatter keratometry | 46 (2.81) | 45.46 (2.39) | 0.22 |
| Maximum keratometry | 55.87 (6.57) | 54.73 (4.63) | 0.32 |
| Pachymetry thinnest point | 502.30(36.84) | 469.46 (80.46) | 0.09 |
| Pachymetry apex | 507.76 (36.22) | 476.69 (79.36) | 0.10 |
| Posterior elevation maximum | 46.15 (16.79) | 53.46 (29.70) | 0.17 |
| Posterior elevation at TP | 34 (17.37) | 42.53 (29.09) | 0.08 |
| Anterior elevation maximum | 24.38 (10.50) | 23.84 (10.19) | 0.76 |
| Anterior elevation at TP | 18.84 (9.77) | 16 (6.04) | 0.11 |
| Corneal astigmatism | 5.20 (3.03) | 5.48 (2.63) | 0.32 |
| Asphericity front | −0.96 (0.37) | −0.87 (0.29) | 0.11 |
| Index of surface variance | 69.76 (28.91) | 64.46 (19.45) | 0.22 |
| Index of high decentration | 0.049 (0.04) | 0.06 (0.04) | 0.28 |
| Index of vertical asymmetry | 0.56 (0.30) | 0.49 (0.17) | 0.17 |

UCVA: uncorrected visual acuity; BCVA: best corrected visual acuity; TP: thinnest point.
p value between pre- and postoperative at 3 years using Student's t test.

prospective comparative cases series of 152 eyes. Follow-up was performed at 48 months and significant improvements in UCVA, BCVA, and $K_{max}$ were found. Padmanabhan et al.[9] used standard epi-off CXL in a retrospective study of 194 eyes with follow-up for more than 2 years and reported significant reductions in the mean simulated keratometry, maximum keratometry, and CDVA. We report the results at 3-year follow-up, and we found stabilization of keratoconus in 76.93% of eyes; significant improvements in BCVA; and no significant changes in mean UCVA, pachymetry, maximum, steeper, and flattest keratometry, anterior and posterior elevation, corneal astigmatism, and asphericity. In our study, the progression rate was 23.07%. However, previous progression rates have ranged between 5% and 88%.[7,10] Despite the high rate of keratoconus stabilization, we did not find an overall improvement in topographic parameters as described by Caporossi et al.[10] and Padmanaban et al.[9] These differences could be attributed to the differences in the studied population. In the study by Caporossi et al.,[10] patients were younger than 18 years (mean age was not provided) and the preoperative $K_{max}$ was 50.22 D. In the Padmanabhan et al.[9] study, the mean age was 15 ± 2.5 years and the preoperative $K_{max}$ for the total population was 61.65 D. In our study, the mean age was 13.69 years, which is younger than that of previous articles, and the preoperative $K_{max}$ was 55.87 D. Six eyes were from patients younger than 12 years, of which four experienced failure; this could be because natural–biological CXL increase as age increases,[10] and this also should be considered that performing this 1-h procedure in a child 12 years of age or younger is difficult because the patient is awake, the ocular and patient movements could affect the real time of the radiation. Our study has some limitations; it shows only results of standard CXL, which requires 30 min of irradiation. However, this was the type of procedure performed at the clinic in 2013.

Some evidence suggests that preoperative keratometry is a risk factor for CXL failure.[17] Values more than 54 D have been associated with a CXL failure rate up to 12% for adults; in our sample size, 50% (13/26) of the eyes had preoperative maximum keratometry more than 54. Among these, corneal CXL was effective for 11 eyes, suggesting that corneal CXL could be and should be performed for advanced cases of keratoconus that meet the inclusion criteria for the procedure.

In conclusion, at 3-year follow-up, it was evident that CXL is effective for halting the progression of keratoconus in pediatric patients younger than 18 years.

## Acknowledgements

This paper was presented in part at ASCRS San Diego, USA, April 2015.

## Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

## References

1. Lowe MT, Keane MC, Coster DJ, et al. The outcome of corneal transplantation in infants, children and adolescents. *Ophthalmology* 2011; 118: 492–497.

2. Reeves SW, Stinnett S, Adelman RA, et al. Risk factors for progression to penetrating keratoplasty in patients with keratoconus. *Am J Ophthalmol* 2005; 140: 607–611.
3. Léoni-Mesplié S, Mortemousque B, Touboul D, et al. Scalability and severity of keratoconus in children. *Am J Ophthalmol* 2012; 154: 56–62.
4. Wollensak G. Crosslinking treatment of progressive keratoconus: new hope. *Curr Opin Ophthalmol* 2006; 17: 356–360.
5. Raiskup F, Theuring A, Pillunat LE, et al. Corneal collagen crosslinking with riboflavin and ultraviolet-A light in progressive keratoconus: ten-year results. *J Cataract Refract Surg* 2015; 41(1): 41–46.
6. Henriquez MA, Izquierdo L Jr, Bernilla C, et al. Riboflavin/ultraviolet a corneal collagen cross-linking for the treatment of keratoconus: visual outcomes and scheimpflug analysis. *Cornea* 2011; 30: 281–286.
7. Chatzis N and Hafezi F. Progression of keratoconus and efficacy of pediatric [corrected] corneal collagen cross-linking in children and adolescents. *J Refract Surg* 2012; 28: 753–758.
8. Hashemi H, Seyedian MA, Miraftab M, et al. Corneal collagen cross-linking with riboflavin and ultraviolet a irradiation for keratoconus: long-term results. *Ophthalmology* 2013; 120: 1515–1520.
9. Padmanabhan P, Rachapalle Reddi S, Rajagopal R, et al. Corneal collagen cross-linking for keratoconus in pediatric patients-long-term results. *Cornea* 2017; 36: 138–143.
10. Caporossi A, Mazzotta C, Baiocchi S, et al. Age-related long-term functional results after riboflavin UV a corneal crosslinking. *J Ophthalmol* 2011; 2011: 608041.
11. Kumar Kodavoor S, Arsiwala AZ and Ramamurthy D. One-year clinical study on efficacy of corneal collagen cross-linking in Indian children with progressive keratoconus. *Cornea* 2014; 33: 919–922.
12. Arora R, Gupta D, Goyal JL, et al. Results of corneal collagen cross-linking in pediatric patients. *J Refract Surg* 2012; 28: 759–762.
13. Soeters N, Van Der Valk R and Tahzib NG. Corneal cross-linking for treatment of progressive keratoconus in various age groups. *J Refract Surg* 2014; 30: 454–460.
14. Vinciguerra P, Albe E, Frueh BE, et al. Two-year corneal cross-linking results in patients younger than 18 years with documented progressive keratoconus. *Am J Ophthalmol* 2012; 154: 520–526.
15. Viswanathan D, Kumar NL and Males JJ. Outcome of corneal collagen crosslinking for progressive keratoconus in paediatric patients. *Biomed Res Int* 2014; 2014: 140461.
16. Wise S, Diaz C, Termote K, et al. Corneal cross-linking in pediatric patients with progressive keratoconus. *Cornea* 2016; 35: 1441–1443.
17. Koller T, Mrochen M and Seiler T. Complication and failure rates after corneal crosslinking. *J Cataract Refract Surg* 2009; 35: 1358–1362.