• **Clinical Research** •

Three-year follow-up in advanced pediatric keratoconus: thin corneas may not have pachymetry properly assessed after crosslinking

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Abstract

● **AIM:** To analyze the crosslinking (CXL) effects in pediatric keratoconus, and to identify the patients' corneal characteristics whose pachymetry could not be adequately evaluated by Scheimpflug method after procedure.

● **METHODS:** Consecutive pediatric patients with progressive keratoconus underwent CXL were included. Best-corrected visual acuity (BCVA) and spheric equivalent (SE) were measured before and after CXL. After CXL, groups 1 and 2 were divided based on the posterior surface Pentacam quality specifications (QS): "OK" (Group 1) and "not OK" (Group 2). The mean (RmF and RmB) and minimum (RminF and RminB) radius of curvatures of the anterior and posterior corneal surfaces, and the thinnest pachymetry (Pmin) were measured preoperatively at 3, 6, 12, 24, and 36mo. Haze was annotated.

● **RESULTS:** Twenty-six patients (14 men, mean age 14±1.8y) and median Kmax of 59.9 D initially and 61.4 D preoperatively were treated. BCVA was not different before and 24mo after CXL. Group 2 statistically differed to group 1 in that SE was more myopic before and with no difference 24mo after CXL; RmF and RmB were steeper and Pmin was thinner pre-surgically. Group 2, in which pachymetric changes could not be adequately evaluated after surgery, presented with significant RmF flattening, a shift to hyperopia, and more haze after CXL.

● **CONCLUSION:** Patients whose pachymetry could not be adequately evaluated after CXL had steeper and thinner

corneas before surgery. The predictive factors for impaired QS after CXL are RmF, RmB, and Pmin. In advanced keratoconus, alternative methods to analyze pachymetry and the posterior surface should be considered.

● **KEYWORDS:** keratoconus; cross-linking; corneal pachymetry; corneal topography; corneal opacity

INTRODUCTION

Keratoconus is a corneal ectasia that leads to progressive stromal thinning and protrusion, resulting in irregular astigmatism, visual impairment, and loss of quality of life[1]. Its progression is more aggressive at puberty[2-4].

The current recommended treatment for halting progression of keratoconus is crosslinking (CXL), which is an ultraviolet A (UVA) light therapy associated with riboflavin eye drops[5]. The most used parameters to indicate disease progression or treatment successes are anterior keratometry, the anterior radius of curvature of the anterior corneal surface, and corneal thickness, which are almost always obtained through corneal tomography. This exam provides a three-dimensional reconstruction of the cornea, based on the data acquired on the anterior and posterior corneal surfaces, creating a pachymetric map[6].

CXL has been used in pediatric patients since 2012[7]. Using the Dresden protocol, many studies demonstrated improved visual and refractive outcomes and long stability in keratometric indices. However, there is not a consensus about corneal thickness behavior after CXL. Some authors observed significant corneal thinning[8-12], while others did not observe this[2,13-14].

The corneal pachymetric map is built based on the anterior and posterior corneal surfaces[6]. Taking into account that corneal haze[8,13,15] may impair the analysis of posterior corneal surface and consequently the corneal thickness evaluation, our aim

was to study CXL effects in progressive pediatric keratoconus, and to better understand the predictive factors associated with impaired corneal surface reading, and consequently impaired corneal thickness evaluation, as well as the associations of impaired quality specifications (QS) on the posterior corneal surfaces with corneal haze. We also assessed visual acuity, refractometry, and history of ocular allergy.

SUBJECTS AND METHODS

Ethical Approval This study adhered to the tenets of the Declaration of Helsinki and was approved by our local Ethics Committee. Informed consent was waived due to the retrospective nature of the study.

This retrospective consecutive, nonrandomized study was performed on a cohort of pediatric keratoconus patients who were treated with the Dresden protocol CXL technique. Consecutive pediatric patients with verified progressive keratoconus, defined as an increase of 1.0 D in maximum keratometry (Kmax) or in the steepest meridian, and minimal corneal thickness of 390 mm were surgically treated with CXL according to Dresden protocol, from May 2015 through May 2016. The keratoconus diagnosis was based on corneal tomography and clinical signs of keratoconus. The CXL procedure consisted of removing 8.0 mm of the central corneal epithelium and applying a solution of riboflavin 0.1% (400 mOsm) on the denuded stroma, at 5min intervals for 60min. The first half of the drug instillations were before the exposure to 370 nm UVA radiation, with an irradiance of 3 mW/cm^2 (Opto XLink, São Carlos, SP, Brazil). The remainder of the instillations were performed during the procedure. Postoperative care consisted of wearing a therapeutic soft contact lens for 5d, using a commercial formulation of moxifloxacin 0.5% and 0.1% dexamethasone eye drops four times a day for 10d, and preservative-free hyaluronic acid lubricants six times daily for 1mo.

All the patients were treated under general anesthesia to ascertain the exact duration of the procedure and the correct distance of UVA source from the apex of the cornea, since in younger patients reduced cooperation and fear of pain can interfere with the procedure. The same ophthalmologist (Antunes-Foschini R) performed all the procedures at Hospital das Clínicas, Medical School of Ribeirão Preto, University of São Paulo, Brazil. The subjects were followed up at 3, 6, 12, 24, and 36mo after CXL. Best-corrected visual acuity (BCVA) was measured using a logMAR chart before the CXL procedure and on the subsequent evaluations. Manifest refractometry was annotated as spheric equivalent (SE) and compared before and 24mo after CXL. The tomographic measurements were obtained with Pentacam (Oculus Optikgeräte GmbH, Wetzlar, Germany) at the first visit before the intervention and at 3, 6, 12, 24, and 36mo postoperatively,

in a dark room, in automatic mode, by the same experienced technician, and without any eye drop before the procedure. When the QS provided for the anterior or posterior corneal surfaces were "not OK", appearing as "yellow" or "red", the exam was repeated more four times, to try the acquisition of better quality data. If this was not possible for the posterior surface, the one with the greatest analyzed area/valid data was chosen. The following parameters were assessed: the mean (RmF) and minimum (RminF) radius of curvature of the anterior corneal surface; the mean (RmB) and minimum (RminB) radius of curvature of the posterior corneal surface; the maximum keratometry; and pachymetry at the thinnest point of the cornea (Pmin).

Those patients showing ocular allergy were treated with mast cell stabilizers, antihistamines, or dual action agents through from the first appointment on, based on the presence of ocular pruritus, photophobia, or papillary hypertrophy.

After CXL, corneal haze was annotated according to the grading scale proposed by Hanna et al[16].

To assess predictors for the evaluation of impaired posterior corneal surface after CXL, we divided the patients into two groups: Group 1: the QS of the anterior and posterior corneal surfaces was graded "OK" both before and after the CXL procedure. In this group, we analyzed the following parameters: RmF, RminF, RmB, RminB, and Pmin. Group 2: the QS of the anterior surface was graded "OK" both before and after CXL. After CXL, the Pentacam data showed impaired posterior QS surface measurements, classified as "yellow" or "red". In this group, only the anterior surfaces (RmF and RminF) were evaluated.

Exclusion criteria included Pmin less than 390 μm (to avoid a possible cytotoxic effect of combined riboflavin-UVA treatment on the corneal endothelium), corneal scarring, or no collaboration to the Pentacam examination.

Statistical Analysis All statistical analysis was performed using Stata (Stata/IC 15.1, College Station, TX, USA). Categorical variables were analyzed using the 2-sided Fisher test. Continuous variables were analyzed as non-parametric unpaired data, using Wilcoxon rank-sum (for intergroup comparison) or Kruskal Wallis rank-sum (for changes through time in each group) and were shown as median (interquartile ranges). A *P*-value of less than 0.05 was considered statistically significant.

RESULTS

Twenty-six eyes of 26 consecutive documented progressive keratoconus patients were surgically treated with CXL and evaluated for this study. The subjects had a mean age of 14±1.8y at the time of the CXL, the male:female ratio was 14:12, with a median (interquartile ranges) Kmax of 59.9 (56.3-63.1) in the first appointment and of 61.4 (58.1-65.3;

Table 1 Demographic data, BCVA, and spherical equivalent in the preoperative period and after 24mo, and preoperative data on history of ocular allergy and tomographic values in Groups 1 and 2

Parameters	Group 1 (QS "OK"), n=14	Group 2 (QS "not OK"), n=12	P
Gender (M:F)	8:6	6:6	0.99[b]
Age before CXL (y)	13.63 (12.78, 15.12)	14.36 (13.73, 15.33)	0.41[a]
BCVA			
Before CXL	0.40 (0.20, 0.60)	0.50 (0.3, 0.50)	0.71[a]
After CXL	0.35 (0.10, 0.60)	0.40 (0.25, 0.45)	0.95[a]
Spheric equivalent			
Before CXL	-1.25 (-2.00, -0.62)	-2.75 (-5.62, -1.50)	0.03[a]
After CXL	-1.25 (-2.50, -0.25)	-1.12 (-2.50, -0.56)	0.70[a]
Haze after CXL	1 (0, 1)	1 (1, 2)	<0.01[a]
Before CXL			
Ocular allergy	11 (78.6)	7 (58.3)	0.40[b]
Kmax	58.9 (57.1, 63.1)	63.5 (59.9, 67.8)	0.05[a]
RminF	5.73 (5.35, 5.91)	5.31 (4.98, 5.63)	0.06[a]
RmF	6.79 (6.55, 6.88)	6.30 (5.98, 6.47)	0.02[a]
Pmin	476 (433, 497)	425 (409.5, 447)	0.01[a]
RminB	4.17 (3.89, 4.41)	3.89 (3.64, 4.25)	0.13[a]
RmB	5.40 (5.37, 5.58)	4.97 (4.72, 5.12)	0.02[a]

[a]Wilcoxon rank-sum test [median (interquartile ranges)]; [b]Fisher exact test [No. of patients (%)]. BCVA: Best-corrected visual acuity; Kmax: Maximum keratometry; RminF: Minimum radius of curvature of the anterior corneal surface; RmF: Mean radius of curvature of the anterior corneal surface; Pmin: Pachymetry at the thinnest point of the cornea; RminB: Minimum radius of curvature of the posterior corneal surface; RmB: Mean radius of curvature of the posterior corneal surface.

$P<0.001$) immediately before CXL. Twenty-two out of 26 patients (84.6%) presented pre-surgical Kmax values greater than 55 D. None of them were contact lens wearers. Group 1 (posterior surface QS graded "OK" after CXL) had 14 subjects. Group 2 (posterior surface QS "not OK" after CXL) had 12 subjects, in which 6 were graded as "red" and 6 as "yellow".

Table 1 shows demographic data, BCVA, and SE data before and after the CXL procedure, history of ocular allergy, and tomographic data (Kmax, RminF, RmF, Pmin, RminB, and RmB) in the preoperative period, in Groups 1 (QS "OK") and 2 (QS "not OK"). None of the subjects treated had corneal infection after CXL. We observed stage 1 haze in 8 patients out of 14 in Group 1, while in Group 2 there were six patients with stage 1 haze and 5 patients with stage 2 haze still in the period from 18 to 24mo after CXL. Haze was statistically more intense in Group 2 ($P<0.01$, Table 1). It was also associated with impaired posterior surface QS ($P<0.01$).

RmF had different behaviors in Groups 1 and 2 through time: RmF of Groups 1 and 2 had significantly different baseline values ($P=0.02$, Table 1) that were still present 3mo after CXL ($P=0.015$). Afterward, RmF increased in both groups through time (G1-RmF and G2-RmF, Table 2), resulting in no significant differences from 6mo on ($P=0.09$ or more). Only Group 2 showed significant changes after 24 and 36mo ($P=0.03$, Kruskall-Wallis test) when compared with pre-

surgical data. That is, there was an intergroup difference before CXL, but as Group 2 showed a more intense flattening, the intergroup difference lost statistical significance after CXL. RminF, which corresponds to maximum keratometry or Kmax, was not significantly different between Groups 1 and 2 ($P=0.06$, Table 1) before CXL and showed no significant changes in the subsequent evaluations through 36mo ($P=0.08$). These values also did not change compared to their baseline values.

In Group 1, the parameters RmB and RminB did not vary from their baseline values through 36mo after CXL. Pmin, however, decreased significantly from baseline, was significantly different after 3 ($P=0.007$) and 6mo ($P=0.02$), and then was no longer statistically significantly different from the 12th to 36th month (Table 2). As explained above, Group 2 pachyemtric measurements could not be adequately measured, due to impaired QS in the posterior corneal surface.

DISCUSSION

This study was conducted to investigate the outcomes of corneal CXL in pediatric patients and develop predictive factors for defining impaired posterior corneal surface QS after the procedhure. These data are necessary because pachymetric measurement cannot be adequately evaluated when the posterior surface reading is impaired[6].

Our study on the effects of CXL in pediatric keratoconus patients presents similar data when compared with previous

Table 2 Tomographic data in the preoperative period, and changes through time, in Groups 1 and 2

Parameters	Pre	3mo	6mo	12mo	24mo	36mo	P
G1-Kmax	58.9 (57.1, 63.1)	58.5 (54.7, 61.6)	57.3 (53.4, 60.8)	57.1 (54.4, 60.2)	57.5 (54.1, 58.7)	55.5 (54.2, 58.1)	0.38
G2-Kmax	63.5 (59.9, 67.8)	61.0 (59.0, 68.3)	59.3 (55.6, 63.0)	59.9 (54.3, 62.6)	60.4 (54.5, 62.2)	61.9 (54.5, 63.8)	0.35
G1-RminF	5.73 (5.35, 5.91)	5.80 (5.48, 6.17)	5.89 (5.55, 6.32)	5.91 (5.60, 6.20)	5.87 (5.75, 6.24)	6.08 (5.81, 6.22)	0.43
G2-RminF	5.31 (4.98, 5.63)	5.55 (5.02, 5.74)	5.70 (5.36, 6.07)	5.63 (5.40, 6.22)	5.59 (5.42, 6.19)	5.46 (5.29, 6.19)	0.41
G1-RmF	6.79 (6.55, 6.88)	6.87 (6.59, 7.09)	6.97 (6.70, 7.11)	6.99 (6.63, 7.16)	6.96 (6.64, 7.07)	7.02 (6.72, 7.06)	0.43
G2-RmF	6.30 (5.98, 6.47)	6.35 (6.09, 6.71)	6.52 (6.35, 7.00)	6.72 (6.58, 7.22)	6.82 (6.61, 7.41)[a]	6.83 (6.66, 7.05)[a]	0.03[a]
G1-Pmin	476 (433, 497)	406 (342, 428)[a]	399 (352, 443)[b]	414.5 (368, 453)	435.5 (382, 461)	430.5 (374, 474)	0.007[a], 0.02[b]
G1-RminB	4.17 (3.89, 4.41)	4.04 (3.76, 4.54)	4.01 (3.70, 4.60)	3.96 (3.85, 4.44)	4.09 (3.77, 4.61)	4.01 (3.85, 4.27)	0.97
G1-RmB	5.40 (5.37, 5.58)	5.34 (5.18, 5.45)	5.37 (5.07, 5.53)	5.33 (5.10, 5.51)	5.35 (5.07, 5.66)	5.33 (5.08, 5.47)	0.90

[a,b]Adjusted P-value, significant compared with pre-surgical values. G1: Group 1 (posterior QS "OK"); G2: Group 2 (posterior QS "not OK"). Kruskal-Wallis rank-sum test [median (interquartile ranges)].

studies also performed in pediatric populations. It demonstrates keratoconus progression by showing increases in Kmax before CXL[2,8,10,13,15,17-19], which stabilized after CXL[2,11,14,20], both in Groups 1 and 2 since RminF did not have significant changes through the 36-months follow-up. Concerning RmF, Group 1 flattened the anterior surface but without significance, seen in previous studies[14,19,21], while it decreased significantly in Group 2, in accordance with other studies[12-13,15,17-18]. In comparing the flattening effect between Groups 1 and 2, the most intense effect occurred in Group 2, the one with more advanced keratoconus, with statistically decreased RmF, RmB and Pmin before CXL (Table 1). These data are in accordance with other studies, which also observed greater corneal flattening, especially in children with advanced keratoconus[9,12,22]. Group 2 had a larger number of patients with more intense haze (P<0.01, Table 1). Others have performed CXL in pediatric keratoconus using the Dresden protocol and also saw higher percentages of subjects with corneal haze[8,15]. Similarly, both described mean thinnest corneal thicknesses of 412 and 443 μm, respectively, before CXL. This is in accordance with our Group 2, which also contains the subjects with the thinnest corneas, with a median thinnest pachymetry of 425 μm; Group 1 exhibited a median thinnest pachymetry of 476 μm.

In addition to a more intense flattening, Group 2 had the greatest SE myopic value before CXL and with a more intense shift to hyperopia (decrease in myopia), resulting in an intergroup difference that was not significant (Table 1) after 24mo. Although in Group 1 the first quartile has changed from 2.00 SE (before) to 2.50 SE (after CXL), the measures of dispersion shown by the interquartile ranges were similar and the median values were equal before and after CXL. Also, these findings were associated with increases in the RmF values (meaning anterior surface flattening). Small differences in refractometric values which are not associated with decreases in RmF (meaning anterior surface curving) may

be interpreted by small fluctuations in refraction due to the fact that these patients do not undergo cycloplegia. The shift to hyperopia in Group 2 is in accordance with some authors[13,15], while Group 1 showing stable refractometry agrees with other studies[7,10,14,23-26]. However, there are studies that show stable refractometry despite a mean thinnest pachymetry of 432 μm[12] or 412 μm[8]. One of the reasons may be not performing cycloplegia, as already mentioned[27]. In our series, the refractometric exams were all performed by the same examiner (Antunes-Foschini R) using manifest refraction.

The parameters measured only in Group 1 (RmB, RminB, and Pmin), were similar to some studies, which described RmB and Rmin returning to baseline values and a decreased pachymetry that lost statistical significance over time[2,13-14]. Their pachymetric findings varied between 473 μm[14] and 467 μm[13], while Group 1 showed a median Pmin of 476 μm. Group 1 behavior may comprise the majority of keratoconus patients who are treated with CXL therapy, which evolves with no or little haze and does not impair the posterior corneal surface evaluation significantly.

We did not observe decreased BCVA in either group, which agrees with a number of studies that describe BCVA maintenance or improvement in these patients[2,8-10,12-21,23,28-32]. Group 2, however, behaved differently, with more intense corneal flattening. Munnerlyn et al[33] developed a theoretical formula that makes a correlation between corneal flattening, the changes in refraction, and the reduction in the amount of stroma. It is a potential mechanism to explain the more intense corneal flattening that occurs in subjects in Group 2. In our data, Group 2, which had the most critical flattening and changes in refraction, had the thinnest and steepest corneas preoperatively. Alternatively, some authors[34-36] observed extensive flattening associated with corneal thinning in advanced keratoconus. As hypothesized by Kymionis et al[34], we agree that "steep corneas (above a certain threshold) are possibly overtreated during CXL", who also suggested that

"a scar-like formation in the posterior corneal stroma could also promote a combined effect of flattening and thinning" and impaired QS. It is important to point out that despite the more intense flattening, more intense haze, and impaired QS of Group 2, the median BCVA was not statistically different before or after the procedure, or when compared with Group 1. This reinforces the view that even advanced forms of keratoconus should be treated with CXL[23].

There are some limitations to our study. The number of patients is small. However, the strength is that it was composed of results of the pediatric advanced and progressive keratoconus patients who were consecutively treated by one surgeon (Antunes-Foschini R) during the years of 2015 and 2016, under general anesthesia to ascertain adequate UVA treatment. We do not have anterior segment optical coherence tomography measurements to evaluate corneal thickness or posterior surface parameters of Group 2. Endothelial cell counts were not performed, which are important data since they would indirectly reinforce the idea that CXL does not penetrate the whole stromal thickness of these patients.

In summary, our study may help to explain different corneal behaviors after CXL and associate them with the predictive factors RmF, RmB, and Pmin (the thinner and the steeper the cornea preoperatively, the greater the risk of presenting impaired QS in tomography and haze, and a more intense flattening, after CXL). In advanced keratoconus, alternative methods to analyze corneal thickness and the posterior corneal surface should be considered to better evaluate the posterior corneal surface and corneal thickness after CXL, especially when the posterior corneal surface QS are impaired.

ACKNOWLEDGEMENTS

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