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REVIEW ARTICLE

Collagen Cross-linking for the Treatment of Keratoconus in Pediatric Patients

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ABSTRACT

Keratoconus (KC) is a bilateral noninflammatory, ectatic corneal disorder. It is the most common primary ectasia affecting approximately 1 in 2,000 in the general population. Classically, the disease starts in puberty and progresses throughout the 3rd or 4th decades of life. Ocular signs and symptoms vary depending on disease severity. As the disease progresses, approximately 20% of KC eyes require penetrating keratoplasty. Collagen cross-linking (CXL) with ultraviolet-A (UVA) light and riboflavin is a new treatment that has emerged in the recent years. It is reported to slow the progression of the disease in its early stages, by increasing corneal rigidity and biomechanical stability. As the number of adult KC patients treated using this procedure grew, proving its safety and high efficacy, the pediatric KC patients population has started to receive special attention. In the pediatric KC patients' eyes, corneas have been shown to be significantly steeper at the time of diagnosis compared to adults, and the severity of KC seems inversely correlated with age. Since treating KC in earlier age may be beneficiary, before developing an advanced disease that may require corneal transplantation, CXL in the pediatric age group has been advocated by many practitioners. The aim of this review is to collect and consolidate all known data regarding the efficacy and safety of CXL in the pediatric population.

Keywords: Cross-linking, Keratoconus, Pediatric, Review.

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INTRODUCTION

Keratoconus (KC) is a bilateral noninflammatory, ectatic corneal disorder, characterized by corneal ectasia and thinning due to changes in collagen structure and biomechanical stromal weakening. Progression of this degenerative process manifests and involves central corneal thinning, corneal protrusion and progressive, irregular astigmatism. It affects approximately 1 in 2,000 in the general population; eventually, approximately 20% of KC eyes require penetrating keratoplasty.[1]

Classically, the disease starts in puberty and progresses throughout the 3rd or 4th decades of life, although the disease has also been found to develop earlier[2] and later in life.[3]

A reduced number of collagen cross-links and a pepsin digestion higher than normal have been suggested as possible mechanisms and as an explanation for an overall structural weakness of the corneal tissue in KC, resulting in a stiffness that is only 60% the stiffness of the normal cornea.[9] Decreased mechanical corneal stability plays an important role in the progressive ectasia of the keratoconic cornea. Clinically, this corneal ectasia leads to myopia and irregular astigmatism and, in severe cases, ruptures in Descemet's membrane may occur, resulting in corneal edema and scarring.[3]

COLLAGEN CROSS-LINKING

Collagen cross-linking (CXL) with ultraviolet-A (UVA) light and riboflavin (vitamin B2) is a relatively new treatment that has been reported to slow the progression of the disease in its early stages, by increasing corneal rigidity and biomechanical stability and by preventing some of the underlying pathophysiologic mechanisms of the disease. This treatment strategy aims to avoid the need for penetrating keratoplasty, which is required many times in advanced cases.[10,11]

The technique of CXL consists of photopolymerization of stromal fibers by the combined action of riboflavin and a UVA source. Photopolymerization increases the rigidity of the corneal collagen and its resistance to keratectasia.[12] Collagen cross-linking requires de-epithelialization before the administration of the photosensitizing agent and UV irradiation. This is because the corneal epithelium constitutes a barrier against penetration of molecules with a high molar mass, such as riboflavin.

Following are two methods of performing the procedure:

Corneal Epithelium Off

In this method, the epithelium of the central 7 mm of cornea is removed followed by the application of riboflavin

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(vitamin B2) 0.1% solution for 30 minutes, beginning 5 minutes before the start of irradiation. Ultraviolet-A radiation of 370 nm wavelength and an irradiance of 3 mW/cm^2 at distance of 1 cm from the cornea is applied for a period of 30 minutes, delivering a dose of 5.4 J/cm.[11]

Corneal Epithelium On

This method is similar to the conventional, but in this method, the corneal epithelium is kept on, which requires a longer riboflavin loading time and additional penetration enhancers. Transepithelial riboflavin is currently available as a formula containing riboflavin 0.1% and enhancers. The presence of the amino alcohol improves bioavailability and, in combination with enhancers, such as ethylenediaminetetraacetic acid (EDTA) disodium salt, enables transepithelial penetration through the intact corneal epithelium.[13,14]

CROSS-LINKING IN THE PEDIATRIC POPULATION

Pediatric KC which manifests before 18 years of age has its own unique characteristics: Léoni-Mesplié et al[17] who investigated the severity of KC in children showed that in the pediatric population, corneas were significantly steeper in children at the time of diagnosis compared to adults. The severity of KC seems inversely correlated with age. Consequently, children with KC are of specific concern when it comes to corneal changes and the rate of progression. When combined with vernal keratoconjunctivitis (which many times is the case) the progression of in ectasiais even more rapid, as shown in Indian pediatric patients with vernal keratoconjunctivitis.[4-7]

Because of the young age of the patients, KC often has an adverse impact on quality of life,[8] thus treating KC in earlier age may be benificiary, before developing an advanced disease that may require corneal transplantation, which has poor prognosis if performed in younger age.

Due to its safety and high efficacy in adults, cross-linking in the pediatric age group has been advocated. The aim of this review is to collect and consolidate all known data regarding the efficacy and safety of CXL in the pediatric population.

REVIEW OF PUBLICATIONS

We reviewed a 12 published articles (standard epithelium off: 10 and transepithelial: 2) that investigated the outcome of CXL in the KC pediatric population. The studies have followed a variety of methodologies—retrospective noncomparative, retrospective comparative, case series and prospective studies and demonstrated outcomes of CXL in terms of efficacy and safety over the follow-up range from 1 year to 3 years after CXL in patients under 18.

The first published data in 2011 by Soeters[18] described four children with progressive KC treated by CXL. Regression of astigmatism was found in 3 of 5 eyes, ranging from 1.1 to 4.6 D after 6 months, whereas one eye remained stable. One eye was treated despite a superficial haze, which resulted in a stromal scar after CXL and required keratoplasty.

Arora et al[19] analyzed primary visual acuity and refractive and topographic outcomes in 15 eyes (15 children) suffering from KC with advanced disease in the fellow eye. The age range was from 10 to 15 years. Mean uncorrected distance visual acuity (UDVA) improved significantly from 1.00 ± 0.30 (20/200) to 0.72 ± 0.29 (20/100) LogMAR and mean corrected distance visual acuity (CDVA) from 0.56 ± 0.21 (20/70) to 0.30 ± 0.15 (20/40) LogMAR at the end of a 12 months follow-up period. Mean change in apical K (1.01 ± 2.40 diopters) was also significant. No significant complications were noted. To note, this study did not show any statistical improvement in uncorrected and corrected visual acuity in the first 3 months *vs* baseline. In addition, no significant changes were noted in flat K, steep K or central power, whereas apical K or maximum K (a topographic indicator of the success of CXL) improved significantly. This study showed that CXL in the pediatric population is with similar initial efficacy as in adults in terms of improvement in visual and topographic outcomes.

Caporossi et al[20] from Siena University, Italy, investigated the effect of CXL in a prospective non-randomized phase II open trial that included 152 patients aged 10 to 18 years, with a 36 months follow-up. Patients were divided into two groups according to corneal thickness (>450 and <450 μm) at the time of enrollment. Functional data at 36 months showed an increase of +0.18 and +0.16 Snellen lines for UCVA and best spectacle-corrected visual acuity (BSCVA) respectively, in the thicker group (>450 mm) and +0.14 and +0.15 Snellen lines respectively, in the thinner group (<450 mm). Patients in the thinner group started to show a better and faster functional recovery than the thicker group at 3 months follow-up. Topographic results showed statistically significant improvement in K readings and asymmetry index values. Coma reduction was also statistically significant.

The results of the Siena CXL pediatrics study demonstrated significant and rapid functional improvement (averaged +0.15 Snellen lines) in patients younger than 18 years with progressive KC undergoing riboflavin-UVA-induced CXL. No adverse events (infections or scars) were recorded in this pediatric series. Transient corneal

edema with glare disability in the first postoperative 4 to 6 weeks was present in 55% of patients. A slight to moderate haze (stromal hyperdensity) occurred in 9.8% of patients without negatively influencing visual acuity.

This study demonstrated significant and rapid functional improvement in pediatric patients younger than 18 years with progressive KC, undergoing riboflavin-UVA-induced CXL, with a good functional response and KC stability during a 36 months follow-up.

Vinciguerra et al[21] retrospectively analyzed the outcome of CXL in 40 eyes of patients aged 9 to 18 years with 24 months follow-up. They found that CXL improved patients' UCVA and BSCVA as well as significantly decreasing patients' corneal sphere and cylinder. Mean LogMAR UCVA and BSCVA were 0.79 ± 0.21 and 0.39 ± 0.10 respectively. Mean UCVA and BSCVA at 2 years were 0.58 ± 0.18 and 0.20 ± 0.09 respectively. The improvement in UCVA and BSCVA was significant throughout the postoperative follow-up. The significant reduction of simulated keratometry, apical corneal power, total and corneal aberrations, and the Klyce indices all documented the progressive flattening of the ectatic cornea. Mean spherical equivalent refraction showed a significant decrease of 1.57 D at 24 months. Mean baseline simulated keratometry was 46.32 D in the flattest meridian and 51.48 D in the steepest meridian; at 2 years, the values were 45.30 D ($p = 0.04$) and 50.21 D ($p = 0.07$) respectively.

The researchers noted that after an initial worsening of all KC indices (it is hypothesized that this worsening is due to epithelial debridement), refractive and topographic outcomes showed a slow but continuous improvement of most of the indices up to 24 months after surgery.

For a 3 mm pupil, there was a significant reduction in whole eye (total), corneal, higher-order and astigmatic wave front aberrations at 24 months in addition to significant differences in total coma and total spherical aberration. Mean baseline pupil center pachymetry decreased significantly at 6 months, but recovered by 12 months and remained stable thereafter through the 2 years follow-up. To note, endothelial cell counts did not change significantly ($p = 0.32$).

Chatzis et al[22] performed a study aimed to investigate the safety and efficacy of CXL for progressive KC in children and adolescents and the rate of KC progression during clinical follow-up. Fifty-nine eyes from 42 children and adolescents with confirmed KC were included in this retrospective interventional cohort study. Fifty-two of the 59 (88%) eyes enrolled in this study showed progression. Forty-six eyes were treated by CXL. The results of this study showed that maximal keratometry, CDVA, and KI showed significant changes over the follow-up period. However, significant K_{max} reduction observed up to 24 months after CXL lost its significance at 36 months of follow-up. The K_{max} values were significantly reduced as early as 3 months after treatment and up to 24 months after CXL. At 36 months after CXL, the flattening effect seemed to halt and K_{max} showed a tendency for progression. This might indicate that although the juvenile cornea reacts to CXL-induced improvement in the short-term, the effect might not be strong enough to show arrest of KC progression at longer follow-up periods. Corrected distance visual acuity showed a similar effect but, with a much greater latency: significant, improvement took longer to occur, and, even after 36 months, when the flattening effect on the cornea came to an arrest, CDVA was still significantly better than before CXL. Similarly, the KI had a greater latency for reaction and the typical reduction of corneal thickness had no lasting effect after CXL. The conclusion of this study was that CXL seemed to be safe in children and adolescents. However, the effect of arrest of disease progression might not be as long-lasting as in adults requiring a longer follow-up period to verify this trend.

Soeters et al[23] performed a cohort study that included 95 patients (119 eyes) to compare the effect of CXL for KC in various age groups and to investigate the influence of the topographic cone location on the outcome of CXL. This study compared the 1 year outcome of CXL for KC in pediatric (<18 years), adolescent (18–26 years), and adult patients (>26 years). The researchers found a better visual improvement and corneal flattening of K_{max} in pediatric patients compared to the older patient groups. Furthermore, this study showed that, in KC, the steepness of the cone is related to the topographical location; centrally located cones were steeper than peripherally located cones. Moreover, more corneal flattening seems to occur after CXL in eyes with centrally located cones, whereas peripherally located cones seem to show the least corneal flattening. In addition, the collected data showed that before CXL, cones of pediatric keratoconic corneas were located more centrally than in the two older age groups. Central cones (0–1 mm) were steeper (62.3 ± 8.3 D) before treatment than peripheral cones (3–4 mm) (55.9 ± 8.9 D). After CXL, pediatric corneas showed more corneal flattening (mean 1.8 D) and more CDVA improvement (0.23 ± 0.40 LogMAR). With regards to adverse events, two eyes (one adolescent and one adult eye) developed sterile infiltrates. One adolescent patient developed herpes simplex keratitis. Two eyes in the adolescent group developed deep stromal haze. One year postoperatively, CDVA decreased two or more lines in one of 29 (3%) pediatric eyes, three of 54 (6%) adolescent eyes, and two of 28 (7%) adult eyes. K_{max} increased by more than 1 D in four of 29 (14%) pediatric eyes, three of 54 (6%) adolescent eyes, and four of 28 (14%) adult eyes.

In the current study, the pediatric group showed worse CDVA at baseline compared to the older age groups, which could explain why this group improved most after CXL. Another explanation for the higher CDVA improvement in pediatric patients could be the improvement of optical aberration values, such as coma which was not studied in this study. In addition, the centrally located cones in the pediatric patient population may explain at least part of the relative improvement in this group *vs* that older patients groups. One year after CXL, corneal thickness had significantly decreased in all patient groups.

Kodavoor et al[24] performed a retrospective study to show the results of riboflavin UVA-involved corneal CXL in an Indian cohort of children affected by documented progressive KC, for a duration of 1 year of follow-up. The study enrolled 35 eyes of 24 children aged 16 years and below (mean 13.6). The mean of preoperative K_{max} was 55.11 ± 5.34 D, whereas the mean of postoperative K_{max} was reduced to 53.87 ± 4.99 D. The mean preoperative pachymetry was 412.31 ± 36.54 µm, which changed to 361.31 ± 58.04 µm postoperatively. At 1 year, improvement in the BCVA was noted in 18 (51.42%) eyes, stabilization in 12 (34.28%), and worsening in five (14.28%) eyes. The worsening of vision in all the five cases was attributed to corneal scar and haze formation.

Overall, the BCVA improved significantly by one line (0.31 ± 0.22 preoperatively compared with 0.21 ± 0.16). There was a nonsignificant reduction in both cylindrical and spherical equivalents.

There was a decrease in the corneal thickness at the end of 1 year (412.31 mm preoperative and 361.31 post-operative, p = 0.0001), which was statistically significant. This study also compared different cornea thicknesses (>400 and <400 mm) but did not reveal difference in BCVA between groups.

Three eyes that had VKC had marginally increased K-values, this may be attributed to persistent rubbing of the eyes.

No intraoperative nor postoperative infection/complications were reported with an exception of aforementioned corneal haze. No correlation between the response and laterality or the sex of the patients in the study.

In a recently published article, the team of Bakshi et al[25] assessed the effect of corneal cross-linking on progressive KC in children aged 11 to 17 (nine patients and nine eyes) followed-up for 6 to 24 months (average 16 ± 8.1 months), which were evaluated for UCVA, BSCVA, manifest refraction and corneal topography. The results showed stability of visual acuity in seven out of nine eyes (77.8%) and long term stability or reduction in K_{max}, with a nonsignificant improvement in UCVA and BSCVA, along with a small reduction of manifest cylinder. Continuing this study with a bigger patient cohort, Bakshi et al[26] enrolled 21 children (31 eyes), from three different and independent medical centers, aged 11 to 17 years that underwent CXL due to progressive KC, which were followed for 3 to 48 months (average 23 ± 13.6 months). They found a nonsignificant improvement in UCVA and BSCVA with small reduction in manifest cylinder and no significant change in spherical equivalent or K-values following CXL, 71 and 77% of treated eyes were found to be stabilized with regards to UCVA and BSCVA respectively.

In another retrospective study, Barbara et al[27] of 20 children (29 eyes) treated with CXL aiming to arrest the progression of KC, with a long follow-up time ranging from 6 to 46 months (mean 25.5 months), long-term results demonstrated significant improvement in UCVA and BSCVA (0.29–0.51 and 0.60–0.80 respectively) and a significant reduction in astigmatism (from –4.15 D to –3.3 D) with no significant change in sphere, keratometry, corneal resistance factor, corneal hysteresis or cornea compensated IOP, highlighting the efficacy of CXL in arresting the progression of KC as well as improving uncorrected and best corrected visual acuity, while reducing astigmatism.

Evaluating the use of transepithelial CXL in the pediatric population, Buzzonetti[28] reported 18 months of follow-up of 13 eyes, after transepithelial CXL in young patient a safe s with a mean patient age of 14.4 ± 3.7 years (8–18). Eighteen months after treatment, CDVA improved significantly, whereas K-readings and higher order aberrations showed statistically significant worsening. Spherical equivalent refraction, sphere and cylinder, coma, spherical aberration, thinnest point, and endothelial cell density did not show statistically significant changes. The mean demarcation line depth was 105 µm. No side effects were observed. The study concluded that transepithelial CXL appears to be a safe treatment in children. Although improved CDVA was noted 18 months after treatment, this technique did not effectively halt KC progression in children compared to standard CXL.

In a prospective nonrandomized comparative case-control study evaluating transepithelial CXL in the pediatric population, Salman[29] et al studied 22 eyes of 22 patients younger than 18 years (median age was 15.7 years) with bilateral KC who had transepithelial CXL treatment with the use of transepithelial riboflavin (Ricrolin TE) in one eye, the other eye was managed conservatively as the control group. The mean follow-up was 12.05 ± 3.45 months.

As in the previous study, this one showed that after transepithelial CXL, the improvement in the mean UDVA was statistically significant (from 0.95 ± 0.34 to 0.68 ± 0.45 LogMar). No eye lost lines of preoperative UDVA; 1 eye lost 1 line of preoperative CDVA. There was no improvement in the control group in UDVA or CDVA. Unlike the previous study, the mean simulated keratometry (K) decreased by a mean of 2.03 diopters (D), with mean flattening of the apical K by 2.20 D. In the control group, the simulated K increased by a mean of 0.59 D, with a mean steepening of the apical K by 2.9 D. No significant changes occurred in endothelial cell counts in either group.

Regarding the safety of transepithelial CXL, no sight-threatening complications were encountered. One eye encountered transient in minimal epithelial defect that was resolved with treatment. One eye had transient hyperemia and nine eyes (40.90%) had a mild foreign-body sensation after treatment; all complications resolved after 24 hours. There was no reported intraoperative or postoperative pain, which is considered an important factor in the pediatric age group because it leads to good postoperative compliance. This study is in agreement with findings in other studies of transepithelial CXL in adults and with a lesser rate of complications reported with conventional CXL, which can cause permanent corneal haze in from 7 to 9% of cases in addition to other complications, such as pain, corneal melting and others. It seems that in the pediatric group, transepithelial CXL safely increased the stability of the cornea and may arrest or reverse the progression of KC, at least in the short-term. This method is considered technically simpler and less invasive than other therapies proposed for KC.

DISCUSSION

In the recent years, there has been a wide spreading debate about corneal CXL in children suffering from KC; if to treat—what decision and corneal parameters to rely on when deciding and the best timing for treatment. It seems the KC behave differently in the pediatric population with a tendency to progress faster that in the adult population. Cross-linking has been utilized in adult keratoconic patients for over 10 years, halting the progression of the disease. Based on the evidence of efficacy and safety in the adult population; this treatment has been recently utilized in management of pediatric KC.

Keratoconus treatment using CXL in the pediatric population is a novel trend of recent years, hence there are not too many studies of young patients going thru this procedure, more so, when it comes to long-term follow-up.

With the growing evidence in pediatric population, it seems that CXL may be considered in the management of progressive pediatric KC, especially due to the higher rate and speed of progression in this age group. The timing of CXL remains a topic of debate, however, these patients should be kept under very close follow-up to look for the earliest signs of progression and upon which, CXL should be promptly offered. We suggest making the effort to document the progression of CXL prior to treatment, because CXL is not yet globally practiced in this population and remains a surgical technique that carries certain risks. In addition, we must always evaluate the risk of visually significant complications from CXL and the risk of visual loss from accelerated progression of KC in young age, ensuring the medical necessity of the treatment by documenting progression of the disease. These findings are in agreement with the fact that KC is most active in the young cornea and the evidence today points to a recommendation that CXL must be performed at the earliest age possible to arrest disease progression in its beginnings.

There seems to be a lack of long-term follow-up data in the pediatric population, but as the trend continues we will probably see more long-term results, helping understand if the comparison to adults when deciding to treat the pediatric population using CXL (CXL for progressive KC in children and adolescents is a procedure with a safety profile similar to the one observed in adults), has a long-term effect as seen in the adult population. Until this issue is investigated, we recommend careful follow-up to detect a decrease of the CXL-induced effect. A study investigating the long-term effects (more than 3 years of follow-up) is required to clarify the eventual progression of KC in the pediatric population. In addition, we recommend that awaiting documentation of progression is not mandatory in children and adolescents and CXL in this population should be performed as soon as the diagnosis has been made and once the individual risk-benefit analysis has been performed and once the patient and legal guardian have received in depth information and enough time for consideration.

The importance of CXL lies in the fact that it is a minimally invasive procedure. It achieves a result not offered by any other modality of treatment so far. Until the introduction of CXL, management of KC has mainly consisted of visual rehabilitation by means of spectacles, contact lenses and intracorneal ring segments (ICRS) implantation for early to moderate stages and lamellar or penetrating keratoplasty in advanced stages with contact lens intolerance and/or corneal scar.[15]

The introduction of corneal collagen CXL in routine clinical practice has changed the management of KC in the adult population and, in the recent years, it is starting to change the management of pediatric patients too.

In epidemiological studies, up to 21% of patients have ended up with a need for keratoplasty for visual

rehabilitation.[16] Cross-linking is superior to conventional treatment in many ways. It is the first treatment option for patients with KC that offers a possibility of mild regression in the condition. It improves vision, helps regression of disease, stabilizes future progression and delays or avoids keratoplasty altogether in a given patient.

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