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Review | Derleme

PEDIATRIC CORNEAL COLLAGEN CROSS-LINKING: A CONCISE REVIEW ON DIFFERENT TECHNIQUES

PEDİATRİK KORNEAL KOLLAJEN ÇAPRAZ BAĞLAMA: FARKLI TEKNİKLER ÜZERİNE DERLEME

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ABSTRACT

Objective: Since the first application of corneal collagen cross-linking (CXL) nearly 20 years ago, the technique has been modified and improved by many clinicians. Pediatric patients in particular are an important population focus for this treatment modality due to their susceptibility to rapid progression and irreversible damage. The standard CXL procedure has been updated to include transepithelial (TCXL), accelerated (ACXL), iontophoretic (ICXL) and synthesis of these approaches (ATCXL). In this review, we aimed to examine the current literature and determine the most effective and safe treatment method for the pediatric patient population.

Method: The results found in Medline via PubMed using the keywords "keratoconus, pediatric keratoconus, corneal collagen cross-linking, pediatric corneal collagen cross-linking, pediatric cross-linking" in English language were reviewed. In addition to those listed in the search engine, relevant citations obtained from the literature search were also included. Retrospective and prospective articles with a follow-up period of at least 1 year were analyzed as part of the review.

Results: In our review, 18 prospective and 14 retrospective studies were analyzed. Eight of these studies were comparative and the follow-up period of all studies ranged between 1-5 years. The age distribution of all patients was between 9-18 years and CXL modalities were compared according to Kmax change and sustainability and presented in tables.

Conclusion: Although a consensus on a gold standard has not yet been reached, an increasing number of studies are being reported in favor of new techniques; however, the standard CXL-Dresden protocol is still the safest and most effective treatment option.

Keywords: Pediatric, keratoconus, collagen cross-linking, cornea

ÖZ

Amaç: Korneal kolajen çapraz bağlama işleminin (CXL) yaklaşık 20 yıl önce ilk uygulanmasından bu yana, işlem tekniği bir çok klinisyen tarafından modifiye edilmiş ve geliştirilmiştir. Özellikle pediatrik hastaların hızlı progresyon ve geri dönüşümsüz hasarlara yatkın olmaları nedeniyle bu tedavi yöntemi için önemli bir popülasyon odağı olmaktadır. Standart CXL prosedürü yapılan güncellemelerle, transepitelyal (TCXL), hızlandırılmış (ACXL), iyontoforetik (ICXL) ve bu yaklaşımların sentezi (ATCXL) şeklinde uygulanabilmektedir. Bu derlememizde pediatrik hasta popülasyonu için güncel literatürün incelenmesi ve en etkili ve güvenilir tedavi yönteminin belirlenmesi hedeflenmiştir.

Yöntem: PubMed aracılığıyla Medline'da İngilizce dilinde "keratokonus, pediatrik keratokonus, korneal kollajen çapraz bağlama, pediatrik korneal kollajen çapraz bağlama, pediatrik çapraz bağlama" anahtar kelimeleri kullanılarak bulunan sonuçlar incelendi. Arama motorunda listelenenlerin dışında literatür taramasından elde edilen ilgili atıflar da dahil edildi. En az 1 yıllık takip süresi olan retrospektif ve prospektif makaleler derleme kapsamında analiz edildi.

Bulgular: Derlememizde 18 prospektif ve 14 retrospektif çalışma incelenmiştir. Bu çalışmaların 8 tanesi karşılaştırmalı vasıfta olup, tüm çalışmaların takip süreleri 1-5 yıl arasında değişmektedir. Tüm olguların yaş dağılımı 9-18 arasında olup, CXL modaliteleri Kmax değişimi ve sürdürülebilirliklerine göre karşılaştırılmış ve tablolarda sunulmuştur.

Sonuç: Henüz bir altın standart üzerinde konsensusa varılamamış olmakla beraber yeni teknikler lehine giderek artan sayıda çalışma bildirilmektedir; ancak standard CXL-Dresden protokolü hala en güvenli ve en etkili tedavi seçeneği olarak bulunmaktadır.

Anahtar Kelimeler: Pediatrik, kolajen çapraz bağlama, keratokonus, kornea

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Introduction

Keratoconus (KC) is the most common non-inflammatory corneal ectatic disease characterized by bilateral asymmetric progression of corneal collagen degeneration that results in corneal thinning, irregular astigmatism, and poor visual acuity. It has been reported that approximately 2-15% of all penetrating keratoplasty surgeries in the pediatric population are due to keratoconus[1-4]. The main reason we separate pediatric cases from their adult counterparts is rapid progression, and the underlying causes of it can be listed as; a pediatric cornea, especially under the age of 15, which has only 60% stiffness of an adult cornea, as children are much more susceptible to vernal keratoconjunctivitis, and its complications and eye rubbing is a particular issue in this population[2-4]. Moreover, higher rates of graft rejection and difficulties in pediatric patient management have led physicians to search for alternative treatment options[2].

Up until 2003, mainstay treatment options were either keratoplasty or hard contact lenses. Although photorefractive keratectomy and intrastromal rings were being applied for selective cases[5], a definitive treatment for the underlying disease itself had not been discovered. Even in early reports such as Weeks presented in 1913, the search for a treatment option that modifies corneal biomechanical structure can be observed. In his publication, he listed some treatment modalities that cause a stiff cornea, such as needling, suturing, or using various forms of cautery[6].

Corneal cross-linking (CXL) was first described by Wollensak et al.[7] in 2003 as a novel treatment protocol that not only improves visual outcomes but also treats the underlying pathology by altering the biomechanical structure of the treated corneas. Their unique protocol (Dresden protocol), which is now the standard CXL (SCXL) modality, is ultraviolet-A (UVA) exposure with riboflavin administration with a parameter and duration of 3mW/cm^2, 30 min. Especially after the U.S. Food and Drug Administration (FDA) approval of SCXL in pediatric patients between 14 and 18 years of age, treatment with CXL has become an area of focus in this population. Despite the lack of an established consensus on pediatric CXL, various studies revealed favorable results for SCXL in this population[8-11].

In this review of literature, we aimed to establish a better understanding of different techniques in pediatric cross-linking and to explore various data regarding their efficacy, safety, and the future of pediatric keratoconus treatment via a thorough examination of comparative studies. This article does not contain any new data on the subject of pediatric collagen cross-linking or pediatric keratoconus; only data from the previous studies were evaluated. We examined 18 prospective and 14 retrospective studies with different CXL techniques; however, our main focus in this review is the comparison studies on the subject.

Current CXL Protocols

Standard Corneal Collagen Cross-Linking (Dresden Protocol) – SCXL: Wollensak et al.[7] summarized their novel technique with the steps of removal of a central 7mm radius with a blunt instrument under local anesthesia, application of 10mg riboflavin-5-phosphate in 10mL dextran-T-500 20% solution as a photosensitizer 5 minutes before and every 5 minutes during the procedure, and appliance of 370nm UVA-light at a 1cm distance at irradiance of 3mW/cm^2 for 30 minutes. They also stated that the minimum corneal thickness requirement for their study was as low as 460um. All reviewed studies declared the minimum threshold of central corneal thickness as 400um.

In their original report of 22 patients, Wollensak et al.[7] reported only one patient in the pediatric age group, and unfortunately, due to a lack of light perception of the subject, their results did not yield any data regarding the use of CXL on the pediatric population.

Accelerated CXL – ACXL: Accelerated epi-off procedures are based on the Bunsen-Roscoe law of reciprocity, which states that the biological effect of the applied radiation is directly related and proportional to the total amount of energy irrespective of the duration or route. The only difference from the SCXL procedure is that UVA is applied for a shorter duration (5 or 10 minutes) with a higher intensity (18 or 9mW/cm^2), all methods resulting in a total energy transmission of 5.4J/cm^2. However, it should be noted that different approaches regarding stromal saturation with riboflavin are observed throughout the literature[12-14].

Transepithelial CXL – TCXL: The procedure is almost identical to SCXL apart from epithelial removal with a blunt instrument. However, different applications of riboflavin administration have been observed in the literature; Magli et al.[15] applied 2 drops every 5 minutes for 30 minutes, and Salman et al.[16] applied 1 drop every 2 minutes for 30 minutes. UVA exposure for 30 minutes with an irradiance of 3mW/cm2 was the same throughout the reviewed studies.

Accelerated-transepithelial CXL – ATCXL: In our review, we included only one study with the accelerated transepithelial CXL method. They described the procedure similar to TCXL with the transposed parameters of 18mW/cm^2 for 5 minutes[17].

Iontophoretic CXL – ICXL: We evaluated two research conducted on the ICXL procedure by Buzzonetti et al.[18,19]. The procedure consists of an application of electric current via stainless steel electrodes, where the negative electrode is embedded in a rubber suction ring, and the positive electrode is placed on the patient's forehead. Iontophoresis was performed under a current rate of 0.5 mA-1.0 mA for 5 minutes. The aim of this method is to enhance riboflavin penetration through the anterior stroma.

CXL Results

All CXL modalities mentioned above had a similar complication and side-effect profile throughout the studies. Transient corneal edema was seen in nearly half of the patients and corneal haze in approximately 10% of patients, both of which resided within 4 to 6 weeks[20,21]. Earlier reports on 36 months' follow-up of SCXL revealed that 80% of the patients benefited from the treatment functionally with a +1.5 Snellen line improvement, and worsening was observed only in 4% of the patients. They also implied that the corneal flattening and lamellar compaction effect of CXL were more prominent in patients with thinner corneas (<450um)[20]. However, >5 years of follow-up results revealed that despite effective CXL treatment, the overall progression rate is still 20%. They attributed their findings to the fact that the SCXL procedure can only lengthen normal corneal turnover rate of 6-7 years up to a maximum of 10 years, and they pointed out that after 10 years, 25% of the patients may require retreatment[22,23]. Most of the short-term studies of 12 months follow-up found SCXL procedure in the pediatric age group to be as safe and effective as in adults[8,9,24-26]. In their study on 40 eyes of pediatric stage-II (Amsler-Krumeich) keratoconus patients, Vinciguerra et al.[21] found SCXL to be effective in reducing astigmatism and spherical aberrations. Moreover, they highlighted that with a stable follow-up period, further treatment options combined with intrastromal rings or customized excimer procedures for residual errors should be considered[21]. In their 5-year follow-up results of 54 eyes, Godefrooij et al.[27] concluded that SCXL has a stable therapeutic effect for up to 5 years. However, 22% progression was observed on keratometry readings. Another point they underlined was cone decentralization is the only major factor for progression, which was also reported by Buzzonetti et al.[19], Sarac et al.[28], and Ucakhan et al.[29] which was the very first long-term results of Schiempflug characteristics of pediatric KC patients who underwent SCXL. Unlike Soeters et al.[24], Ucakhan et al.[29] found a lower Kmax flattening rate of 32%. Another long-term study evaluated 20 eyes over a span of more than 5 years, and they showed stable keratometric parameters and stable visual acuity even after 7.5 years. However, they, too, were reminded to be cautious of progression, which may be seen in 20-25% of the patients[30]. Unlike the majority of the studies with the inclusion criteria of Amsler-Krumeich stage I-II, Knutsson et al. highlighted an important fact that SCXL in the pediatric population is beneficial even in cases with advanced KC with Kmax value >60D[31]. Moreover, they expressed that reapplication of CXL can be addressed for reserved cases with progression.

Being the first study of TCXL on the pediatric population, Magli et al.[15] reported similar Kmax-min results from TCXL and SCXL groups at 12 months, which paved the way for new comparative studies of novel CXL techniques. Salman AG.[16] also successfully showed that TCXL is an effective and safe method with their 12-month follow-up results of 22 eyes. Although they managed to halt KC's progression, they failed to show an improvement in astigmatism. In their comparative study of 18 months follow-up, Buzzonetti et al.[18] showed that transepithelial CXL (TCXL) is not as effective as SCXL in terms of slowing the progression. However, their study on iontophoretic CXL (ICXL) gave more promising results in terms of halting the progression[32]. Yet they stated that ICXL could not outperform SCXL topographically, and they reported no improvement in higher-order aberrations. In their comparative study of ICXL and SCXL, keratoconus progression was observed in half of the patients treated with ICXL, compared to only 25% in the SCXL group. They also found cone location to be an important determinant of disease progression in both groups[19]. Another comparative study of SCXL versus TCXL in pediatric groups resulted in favor of SCXL procedure, and they suggested TCXL should be reserved for patients with thinner corneas (<420um) and intolerance to standard procedure[33].

Shetty et al.[34] published the first known study of accelerated CXL procedure on pediatric patients. Although they showed favorable results, they recommended limbal guard use, especially in pediatric cases, and they emphasized that extensive eye rubbing and undertreated vernal keratoconjunctivitis account for the majority of post-treatment progression. In their contralateral eye study with 34 patients, Eissa et al.[13] reported that the ACXL method gave better results in a 3-year follow-up period in terms of visual acuity and Kmax values.

The only publication on the long-term results of accelerated transepithelial CXL on 78 eyes failed to show a comparable efficacy and safety to SCXL[17]. Mean K change was observed as 3.18 in the SCXL group compared to 0.09 in the ATCXL group in year 5. Also, a slight loss of visual acuity along with disease progression was observed in 3 cases in the ATCXL group. Iqbal et al. recently compared 3 modalities (SCXL, TCXL, ACXL) of cross-linking with a substantial number of subjects. The overall success rate for SCXL was 94% compared to TCXL, with only a 71% success rate. Moreover, SCXL and ACXL groups showed significant improvement in mean K values, which were lower than 5% post-treatment progression. However, the TCXL procedure not only failed in halting progression but also resulted in increased mean K values[35]. Two studies with the same accelerated protocol compared its efficacy and safety with the standard procedure. With their combined number of 88 eyes that underwent ACXL procedure, they revealed that ACXL is as safe and efficacious as SCXL with a progression rate of around 10% at 2 years follow-up[36,37]. A summary of prospective and retrospective studies can be viewed in Tables -1 and -2.

Along with other reports, the recent results of the KERALINK trial remind one of the fact that although half of the pediatric KC patients may show spontaneous regression, it is crucial to screen at an earlier age for patients with astigmatism with frequent follow-ups and early CXL in this particular group should be considered[38,39]. In contrast to earlier reports suggesting prompt application of CXL as soon as clinical diagnosis has been made without further investigation for a progression[40], due to similar efficacy of pediatric CXL to adult CXL[24-26], recent results from a 5-year follow-up study counteracted

the idea. Or et al. advised against the treatment without proof of progression[41].

Table 1. Study characteristics of prospective articles evaluated in the review

Study	Year	Age (years)	No. of Eyes	Protocol	Follow-up (months)
Caporossi et al. (20)	2012	10-18	56	SCXL	36
Arora et al. (8)	2012	10-15	15	SCXL	12
Buzzoneti et al. (18)	2012	11-17	13	TCXL	18
Vinciguerra et al. (21)	2012	9-18	40	SCXL	24
Salman AG. (16)	2013	13-18	22	TCXL	12
Viswanathan et al. (38)	2014	8-17	25	SCXL	20
Shetty et al. (34)	2014	11-14	30	ACXL	24
Buzzonetti et al. (32)	2015	10-18	14	ICXL	12
Godefrooij et al. (27)	2016	11-17	54	SCXL	60
Uçakhan et al. (29)	2016	10-18	40	SCXL	48
Eraslan et al. (33)	2016	12-18	18 / 18	SCXL / TCXL	24
Badawi AE. (12)	2017	8-15	33	ACXL	12
Knutson et al. (31)	2018	12-17	52	SCXL	36
Mazzotta et al. (22)	2018	8-18	62	SCXL	120
Eissa et al. (13)	2018	9-16	34 / 34	SCXL / ACXL	36
Henriquez et al. (17)	2020	10-17 / 8-16	46 / 32	SCXL / ATCXL	60
Iqbal et al. (35)	2020	9-17	91 / 92 / 88	SCXL / ACXL / TCXL	24
Larkin et al. (39)	2021	10-16	29	SCXL	18

*SCXL: Standard corneal cross-linking, Dresden protocol; TCXL: transepithelial corneal cross-linking; ACXL: Accelerated corneal cross-linking; ATCXL: Accelerated transepithelial corneal cross-linking

Table 2. Study characteristics of retrospective articles evaluated in the review

Study	Year	Age (years)	No. of Eyes	Protocol	Follow-up (months)
Chatzis et al (40)	2012	10-19	46	SCXL	24
Magli et al. (15)	2013	12-17	23 / 16	SCXL / TCXL	12
Kumar Kodavoor et al. (25)	2014	9-16	35	SCXL	12
Soeters et al. (24)	2014	12-17	31	SCXL	12
Ozgurhan et al. (14)	2014	9-18	44	ACXL	24
Sarac et al. (28)	2016	9-17	72	SCXL	24
Wise et al. (9)	2016	11-18	39	SCXL	12
Zotta et al. (30)	2017	10-17	20	SCXL	60-108
Baenninger et al. (37)	2017	10-18	39 / 39	SCXL / ACXL	12
Padmanabhan et al. (23)	2017	8-18	197	SCXL	80
Sarac et al. (36)	2018	10-17	38 / 49	SCXL / ACXL	24
Or et al. (41)	2018	11-18	88	SCXL	60
Buzzonetti et al. (19)	2019	9-18	20 / 20	SCXL / ICXL	36
Barbisan et al. (26)	2020	10-16	105	SCXL	12

*SCXL: Standard corneal cross-linking, Dresden protocol; TCXL: transepithelial corneal cross-linking; ACXL: Accelerated corneal cross-linking; I-ON CXL: Iontophoretic transepithelial corneal cross-linking

Discussion

Our aim in this review was to summarize the different CXL modalities used in pediatric patients and try to make a better rationale for each modality used. A summary of trials comparing different CXL protocols can be viewed in Table 3. Although there is not an agreed consensus on which treatment option is best suited for pediatric cases, it is clear from these comparative studies that the SCXL procedure is still considered the best option in terms of arresting progression, improving visual acuity, regressing, and stabilizing keratometry values even at longer terms. Novel treatment methods for ICXL and ATCXL seem to be still in their early stages of development toward an established treatment option for the pediatric population. All aforementioned methods have been shown to be safe

in terms of corneal endothelial damage[21,30], and it has been reported in many cases that the stromal stiffening effect of CXL is limited to the anterior stroma. However, we noted that only a few numbers of studies reported the demarcation line depth of their CXL procedures, and it is clear from the study of Eraslan et al. that demarcation line depth is an important indicator of Kmax flattening and how long the effect of CXL will last[33]. Another point of interest is that these studies have all used different criteria and thresholds for diagnosing and evaluating progression. Although in this era of advanced imaging technology, many authors stated ultrasound pachymetry is still one of the most reliable indicators to evaluate KC progression[12,29,40].

It is without doubt that since 2003, CXL has reduced the need for keratoplasty at a remarkable rate; however, due to its effects' biochemical life span, further data is necessary to evaluate the success rate of different CXL techniques beyond 10 years. As for now, the SCXL procedure is yet to be seen as the best and safest treatment option for pediatric KC patients.

Table 3. Characteristics of comparative studies evaluated in the review

Study	Design	Year	Age (years)	No. of Eyes	Protocol	Follow-up	Demarcation line depth(um)	Mean K change (D)	Favored procedure
Magli et al. (15)	Retrospective	2013	12-17	23 / 16	SCXL / TCXL	1 year	N/A	-1.47 / -1.63	TCXL
Eraslan et al. (33)	Prospective	2016	12-18	18 / 18	SCXL / TCXL	2 years	272/137	-1.4 / - 0.63	SCXL
Baenninger et al. (37)	Retrospective	2017	10-18	39 / 39	SCXL / ACXL	1 year	N/A	-1.5 / -0.71	SCXL=ACXL
Sarac et al. (36)	Retrospective	2018	10-17	38 / 49	SCXL / ACXL	2 years	N/A	-0.61 / -1.01	ACXL
Eissa et al. (13)	Prospective	2018	9-16	34 / 34	SCXL / ACXL	3 years	N/A	-0.78 / -1.4	ACXL
Buzzonetti et al. (19)	Retrospective	2019	9-18	20 / 20	SCXL / ICXL	3 years	N/A	+0.8 / +2.8	SCXL
Henriquez et al. (17)	Prospective	2020	8-17	46 / 32	SCXL / ATCXL	5 years	N/A	-3.18 / -0.09	SCXL
Iqbal et al. (35)	Prospective	2020	9-17	91 / 92 / 88	SCXL / ACXL / TCXL	2 years	N/A	-1.17 / -0.23 / +0.92	SCXL

*SCXL: Standard corneal cross-linking, Dresden protocol; TCXL: transepithelial corneal cross-linking; ACXL: Accelerated corneal cross-linking; ICXL: Iontophoretic transepithelial corneal cross-linking

Method of Literature Search

A comprehensive literature search for the articles written on the subject in the English language was done on Medline via PubMed using the following keywords: keratoconus, pediatric keratoconus, corneal collagen cross-linking, pediatric corneal collagen cross-linking, pediatric cross-linking. The related citations from the literature search were also examined. Retrospective and prospective articles with a minimum follow-up period of 1 year were included. All the articles cited in the review were obtained and reviewed.

Compliance with Ethical Standards

This review article did not require institutional review board approval as no new patient data were submitted.

Conflict of Interest

The authors declare no conflict of interest.

Author Contribution

AB and SD: Both contributed to the design and implementation of the review, to the analysis of the results from the literature and to the writing of the manuscript.

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