Comparison of Standard Versus Accelerated Epithelium-Off and Transepithelial Corneal Cross-Linking in Pediatric Keratoconus: An Up-to-date Meta-Analysis

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Abstract

Purpose:

To compare the efficacy of four corneal cross-linking (CXL) protocols: standard epithelium-off (SCXL), accelerated epithelium-off (ACXL), transepithelial (TCXL), and accelerated transepithelial (A-TCXL) for pediatric keratoconus.

Methods:

A comprehensive literature search on the efficacy of SCXL, ACXL, TCXL and A-TCXL in treating keratoconus patients age 18-year or under was conducted using PubMed and EMBASE up to March 2020. Primary outcomes included uncorrected visual acuity (UCVA) and maximum keratometry (Kmax). Secondary outcomes included best-corrected visual acuity (BCVA), central corneal thickness (CCT), and mean refractive spherical equivalent (MRSE). Estimations were analyzed by weighted mean difference (WMD) and 95% confidence interval (95% CI) for the outcomes during observation periods from 6 to 36 months.

Results:

Eight papers involving total 704 eyes were enrolled. In pediatrics, ACXL resulted in significantly better postoperative UCVA than SCXL at 12-month observation (WMD = 0.08, 95% CI: 0.02 to 0.14, $P = 0.007$), while SCXL provided statistically better BCVA (WMD = -0.07, 95% CI: -0.12 to -0.01, $P = 0.01$) and MRSE (WMD = 0.31, 95% CI: 0.06 to 0.56, $P = 0.01$) than ACXL at 24 months. Furthermore, SCXL provided significantly improved BCVA compared with TCXL at 12- to 24-month observation. (WMD = -0.13, 95% CI: -0.21 to -0.05, $P = 0.001$).

Conclusions:

In pediatric keratoconus, although UCVA in short-term follow-up after ACXL was better than that after SCXL, the long-run results showed that SCXL may provide superior visual acuity than either ACXL or TCXL. Further investigation is required to compare the efficacy of different CXL protocols for the management of pediatric keratoconus.

1. Introduction

Keratoconus is a corneal ectatic disorder characterized by asymmetric, non-inflammatory, and progressive conical steepening and thinning.¹ The prevalence of keratoconus varies among populations with an estimate of 1/2000 worldwide.² In pediatric population, the prevalence of pediatric keratoconus is reported to be higher from 1/375 to 1/2000.³ Keratoconus commonly presents in the second decade and progresses until the third or fourth decade of life; compared with adults, pediatric keratoconus is more severe with higher risk of deterioration and faster progression.^{4,5} The clinical characteristics of keratoconus include progressive loss of vision and increasing irregular astigmatism, resulting from a more conical shape in thinning and steepening cornea.⁶ Vision loss is often caused by myopia and irregular astigmatism, and in rare cases the rupture of Descemet's membrane, acute corneal edema and scarring. In comparison with adults, keratoconus in children appears more centrally located ectatic cornea, and often progresses asymmetrically, leading to good binocular visual performance until both eyes are affected. These factors may contribute to a late seeking in medical care and more deteriorated visual function in pediatric patients.³ Visual impairment in keratoconus severely affects educational, economical, and social development, which may decrease patients' quality of life. Thus early and prompt intervention to halt the progression and improve visual quality is very important.

Multiple factors at cellular, physiological, biomechanical, and genetic levels contribute to the progression of keratoconus, and main changes among them are alterations in collagen fiber, including the gradual loss of fibril orientation, and weaken intra- and inter-fibrillary collagen cross-links.^{7,8} Based on an interaction between riboflavin (as a photosensitizer) and ultraviolet A (UVA) radiation, CXL aims to mitigate the progression of the disease by strengthening rigidity of corneal stroma, and avoid the need for corneal transplantation.^{9,10}

Although previous clinical trials have studied the postoperative efficacy of CXL in pediatric keratoconus and several have compared two or three protocols, none of them provided comprehensive comparison of four protocols including standard epithelium-off (SCXL), accelerated epithelium-off (ACXL), accelerated transepithelial (A-TCXL), and transepithelial CXL (TCXL). The small sample sizes in single study cast doubt on the validity of their conclusions. Meta-analysis about the comparison of epithelium-off versus transepithelial CXL in adult or mixed-age (both adult and children) patients suggests SCXL and TCXL might provide a comparable effect on visual, refractive, pachymetric and endothelial outcomes post-surgery,¹¹ however in pediatric population such an analysis is still unavailable. Given the publications of new trials and comparative observations for CXL of different protocols in long-term follow-ups,¹²⁻¹⁶ an update of summary is necessary. Hence, we conducted a meta-analysis to compare the efficacy of SCXL with ACXL, TCXL and A-TCXL in pediatric keratoconus.

2. Methods

2.1 Evidence acquisition

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA checklist guidelines).¹⁷

2.2 Search strategy and study selection

A comprehensive literature search was conducted in several databases including PubMed and Embase from earliest available dates to March 2020, in all languages. The keywords “keratoconus”, “pediatric”, and “corneal collagen cross-linking” OR “corneal collagen cross-linking” OR “CXL” were searched. The related-articles function were also applied to broaden results from the search engine. Reference lists from the publications were also checked for relevant studies. Retrieved papers were screened by two authors independently and duplicated studies were removed. Using inclusion and exclusion criteria described below, the papers were then assessed for meta-analysis. The literature search and selection were shown as flowchart (Fig. 1).

2.3 Inclusion and exclusion criteria

Articles were retained if they met the following inclusion criteria: (1) observational comparative studies; (2) focused on keratoconus in patients aged 18 or younger; (3) involved at least two types of CXL protocols including SCXL, ACXL and epi-on; (4) outcomes containing at least UCVA (transferred to the log minimum angle of resolution, LogMAR), BCVA, Kmax, and CCT; (5) a minimum follow-up of 12 months. Articles were excluded if any of the following conditions existed: (1) studies with inadequate information for calculating data on outcomes; (2) duplicated report; (3) study with a sample size smaller than 10 eyes in each arm. If multiple studies by the same research team derived from different population were available, all of them were deemed eligible and included in the meta-analysis.

2.4 Data extraction

Two authors (YJL, YL) extracted data independently with a standardized form. The following information was retrieved in all the included publications: first author name, year of publication, country, sample size of patients and eyes, mean age, gender, study design, type of CXL protocol, Amsler-Krumeich stage, follow-up time, UCVA, BCVA, Kmax, and CCT at the observation point (at specific time-points or at the last follow-up). Any discrepancies in data extraction or disagreements in the data were resolved by discussion and re-assessment with the senior author (DW).

2.5 Quality assessment

Risk of bias of each included study was evaluated for the level of evidence according to criteria provided by the Center for Evidence-Based Medicine in Oxford.¹⁸ The quality of the randomized controlled trials (RCTs) was evaluated using Cochrane risk of bias tool,¹⁹ and the quality of the comparative non-randomized studies (CNSs) was evaluated using the ROBINS-I assessment tool.²⁰

2.6 Statistical analysis

Meta-analysis was performed using Review Manager Version 5.3.5 (Cochrane Collaboration, London, UK). Dichotomous and continuous variables were compared using the odds ratio (OR) and weighted mean difference (WMD), respectively. Pooling estimates and their 95% confidential intervals (95% CI) were calculated. The fixed-effect model was applied, and heterogeneity was quantified using the I^2 value, which represents the percentage of the total variation among studies. Cochrane Q-test P value > 0.1 was considered as no significant heterogeneity, and the random-effects model was used to calculate pooling estimates and address within- or between-study variances. For a clear visualization, forest plots were produced. An I^2 value of 25%-50%, 50%-75%, > 75% was defined as low, moderate, and high heterogeneity, respectively. Statistical significance was measured by a P value of less than 0.05 ($P < 0.05$). Analyses were stratified by types of CXL protocol and follow-up time.

3. Results

3.1 Study selection

The flow diagram of the study selection is illustrated in Fig. 1. Initially, a total of 1722 articles were retrieved from databases. After removing the duplicates, 1595 potential papers left, and the titles and abstracts were reviewed. Among them, 1568 articles were excluded because of irrelevant topics. Full texts of the remaining 27 papers were assessed in their entirety, and 19 articles were excluded as no comparative data or not suitable for analysis. Eventually, 8 articles that provided detailed quantitative data were included in this meta-analysis. Informed consent was obtained in all included studies.

3.2 Characteristics of the included studies and quality assessment

Details of characteristics of included 8 studies are summarized in Table 1. The studies were published between 2013 and 2020, totally examining 704 eyes from 466 pediatric patients. The follow-up time of each research was ranging from 6 months to 48 months. Two studies were RCTs,^{12,14} while the others were CNSs.^{13,21-25} Each study compared the UCVA, BCVA, Kmax and CCT of different CXL protocols. The surgical procedures of the included studies were either SCXL, ACXL, TCXL or A-TCXL. The detailed information about the CXL procedures was listed in Table 2. There were 8 included studies involving the application of SCXL, 5 studies involving ACXL, 2 studies employing the TCXL and 2 studies the A-TCXL. The quality assessment of the RCTs is shown in Table 3. All CNSs were judged by the ROBINS-I assessment tool (shown in Table 4).

Table 1
Characteristics of all included studies in the meta-analysis.

Reference	Country	Inclusion criteria*	Study design	Longest follow-up duration	No. of Patient/eyes	Mean age (SD) in years	% male	Surgery protocols			
								SCXL (n#=305)	ACXL (n = 241)	TCXL (n = 34)	A-TCXL (n = 124)
Baenninger 2017	Switzerland	Stage 1–2	CNS	12 m	58/78	SCXL: 16.31 (1.78) ACXL: 15.54 (2.15)	77%	□	□		
Eissa 2019	Egypt	Stage 1–2	RCT	36 m	34/68	12.3 (2.4)	NA	□	□		
Eraslan 2017	Turkey	Stage 1–3	CNS	24 m	27/36	SCXL: 15.5 (1.7) TCXL: 15.4 (1.7)	48.1%	□		□	
Henriquez 2017	Peru	Stage 1–2	CNS	12 m	51/61	A-TCXL: 14.9 (NA) SCXL: 13.2 (NA)	60.8%	□			□
Iqbal 2019	Egypt	Stage 1–3	RCT	24 m	136/271	14.36 (2.11)	49.26%	□	□		□
Magli 2013	Italy	Any stage	CNS	12 m	SCXL: 19/23 TCXL: 11/16	15.2 (1.7)	73.3%	□		□	
Nicula 2019	Romania	Stage 1–4	CNS	48 m	SCXL: 37/37 ACXL: 27/27	SCXL: 16.43 (1.28) ACXL: 16.77 (1.53)	SCXL: 64.9% ACXL: 74.1%	□	□		

SCXL, standard epithelium-off CXL; ACXL, accelerated epithelium-off CXL; TCXL, standard epithelium-on or trans-epithelium CXL; A-TCXL, accelerated epithelium-on or accelerated trans-epithelium CXL; UCVA, uncorrected visual acuity; Kmax, maximum keratometry; BCVA, best-corrected visual acuity; MRSE, mean refractive spherical equivalent; CCT, central corneal thickness; ECD, endothelial cell Count; SD, standard deviation; CNS, comparative non-randomized study; RCT, randomized controlled trial

* Amsler-Krumeich Staging.

n, the total number of eyes in each CXL protocol

Reference	Country	Inclusion criteria*	Study design	Longest follow-up duration	No. of Patient/eyes	Mean age (SD) in years	% male	Surgery protocols			
								SCXL (n#=305)	ACXL (n = 241)	TCXL (n = 34)	A-TCXL (n = 124)
Sarac 2018	Turkey	Stage 1–2	CNS	24 m	64/87	SCXL: 15 (0.30) ACXL: 14.92 (0.34)	SCXL: 72.5% ACXL: 71.5%	□	□		
SCXL, standard epithelium-off CXL; ACXL, accelerated epithelium-off CXL; TCXL, standard epithelium-on or trans-epithelium CXL; A-TCXL, accelerated epithelium-on or accelerated trans-epithelium CXL; UCVA, uncorrected visual acuity; Kmax, maximum keratometry; BCVA, best-corrected visual acuity; MRSE, mean refractive spherical equivalent; CCT, central corneal thickness; ECD, endothelial cell Count; SD, standard deviation; CNS, comparative non-randomized study; RCT, randomized controlled trial											
* Amsler-Krumeich Staging.											
# n, the total number of eyes in each CXL protocol											

Table 2
Surgical procedures of the included studies in the meta-analysis.

Surgery protocol	Reference	Epithelium removal	Riboflavin soaking		UVA exposure		Total Energy (J/cm ²)
			Solution	Duration/ Ribo. instilment frequency (min/min)	Power (mW/cm ²)	Duration/Ribo. instilment frequency (min/min)	
(a) SCXL	Baenninger 2017	20% ethanol 10 s	Riboflavin 0.1%	30/3	3.0	30/3	NG
	Eissa 2019	50% alcohol 20 s	Riboflavin 0.1%	30/NG	3.0	30/5	NG
	Eraslan 2017	Mechanical debridement	Riboflavin 0.1%	30/NG	3.0	30/2	NG
	Henriquez 2017	Mechanical debridement	Riboflavin 0.1%	30/NG	3.0	30/5	NG
	Iqbal 2019	Mechanical debridement	Riboflavin 0.1%	30/3	3.0	30/2	5.4
	Magli 2013	Mechanical debridement	Riboflavin 0.1%	30/NG	3.0	30/2	NG
	Nicula 2019	NG	Riboflavin 0.1%	30/3	3.0	30/3	NG
	Sarac 2018	Mechanical debridement + 20% alcohol 20 s	Riboflavin 0.1%	30/3	3.0	30/NG	5.4
(b) ACXL	Baenninger 2017	20% alcohol 10 s	Riboflavin 0.1%	30/NG	9.0	10/NG	NG
	Eissa 2019	50% alcohol 20 s	Riboflavin 0.1%	30/NG	18.0	5/NG	5.4
	Iqbal 2019	Mechanical debridement	Riboflavin 0.1%	10/2	30.0	8 min of pulsed mode*	7.2
	Nicula 2019	NG	Riboflavin 0.1%	20/2	9.0	10/NG	NG
	Sarac 2018	Mechanical debridement	Riboflavin 0.1%	30/3	9.0	10/NG	5.4
(c) TCXL	Eraslan 2017	-	Riboflavin 0.25%	30/2	3.0	30/2	NG
	Magli 2013	-	Riboflavin 0.1%	30/5	3.0	30/NG	NG
(d) A-TCXL	Henriquez 2017	-	Riboflavin 0.25%	30/5	18.0	5/NG	NG
	Iqbal 2019	-	Riboflavin 0.22%	6/1.5	45.0	40 min of pulsed mode	7.2
NG, not given; Pulsed mode, 1 second on, 1 second off.							

Table 3
Quality assessment of RCTs according to Cochrane Collaboration's tool

Reference	Random Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Eissa 2019	L	L	M	M	L	L	/
Iqbal 2019	L	L	M	M	L	L	/
L, low risk of bias; M, moderate risk of bias							

Table 4
Quality assessment of CNSs according to ROBINS-I assessment tool

Reference	Pre-intervention		At intervention	Post-intervention				Overall risk of bias
	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported result	
Baenninger 2017	M	L	L	L	M	M	L	M
Eraslan 2017	M	M	L	L	L	M	L	M
Henriquez 2017	M	L	L	L	L	M	L	M
Magli 2013	M	M	L	L	L	L	L	M
Nicula 2019	M	L	M	L	L	M	L	M
Sarac 2018	M	L	L	L	L	M	L	M
L, low risk of bias; M, moderate risk of bias								

3.3 Comparative effectiveness of SCXL and ACXL

To evaluate the clinical treatment effect of different CXL protocols, the UCVA and BCVA (logMAR) at follow-up after the surgery were analyzed. Overall, children treated with the ACXL CXL were as likely to attain vision gain as those treated with the SCXL (WMD = 0.05, 95% CI: 0.01 to 0.09, $P = 0.01$, $I^2 = 63.6\%$, Fig. 2A). Subgroup studies were assessed according to the duration of follow-up ranging from 6 months to 3 years or longer (the longest follow-up was 4 years in only one study. In the subgroup of '3 years or longer' we used the longest follow-up data to compare the long-term effect). Results revealed a significant superiority of the ACXL group over SCXL group in the means of UCVA gain at 6 and 12 months visit (WMD = 0.16, 95% CI: 0.04 to 0.28, $P = 0.009$, $I^2 = 23\%$; WMD = 0.08, 95% CI: 0.02 to 0.14, $P = 0.007$, $I^2 = 50\%$, respectively). However, this superiority lost statistical significance at 24 and 36-month follow-up (WMD = -0.02, 95% CI: -0.08 to 0.05, $P = 0.65$, $I^2 = 64\%$; WMD = 0.02, 95% CI: -0.10 to 0.14, $P = 0.71$, $I^2 = 0\%$, respectively). With respect to BCVA, there was a significant superiority of ACXL group over SCXL at 6-month visit, but at long-term of 24 months, the latter was significantly better with high heterogeneity (Fig. 2B. WMD = 0.06, 95% CI: 0.00 to 0.11, $P = 0.04$, $I^2 = 0\%$; WMD = -0.07, 95% CI: -0.12 to -0.01, $P = 0.01$, $I^2 = 70\%$, respectively). Pooling results showed no statistically difference of BCVA post-operation between the SCXL group and ACXL group (WMD = 0.01, 95% CI: -0.02 to 0.03, $P = 0.63$, $I^2 = 57\%$). Besides, the intergroup analysis of spherical equivalent (SE) after CXL was conducted. At 24-month visit, patients in the ACXL group gained superior SE over those in the SCXL group (WMD = 0.31, 95% CI: 0.06 to 0.56, $P = 0.01$, $I^2 = 26\%$) (Fig. 4). However, the overall result showed no statistical difference between the two CXL types in terms of SE (WMD = 0.13, 95% CI: -0.01 to 0.27, $P = 0.06$, $I^2 = 40\%$).

In addition to visual acuity, Kmax and CCT are important to assessment of the treatment effect. The ACXL resulted in statistically smaller Kmax as compared to that of the SCXL group at 1 year post-operation (Fig. 4A. WMD = 0.70, 95% CI: 0.24 to 1.17, $P = 0.003$, $I^2 = 75\%$). At 2 years after the surgery the Kmax in ACXL group was also significantly smaller than that in SCXL group with high heterogeneity (WMD = 0.70, 95% CI: 0.25 to 1.14, $P = 0.002$, $I^2 = 83\%$). The overall results were similar, with WMD = 0.76, 95% CI: 0.50 to 1.02, $P < 0.00001$, $I^2 = 70\%$, which suggest that the ACXL may result in a smaller Kmax as compared to the SCXL. The CCT post-operation were not significantly different between the two types of CXL at either short or long follow-up term ranging from 6 months to 36 months (Fig. 4B. WMD = -2.98, 95% CI: -6.40 to 0.44, $P = 0.09$, $I^2 = 13\%$).

3.4 Comparative effectiveness of SCXL and TCXL

Results from two CNSs (total 75 eyes) showed the comparison of efficacy of the SCXL and the TCXL in pediatric patients, but the follow-up duration were different: Magli *et al* visited the patients at 3-, 6- and 12-month post-operation, while Eraslan *et al* at 24-month.^{22,26} The observations at the final visit from these two researches were analysed. There was no significant difference in the postoperative UCVA between the two groups (Fig. 5A. WMD = 0.06, 95% CI: -0.05 to 0.18, $P = 0.26$, $I^2 = 48\%$). However, patients treated with the SCXL were as likely to attain BCVA gain as those treated with the TCXL (Fig. 5B. WMD = -0.13, 95% CI: -0.21 to -0.05, $P = 0.001$, $I^2 = 22\%$). No significant difference was reported between the two groups in the postoperative Kmax (Fig. 5C. WMD = -0.32, 95% CI: -2.80 to 2.17, $P = 0.80$, $I^2 = 22\%$) and CCT (Fig. 5D. WMD = 8.58, 95% CI: -1.85 to 19.01, $P = 0.11$, $I^2 = 23\%$).

3.5 Comparative effectiveness of SCXL and A-TCXL

Among the two articles (total 240 eyes) included, the comparisons between the SCXL and the A-TCXL at 6 months, 12 months and 24 months were described. Intergroup analysis showed no significant difference between the 2 groups in either the UCVA or BCVA gain at 6 months (Fig. 6A, WMD = -0.01, 95% CI: -0.13 to 0.12, $P = 0.90$, $I^2 = 0\%$; Fig. 6B, WMD = -0.04, 95% CI: -0.09 to 0.00, $P = 0.06$, $I^2 = 61\%$). At the end-point visit, however, there seems a superiority of the vision gain in the SCXL group over the A-TCXL group with relatively high heterogeneity (UCVA: WMD = -0.14, 95% CI: -0.19 to -0.08, $P < 0.00001$, $I^2 = 82\%$; BCVA: WMD = -0.11, 95% CI: -0.13 to -0.08, $P < 0.00001$, $I^2 = 96\%$).

With respect to the postoperative values of Kmax, there was no significant difference between the SCXL group and the A-TCXL group at 6-month follow-up (Fig. 7A. WMD = -0.55, 95% CI: -1.33 to 0.23, $P = 0.16$, $I^2 = 55\%$). At 12-month visit, however, patients treated with the SCXL were as likely to achieve Kmax reduction as those with the A-TCXL (WMD = -0.93, 95% CI: -1.71 to -0.15, $P = 0.02$, $I^2 = 0\%$). Similarly, there was a superiority of the Kmax reduction in the SCXL group over the A-TCXL group in the pool analysis (WMD = -1.12, 95% CI: -1.58 to -0.66, $P < 0.00001$, $I^2 = 56\%$). In terms of the postoperative CCT, there was no significant difference between the two groups at all the follow-up time-point (Fig. 7B).

4. Discussion

Because of the asymmetrical progression, and inverse correlation between onset age and severity of the disease, keratoconus in pediatric population are often more advanced at the time of diagnosis. Corneal cross-linking is recommended to apply to halt progression of the disease in mild-to-moderate corneal ectasia.³ Conventional epithelium-off CXL, usually referred to as 'Dresden' protocol, was applied in the majority of keratoconus. However, recently increasing attention is being paid to the faster alternate, the accelerated protocols.¹⁵ Transepithelial approach is another choice which allows intact epithelium with newer preparation of riboflavin, seems to be ideal for pediatric cases to avoid epithelial debridement.²⁷ Shortening the treatment time and lowering the risk of postoperative pain or infections are essential for children patients, however, these adaptations in protocol may also lead to decreased permeability of riboflavin passing through intact epithelium. Thus it was reported that the epi-off CXL is less effective in stopping the disease as compared to the epi-off,²⁸ which also showed in our meta-analysis. Similarly, a multi-center trial by Iqbal *et al* showed that standard epithelium-off was more effective in pediatric keratoconus, attaining great stability as compared to either accelerated or transepithelial CXL.¹² On the other hand, Eissa *et al* reported that at 12-month follow-up, postoperative mean LogMAR UCVA, BCVA and Kmax of accelerated CXL were statistically less than those of conventional CXL in pediatric keratoconus eyes.¹⁴ The conflicting results might result from varied follow-up duration and small sample sizes. Our meta-analysis could provide pooling data from multiple studies updated to 2020 and offer potential important insights into the CXL strategy prior to carrying out a large-scale clinical trial.

The included studies compared the efficacy and stability of either two or three of the standard epithelium-off, accelerated epithelium-off, trans-epithelial and accelerated epithelium-off CXL in pediatric keratoconus. Although only two among the eight studies were RCTs, most of the researches were relatively high quality, according to the quality assessment. These studies contained the newest surgical outcomes and observations of total 704 eyes (number of eyes in each protocols shown in Table 1) for the pediatric keratoconus treatment. An earlier meta-analysis by McAnena *et al*/has evaluated 13 papers including 490 eyes of 401 pediatric patients with keratoconus, which compared the pre- and postoperative CXL outcomes in standard epithelium-off and trans-epithelial protocol.¹⁵ However, they only analyzed the outcomes in either protocol but not between the two groups, likely due to the lack of enough published data at that time. The McAnena study found that standard protocol might be effective in halting progression of pediatric keratoconus, with significant improvement in UCVA and BCVA at 1 year and statistical reduction in Kmax at 2 years. In their results, no significant vision gain or change in Kmax was observed in the trans-epithelium group at 1 year visit. Our study excluded the old publications and included some recent ones which contained comparative data about different protocols. Besides, most of the included studies have multiple observing time-points and longer term of postoperative follow-up, ranging from 12 months to 48 months (Table 1), which allowed subgroup analysis according to different follow-up time. This meta-analysis compared post-operative outcomes between different CXL protocols in both short- and long-term.

Our results indicated that the long-term best spectacle-corrected visual outcomes (BCVA, SE at 24 months) were in favor of SCXL as compared with ACXL (Fig. 2B and Fig. 3). Furthermore, the postoperative UCVA and BCVA in SCXL were significantly superior to those in A-TCXL group (Fig. 6). These results are similar to those in Kobashi and Tsubota study, which focused on adult population and showed that ACXL has less effect on improving corrected visual acuity than SCXL after 1-year follow-up.³³ Kmax in SCXL was also significant lower than those in A-TCXL group (Fig. 7A). Soeters *et al*/reported that in adult population, transepithelial CXL might result in a continued keratoconus progression after 1 year.²⁸ Ng *et al*/also showed that standard CXL resulted in a significantly greater reduction in Kmax and Kmean than its accelerated counterpart.²⁹ Our results in pediatric patients are in accordance with these previous studies. Although there was no significant difference of UCVA between the SCXL and TCXL group, the BCVA in the SCXL group was significantly superior over that in the TCXL group (Fig. 5A and B). However, the data was documented in only two studies, and sample size was small, which required further clinical trials. The results indicated that in terms of halting progression and improving visual acuity, the standard epithelium-off CXL might be more efficacious than the others, in accordance with the conclusions of McAnena.

Corneal thickness was reported to increase after standard epithelium-off CXL possibly due to scattering formation.¹⁵ However, comparing to the thinning from natural progression of keratoconus, some other studies reported stable CCT after CXL.^{30,31} Different measurement techniques such as the Orbscan II and Pentacam HR might be the cause for this variable. Previously it was reported that for adult patients with keratoconus, transepithelial CXL provided a more protective influence on corneal thickness than standard CXL.³² Early meta-analysis showed that accelerated CXL might lead to a less reduction in CCT than standard CXL,^{33,34} but recent studies suggests no difference between the ACXL and SCXL when comparing the CCT.^{35,36} In pediatric population, our meta-analysis also observed no statistical difference in CCT among different CXL protocols, regardless of different follow-up time (Fig. 4B, Fig. 5D, Fig. 7B). Endothelial cell count was also an important factor which affects the recovery of pediatric patients. Salman 2013 reported no significant changes occurred in the endothelial cell count in either transepithelial CXL or conventional treatment group of pediatric patients.³⁷ Another trial also showed that counting of endothelial cell did not change significantly during follow-up in iontophoretic CXL.²⁴ This meta-analysis, however, did not enroll the endothelial cell count due to little records in the included studies. So, more clinical trials should be conducted in the future about specific perioperative outcomes, especially the endothelial cell count that could affect the postoperative vision quality. Besides, although being relatively rare, adverse events such as corneal edema, transient haze, permanent scar, sterile ulcer, and infectious keratitis should be recorded to provide more detailed observations of CXL complications in pediatrics. A recent study showed that three of 968 eyes developed infectious keratitis and seven sterile infiltrates after accelerated CXL over 4 years follow-up, but the studied population included both children and adults.³⁸ Maharana *et al*/2018 reported microbiological test results of the microbial keratitis after accelerated CXL, showing mixed and simple infection in the cases.³⁹ The mixed infections included coagulase-negative Staphylococcus (CoNS) with *Aspergillus fumigatus*, Staphylococcus aureus with *Mucor* spp., Staph. aureus with *Acanthamoeba*, and simple infection included Staph. Aureus, CoNS, and *Alternaria* spp.³⁹

There are some limitations in this meta-analysis that should be discussed. Firstly, the surgical procedures of CXL in each protocol were not exactly the same, as shown in Table 2. In the Epi-off groups, the process of epithelium removal was different in concentration of ethanol and soaking time, and the riboflavin instilment interval during UVA exposure was not uniform. In the Epi-on groups, the concentrations of riboflavin in soaking, the UVA power, and the process of UVA exposure were varied. Second, most of the included studies were not randomized comparative. This would increase the risk of potential selection and publication bias. Lastly, some outcomes had high heterogeneity, such as the Kmax in subgroup analysis between SCXL and ACXL, and the UCVA and BCVA between SCXL and A-TCXL, which were possibly caused by different baseline features or surgical techniques.

Due to limited number of included studies, conclusions from this meta-analysis should be interpreted cautiously. The stability and efficacy of different CXL protocols may differ in different follow-up time.

Overall, in the treatment of pediatric keratoconus, SCXL seems to provide better BCVA and refraction at 2-year visit, though ACXL seems to provide a better UCVA at 1-year follow-up. SCXL also shows superiority over TCXL and A-TCXL by exhibiting a better BCVA or achieving more reduction in Kmax at the final follow-up. Although the long-term results are in favor of SCXL to serve as a preferred strategy in pediatric patients, larger trials with longer and detailed observations are required to confirm the clinical outcomes.

Abbreviations

ACXL: accelerated epithelium-off corneal cross-linking; A-TCXL: accelerated transepithelial corneal cross-linking; BCVA: best-corrected visual acuity; CCT: central corneal thickness; CI: confidence interval; CNS: comparative non-randomized studies; CoNS: coagulase-negative Staphylococcus; CXL: corneal cross-linking; Kmax: maximum keratometry; MRSE: mean refractive spherical equivalent; OR: odds ratio; PRISMA: Preferred reporting items for systematic reviews and meta-analysis; RCT: randomized controlled trial; SCXL: standard epithelium-off corneal cross-linking; TCXL: transepithelial corneal cross-linking; UCVA: uncorrected visual acuity; UVA: ultraviolet A; WMD: weighted mean difference

Declarations

Availability of data and materials

All data are fully available without restriction.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors have no conflicts of interest to disclose.

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Authors' contributions

Yuanjun Li and Yewei Yin searched the literature and wrote the manuscript. Tu Hu and Kaixuan Du extracted the data. Ying Lu, Yanyan Fu, and Aiqun Xiang analyzed the patient data. Xiaoying Wu, Xiaobo Xia, and Dan Wen gave suggestions on the topic. All authors read and approved the final manuscript.

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References

1. Krachmer JH, Feder RS, Belin MW. Keratoconus and related noninflammatory corneal thinning disorders. *Surv Ophthalmol*. 1984;28(4):293–322.
2. Mukhtar S, Ambati BK. Pediatric keratoconus: a review of the literature. *Int Ophthalmol*. 2018;38(5):2257–66.
3. Olivo-Payne A, Abdala-Figuerola A. Optimal management of pediatric keratoconus: challenges and solutions. *Clin Ophthalmol*. 2019;13:1183–91.
4. Tuft SJ, Moodaley LC, Gregory WM, et al. Prognostic factors for the progression of keratoconus. *Ophthalmology*. 1994;101(3):439–47.
5. Leoni-Mesplie S, Mortemousque B. Scalability and severity of keratoconus in children. *Am J Ophthalmol*. 2012;154(1):56–62 e1.
6. El Rami H, Chelala E. An Update on the Safety and Efficacy of Corneal Collagen Cross-Linking in Pediatric Keratoconus. *Biomed Res Int*. 2015, 2015 257927.
7. Sinha Roy A, Shetty R. Keratoconus: a biomechanical perspective on loss of corneal stiffness. *Indian J Ophthalmol*. 2013;61(8):392–3.
8. Sharif R, Sejersen H. Effects of collagen cross-linking on the keratoconus metabolic network. *Eye (Lond)*. 2018;32(7):1271–81.
9. Brooks NO, Greenstein S. Patient subjective visual function after corneal collagen crosslinking for keratoconus and corneal ectasia. *J Cataract Refract Surg*. 2012;38(4):615–9.
10. Wollensak G, Spoerl E. Stress-strain measurements of human and porcine corneas after riboflavin-ultraviolet-A-induced cross-linking. *J Cataract Refract Surg*. 2003;29(9):1780–5.
11. Wen D, Song B. Comparison of Epithelium-Off Versus Transepithelial Corneal Collagen Cross-Linking for Keratoconus: A Systematic Review and Meta-Analysis. *Cornea*. 2018;37(8):1018–24.
12. Iqbal M, Elmassry A. Standard cross-linking protocol versus accelerated and transepithelial cross-linking protocols for treatment of paediatric keratoconus: a 2-year comparative study. *Acta Ophthalmol*, 2019, Oct 25. doi:10.1111/aos.14275.
13. Nicula CA, Rednik AM. Comparative Results Between "Epi-Off" Conventional and Accelerated Corneal Collagen Crosslinking for Progressive Keratoconus in Pediatric Patients. *Ther Clin Risk Manag*. 2019;15:1483–90.
14. Eissa SA, Yassin A. Prospective, randomized contralateral eye study of accelerated and conventional corneal cross-linking in pediatric keratoconus. *Int Ophthalmol*. 2019;39(5):971–9.
15. McAnena L, Doyle F. Cross-linking in children with keratoconus: a systematic review and meta-analysis. *Acta Ophthalmol*. 2017;95(3):229–39.
16. Tian M, Jian W. One-year follow-up of accelerated transepithelial corneal collagen cross-linking for progressive pediatric keratoconus. *BMC Ophthalmol*. 2018;18(1):75.
17. Moher D, Liberati A. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. *Open Med*. 2009;3(3):e123-30.
18. Petrisor BA, Keating J. Grading the evidence: levels of evidence and grades of recommendation. *Injury*. 2006;37(4):321–7.
19. Higgins JP, Altman DG. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*, 2011, 343 d5928.
20. Sterne JA, Hernan MA. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*, 2016, 355 i4919.
21. Baenninger PB, Bachmann LM. Pediatric Corneal Cross-linking: Comparison of Visual and Topographic Outcomes Between Conventional and Accelerated Treatment. *Am J Ophthalmol*. 2017;183:11–6.
22. Eraslan M, Toker E. Efficacy of Epithelium-Off and Epithelium-On Corneal Collagen Cross-Linking in Pediatric Keratoconus. *Eye Contact Lens*. 2017;43(3):155–61.
23. Henriquez MA, Rodriguez AM. Accelerated Epi-On Versus Standard Epi-Off Corneal Collagen Cross-Linking for Progressive Keratoconus in Pediatric Patients. *Cornea*. 2017;36(12):1503–8.
24. Magli A, Chiariello Vecchio E. Pediatric keratoconus and iontophoretic corneal crosslinking: refractive and topographic evidence in patients underwent general and topical anesthesia, 18 months of follow-up. *Int Ophthalmol*. 2016;36(4):585–90.
25. Sarac O, Caglayan M. Accelerated versus standard corneal collagen cross-linking in pediatric keratoconus patients: 24 months follow-up results. *Cont Lens Anterior Eye*. 2018;41(5):442–7.
26. Magli A, Forte R. Epithelium-off corneal collagen cross-linking versus transepithelial cross-linking for pediatric keratoconus. *Cornea*. 2013;32(5):597–601.
27. Filippello M, Stagni E. Transepithelial corneal collagen crosslinking: bilateral study. *J Cataract Refract Surg*. 2012;38(2):283–91.
28. Soeters N, Wisse RP. Transepithelial versus epithelium-off corneal cross-linking for the treatment of progressive keratoconus: a randomized controlled trial. *Am J Ophthalmol*, 2015, 159 (5): 821–8 e3.
29. Ng AL, Chan TC. Conventional versus accelerated corneal collagen cross-linking in the treatment of keratoconus. *Clin Exp Ophthalmol*. 2016;44(1):8–14.

30. Wittig-Silva C, Chan E. A randomized, controlled trial of corneal collagen cross-linking in progressive keratoconus: three-year results. *Ophthalmology*. 2014;121(4):812–21.
31. Chunyu T, Xiujun P. Corneal collagen cross-linking in keratoconus: a systematic review and meta-analysis. *Sci Rep*. 2014;4:5652.
32. Zhang X, Zhao J. Conventional and transepithelial corneal cross-linking for patients with keratoconus. *PLoS One*. 2018;13(4):e0195105.
33. Wen D, Li Q. Comparison of Standard Versus Accelerated Corneal Collagen Cross-Linking for Keratoconus: A Meta-Analysis. *Invest Ophthalmol Vis Sci*. 2018;59(10):3920–31.
34. Shajari M, Kolb CM. Comparison of standard and accelerated corneal cross-linking for the treatment of keratoconus: a meta-analysis. *Acta Ophthalmol*. 2019;97(1):e22–35.
35. Jiang Y, Yang S. Accelerated Versus Conventional Corneal Collagen Cross-Linking in the Treatment of Keratoconus: A Meta-analysis and Review of the Literature. *Interdiscip Sci*. 2019;11(2):282–6.
36. Kobashi H, Tsubota K. Accelerated Versus Standard Corneal Cross-Linking for Progressive Keratoconus: A Meta-Analysis of Randomized Controlled Trials. *Cornea*. 2020;39(2):172–80.
37. Salman AG. Transepithelial corneal collagen crosslinking for progressive keratoconus in a pediatric age group. *J Cataract Refract Surg*. 2013;39(8):1164–70.
38. Kodavoor SK, Tiwari NN. Profile of infectious and sterile keratitis after accelerated corneal collagen cross-linking for keratoconus. *Oman J Ophthalmol*. 2020;13(1):18–23.
39. Maharana PK, Sahay P. Microbial Keratitis After Accelerated Corneal Collagen Cross-Linking in Keratoconus. *Cornea*. 2018;37(2):162–7.

Figures

Figure 1

Flowchart of studies included in the meta-analysis

Fig 2

SCXL vs ACXL

Figure 2

Postoperative visual acuity in standard epi-off cross-linking (SCXL) and accelerated epi-off cross-linking (ACXL) treated pediatric patients. (A) Uncorrected visual acuity (UCVA, LogMAR). (B) Best corrected visual acuity (BCVA, LogMAR). WMD, weighted mean difference

Fig 3

SCXL vs ACXL

Figure 3

Postoperative keratometry and corneal characteristics in standard epi-off cross-linking (SCXL) and accelerated epi-off cross-linking (ACXL) treated pediatric patients. (A) Maximal keratometry (Kmax, diopters). (B) Central corneal thickness (CCT, μm). WMD, weighted mean difference