• Meta-Analysis •

Systematic review and Meta-analysis comparing modified cross-linking and standard cross-linking for progressive keratoconus

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Abstract

• AIM: To compare the effectiveness and safety between modified cross-linking (MC) and standard cross-linking (SC) in mild or moderate progressive keratoconus.

• METHODS: Eligible studies were retrieved from four electronic databases, including CENTRAL, Clinical Trials gov, PupMed and OVID MEDLINE. We set post-surgical maximum K value (Kmax) as the primary outcome. In addition, uncorrected and corrected distant visual acuity (UDVA and UDVA), spherical equivalent (SE), endothelial cell density (ECD), central cornea thickness (CCT) and depth of demarcation line (DDL) were Meta-analyzed as secondary outcomes. Mean differences for these outcomes were pooled through either a random-effect model or fixed-effect model according to data heterogeneity.

• RESULTS: Twenty-four comparative studies either on accelerated cross-linking (AC) compared with SC or on trans-epithelial cross-linking (TC) compared with SC were included and pooled for analysis. The results indicated that MC was significantly inferior to SC at delaying Kmax deterioration [AC *vs* SC 0.49 (95% CI: 0.04-0.94, I^2=75%, *P*=0.03); TC *vs* SC 1.15 (95% CI: 0.54-1.75, I^2=50%, *P*=0.0002)]. SE decreased significantly for SC when compared to AC [0.62 (95% CI: 0.38-0.86, I^2=22%, *P*<0.00001)]. DDL of SC was more significantly deeper than that of TC [-133.49 (95% CI: -145.94 to -121.04, I^2=33%, *P*<0.00001)]. Other outcomes demonstrated comparable results between MC and SC.

• CONCLUSION: SC is more favorable at halting the progression of keratoconus, but visual acuity improvement showed comparable results between MCs and SC.

• KEYWORDS: progressive keratoconus; cross-linking; standard cross-linking; accelerated cross-linking; trans-epithelial cross-linking; Meta-analysis

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INTRODUCTION

Keratoconus is the most common corneal degeneration disease, characterized by cornea conical protrusion, progressive local stroma thinning, increased cornea curvature and irregular astigmatism[1]. The incidence rate of keratoconus is as high as 54.5 per 100 000, which means one person would suffer the disorder within a general population of 2000[2]. Spectacles and contact lens, especially rigid gas permeable lens (RGP), are routine ways to treat mild or moderate keratoconus[3]. However, ocular infection, cornea pannus and other complications from improper wearing and poor hygiene habits are not rare[4]. In addition, some studies have suggested that RGP could not halt progressive keratoconus effectively in the long run[5-6]. Thus, it is essential to exploit new ways to stop the progression of keratoconus more effectively and more safely.

In 2003, Wollensak *et al*[7] first reported their practice of using cross-linking (CXL) to halt progressive keratoconus effectively, and the protocol they used was established as standard cross-linking (SC)-cornea epithelium stripping, riboflavin instillment and 370 nm ultraviolet A (UVA) radiation with an intensity of 3 mW/cm^2 for 30min. Although more and more clinical trials have attested to the effectiveness and safety of SC[8-11], complications caused by epithelium stripping and long exposure to ultraviolet radiation, such as unbearable postoperative ocular pain, sub-epithelial haze,

sterile infiltration and infectious keratitis, could not be avoided completely[12]. Given that, several modifications have been made to SC to avoid these complications[13], including keeping the corneal epithelium *in situ* (trans-epithelial CXL, TC)[14] and using radiation of higher intensity and shorter duration (accelerated CXL, AC)[15].

Although these modified cross-linkings (MCs) are superior to SC at reducing associated complications, it is still controversial whether the ability of MCs to stop progression of keratoconus is equivalent to that of SC. Al Fayez *et al*[16] reported that Kmax decreased 2.4 D in the SC group while it increased 1.1 D in the TC group postoperatively, which showed more effectiveness for SC in halting progressive keratoconus (P<0.0001). However, Magli *et al*[17] found equivalent effects between TC and SC since there was no significant difference in terms of Kmax or mean K (P>0.05). This controversial situation is also observed in some studies regarding comparison between AC and SC. Ng *et al*[18] reported that significant reductions for Kmax and mean K were found in the SC group when compared to AC group (P=0.001 and 0.015, respectively). In contrast, Hashemi *et al*[19] found that the mean decrease in neither Kmax (P=0.865) nor mean K (P=0.974) was significantly different between the AC group and SC group. For this reason, it is difficult for clinical practitioners to judge which CXL protocol is more excellent at halting progressive keratoconus and which CXL protocol should be carried out in their own clinical settings, especially when MCs have obvious benefits for certain keratoconic patients. To answer this question, it is essential to conduct a systematic review and Meta-analysis on the basis of current comparative clinical trials to compare the effectiveness and visual improvement comprehensively between SC and MCs in the treatment of progressive keratoconus.

MATERIALS AND METHODS

Search Strategy We utilized four main electronic databases to retrieve clinical trials on comparison between SC and MCs, including CENTRAL, Clinical Trials gov, PUBMED, and OVID MEDLINE. As the earliest CXL clinical practice was reported in 2003, our searching data ranged from Jan 2003 to Aug 2016, and the language was restricted to English only. To expand the search, alternative text words used for standard CXL, accelerated CXL and trans-epithelial CXL were "conventional, epithelium-off, epithelium-without CXL", "high-tense, high-fluence CXL" and "epithelium-on, epithelium-with CXL" respectively. Meanwhile, Boolean logic operators, wildcard and position characters were employed to combine the text words to obtain more precise outcomes. In addition, we also scanned the reference lists of included citations to identify any additional reports. However, we did not search any journals or conference proceedings manually, so there was no "gray literature" in this review.

Studies, Participants and Interventions Considering that MCs are relatively new techniques and only a few comparative studies could be harvested, studies with respect to comparison between MCs and SC, either retrospective case series (RCS) or prospective case series (PCS) or randomized controlled trials (RCT), were all included.

Patients with mild or moderate progressive keratoconus, regardless of gender, age or ethnic group, regardless of how long the disease had progressed, and regardless of when the surgery was carried out, were all included. Progressive keratoconus was defined as continuous increases in K value and astigmatism or a decrease in cornea stroma thickness, regardless of specific definition criteria of each study. TC was defined as corneal epithelium *in situ* with or without methods used to change epithelial barrier permeability; AC was defined as intensity greater than 3 mW/cm^2 and exposure duration less than 30min no matter the specific parameters used in each study.

Outcomes Since the primary aim of treating keratoconus with CXLs is to halt the progression of the disorder, we chose Kmax at terminal follow-up point as our primary outcome because it is the most sensitive and significant parameter for demonstrating progression of keratoconus. Secondary outcomes included not only visual functional parameters but also histological and morphological indices, including uncorrected distant visual acuity (UDVA), corrected distant visual acuity (CDVA), spherical equivalent (SE), depth of demarcation line (DDL), central cornea thickness (CCT), endothelium cell density (ECD) and adverse events.

Selection of Studies Two reviewers selected the literatures independently by the same method. Primary selection was conducted through browsing titles and abstracts so that obviously unrelated studies could be excluded; then, the full copies of the remaining studies were obtained to determine whether inclusion or not. At last, the two reviewers compared their reviewing results and solved disagreements with discussion.

Assessment of Risk of Bias in Included Studies The two independent reviewers assessed bias of the included studies by referring to a validated checklist consisted of 14 questions (http://links.lww.com/ICO/A265)[20]. This checklist is suitable for evaluating both RCT and non-RCT, as the 14 questions cover every element of a clinical study. According to the checklist, we defined "long enough follow-up" as 12mo, defined "all important outcomes considered" as primary and main secondary outcomes included in the study, and defined "representative sample" as patients with mild or moderate progressive keratoconus. Three ranks marked "yes", "no" and "unclear" were used to score each question of the checklist and as tudy with 8-9 "yes" answers could be deemed as high qualification[21]. Results from the two independent reviewers

were compared, and discrepancies were resolved through discussion or consultation with a third reviewer.

Data Extraction and Management Study characteristics, such as study design, participant demographics, definition of progressive keratoconus, details of intervention (*e.g.* riboflavin ingredientsand frequency of riboflavin instillment, wave length of UVA, intensity and radiation duration), clinical outcomes and adverse events, were extracted by the two independent reviewers. Disagreements between the two reviewers were resolved through discussion until consensus was reached.

Measures of Treatment Effect and Statistical Analysis Review Manager 5.3 (www.ims.cochrane.org/revman) was used for data entry and Meta-analysis. Since Kmax, visual acuity (VA; logMAR), SE, CCT, DDL and ECD were all continuous data, mean difference (MD) and its 95% confidence interval (CI) were utilized as the measure of treatment effect. To reduce heterogeneity generated from variations of baseline and increase comparability among the included studies, the difference value (terminal value minus baseline) and its standard deviation (SD) of each outcome was calculated for comparison. Moreover, we addressed statistical heterogeneity systematically through three different methods: assessing forest plot overlap, calculating Chi-square and I^2. If heterogeneity proved significantly by Chi-square or I^2 (either $P<0.1$ or $I^2>50\%$), a randomized effects pattern was used for pooling the data; otherwise fixed effects was used. A P value of 0.05 was used as the threshold for statistical significance.

RESULTS

Study Selection Figure 1 shows the procedure for selecting citations. A total of 628 records were retrieved by searching the electronic databases and by indexing references of related literature. There were 72 duplications and 522 obviously unrelated records, which were recognized by titles and abstracts easily. Then, we excluded 10 citations by browsing full texts, and 24 eligible studies were included finally.

Characteristics of Included Studies Characteristics of all the 24 eligible studies are shown in Tables 1 and 2. Among these studies, only one study (4%)[22] was with respect to comparison of the three CXLs,13 studies (54%)[18,23-34] were comparing between AC and SC, 10 studies (42%)[16-17,35-42] were on TC versus SC, and as for study design, 11 studies (46%)[16,26-28,32-33,35,39-42] were RCT, 8 studies (33%)[22-24,29-30,34,37-38] were PCS and 5 studies (21%)[17-18,25,31,36] were RCS. The sample size varied widely among the studies, the largest sample size enrolled 153 patients (153 eyes)[27], the smallest one just enrolled 13 patients (13 eyes)[35], and the sample sizes of most were 30-70 eyes.

All the studies enrolled progressive keratoconus patients as their participants. Three studies (13%)[17,24,37] took juveniles (less than 18 years old) as their objects, the others (87%) were all adult patients. All eligible studies included both genders, and 18 studies[16-18,22-24,27,29-32,35-41] mentioned the demographic balance within inter-groups. Moreover, the most common participant race was Caucasian (10 studies, 42%)[17,22,25,28-30,33,40-42], the others were Mongolian (4 studies, 17%)[18,23,31,43], Middle Eastern Ethnicity (4 studies, 17%)[16,26,27,32], Turks (5 studies, 21%)[24,35-38] and Indian (1 study, 4%)[39].

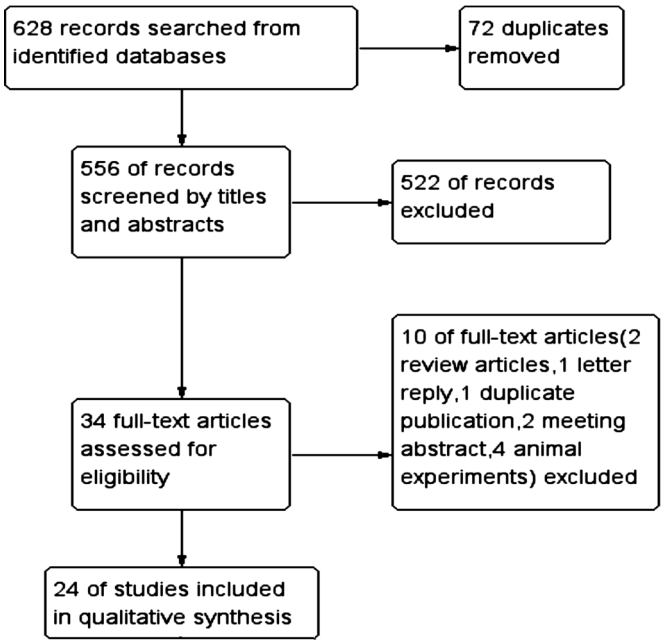

Figure 1 Flow diagram for selecting citations.

All SC in the studies[16-17,22-42] used UVA radiation for 30min with 3 mW/cm^2. However, the combinations of duration and intensity used for AC were different in some studies, *e.g.* 30 mW/cm^2 with 3min, 30 mW/cm^2 with 4min, 18 mW/cm^2 with 5min, 9 mW/cm^2 with 10min, *etc*[18,23-27,31-33]. Except for one TC protocol[22] that used 10 mW/cm^2 with 9min, all the other TC followed SC protocol. However, the riboflavin used in TC were different from that in SC and AC, containing some loosened or permeable ingredients, such as EDTA and tromethamine[17,35-38,40-41]. As an essential process for SC and AC, most studies scraped the corneal epithelium mechanically, but others used excimer laser or chemical means to remove epithelium such as ethanol or topical anesthetics[28,31] and the diameter of epithelium removal varied in the range of 6.5-10 mm[27-28,38]. Although the apparatus and wave length of UVA used in these studies were different, the 365 nm or 370 nm wavelength was the most commonly used except for one study that used 765 nm UVA[39].

Risk of Bias in Included Studies Qualities of included studies assessed according to the checklist consisted of 14 questions are shown in Table 3 and Figure 2. The included studies could be considered as qualified, for all of them scored more than 8 “yes” which conformed to our evaluation standard. For each question marked from 1 to 14, “yes” took account for 100% in the questions 1, 5, 10, 14, “no” accounted for more than 50% in the questions 7 and 13, and “unclear” was higher in the questions 4, 8 and 9.

Table 1 Characteristics of included studies (Accelerated CXL *vs* Standard CXL)

Author	Region	Study design	Group	Eye/ patient (*n*)	Age (a)	Gender (M/F)	Baseline balance (Y/N)	Follow-up (mo)	Definition for progressive keratcous	Intensity (mW/cm^2)	Duration (min)	Wave legth (nm)	Riboflavie	Apparatus
Bouheraoua *et al*[22]	France	PCS	SC TC AC	15/15 15/15 15/15	25.4±5.6 32.4±6.6 26.7±6.2	12/3 11/4 9/6	N	6	Kmax≥0.75 D/ 3mo, AST ≥0.75 D/12mo, CCT↓≥30 μm/ 6mo	3.0 10 30	30 9 5	370 NA NA	Ri 0.1% in 20% dex	X-Vega (Sooft, SPA)
Chow *et al*[23]	China	PCS	SC AC	19/32 19/32	27.8±10.9 26.3±3.7	13M 12M	N	12	Kmax≥1 D/1y, AST≥1 D/1y	3.0 18	30 5	365 365	Ri 0.1% in 20% dex	UV-X CCL-Vario
Cinar *et al*[24]	Turkey	PCS	SC AC	13/13 13/13	17.0±2.7 18.8±4.5	6/7 2/11	Y	6	Kmax≥1 D/1y, CDVA≥1/2y	3.0 9	30 10	NA NA	Ri 0.1% in 20% dex	Vega CBM X CCL-Vario
Cummings *et al*[25]	Ireland	RCS	SC AC	66/53 36/34	30.0±8.00 27.9±7.6	39/14 28/6	NA NA	12	Kmax≥1 D/2y, ASTIG≥1 D/2y, SE≥0.5 D/3y	3 9	30 10	365 365	Ri 0.1% in 0-20% dex	UV-X 1000 lamp
Hashemian *et al*[26]	Iran	RCT	SC AC	31/31 31/31	25.13±4.21	18/13	NA NA	18	Kmax≥1 D/y, AST≥1 D/y, VA↓≥2 line/y	3 18	30 5	370 370	Ri 0.1% in 20% dex	UV-X system
Hashemian *et al*[27]	Iran	RCT	SC AC	76/76 77/77	22.3±4 22.6±4	38/38 32/45	Y	15	Kmean≥1.5 D/ 6mo, CCT↓≥5%	3 30	30 3	365 365	Ri 0.1% in 20% dex	CCL-Vario
Kanellopoulos[28]	Greece	RCT	SC AC	21/21 21/21	NA NA	NA NA	NA NA	48	Kmax≥1 D/y	3 7	30 15	370 370	Ri 0.1%	NA NA
Kymionis *et al*[29]	Greece	PCS	SC AC	16/29 16/29	27.56±6.20 25.06±6.34	22/7	Y	1	Kmax≥0.75 D/ 6mo, SE≥0.75 D/6mo	3 18	30 7	365 365	Ri 0.1% in 20% dex	CCL-365
Kymionis *et al*[30]	Greece	PCS	SC AC	26/43 26/43	26.15±6.32 26.23±6.9	34/9	Y	1	NA NA	3 9	30 14	NA NA	Ri 0.1% in 20% dex	UV-A illuminator
Ng *et al*[18]	China	RCS	SC AC	14/12 12/12	36.1±10.7 32.6±6.6	13/1 9/3	Y	13.9±6.3	Kmax≥1 D/ 6mo, AST≥1 D/ 6mo	3 9	30 10	NA NA	Ri 0.1% in 20% dex	UV-X 1000 UV-X 2000
Ng *et al*[31]	China	RCS	SC AC	18/17 15/14	32.8±9.3 33.0±6.1	16/2 12/3	Y	1	Kmax≥1 D/ 12mo, ASTIG ≥1 D/12mo, SE≥0.5 D/12mo	3 9	30 10	NA NA	Ri 0.1% in 20% dex	UV-X 1000 UV-X 2000
Sherif[32]	Eygpt	RCT	SC AC	11/18 14/18	23.64±4.03 21.58±5.78	6/2 5/5	Y	12	Kmax≥1 D/ 6mo, AST≥1 D/ 6mo, SE≥0.5 D/ 6mo	3 30	30 4	370 370	Ri 0.1%	UV-X KXL® system
Shetty *et al*[33]	The Netherlands	RCT	SC AC AC AC	36/36 36/36 33/33 33/33	22.8±5.0 23.1±4.7 19.9±5.8 24.2±7.1	NA NA NA NA	N	15.32±3.39	Kmax≥1-1.5 D/ 6mo, AST ≥1-1.5 D/6mo, thinnest CT↓ ≥5%/6mo	3 9 18 30	30 10 5 3	365 365 365 365	Ri 0.1% in 20% dex	Avedro KXL system
Tomita *et al*[34]	Japan	PCS	SC AC	18/18 30/21	30.83±5.2 31.17±5.5	NA NA	NA NA	12	NA NA	3 30	30 3	365 365	Ri 0.1% in 20% dex	CCL-365 Vario KXL

SC: Standard cross-linking; AC: Accelerated cross-linking; TC: Trans-epithelial cross-linking; Kmax: Maximum K value; UDVA: Uncorrected distant visual acuity; CDVA: Corrected distant visual acuity; AST: Astigmatism; SE: Spherical equivalent; CCT: Central cornea thickness; RCT: Randomized clinical trial; RCS: Retrospective case series; PCS: Prospective case series; Ri: Riboflavin; Dex: Dextran; BZK: Benzalkonium chloride; THAM: Tromethamine.

Effects of Interventions Comparative outcomes between AC and SC are shown in Table 4. As shown in Figure 3, Kmax reduction was significantly greater in SC than in AC; the pooled mean difference of Kmax was 0.49 (95% CI: 0.04-0.94, I^2=75%, P=0.03). In addition, SE decreased significantly for SC when compared to AC. The mean difference which was 0.62 (95% CI: 0.38-0.86, I^2=22%, P<0.00001) (Figure 4). However, comparative outcomes of UDVA, CDVA, DDL, CCT and ECD indicated no significant differences between the two CXLs shown by the pooled data.

When comparing TC to SC, significant difference of Kmax between the groups was observed by pooled mean difference, which was 1.15 (95% CI: 0.54-1.75, I^2=50%, P=0.0002) (Figure 5). Similarly, the DDL of SC was more significantly deeper than that of TC, the mean difference of DDL was -133.49 (95% CI: -145.94 to -121.04, I^2=33%, P<0.00001) (Figure 6). However, UDVA, CDVA, CCT, ECD and SE demonstrated no significant differences between TC and SC.

The main side effects reported in these studies were delayed epithelium healing and anterior stromal scarring or opacity. In

Table 2 Characteristics of included studies (Trans-epithelial CXL *vs* Standard CXL)

Author	Region	Study design	Group	Eye/ patient (*n*)	Age (a)	Gender (M/F)	Baseline balance (Y/N)	Follow-up (mo)	Definition for progressive keratcous	Intensity (mW/cm^2)	Duration (min)	Wave legth (nm)	Riboflavie	Apparatus
Acar *et al*[35]	Turkey	RCT	SC TC	7/7 6/6	22.71±10.14 24.50±68.11	3/4 4/2	Y	6	Kmax≥1 D/y, SE≥0.5 D/2y, AST≥1.0 D/2y	3 3	30 30	NA NA	Ri 0.1% in 20% dex Ri 0.1%+dex 20%+THAM+EDTA	Peschke Meditrade, GmbH,
Al Fayez *et al*[16]	Saudi Arabia	RCT	SC TC	36/36 34/34	24.1±5.3 24.8±4.2	15/21 16/18	Y	36	Kmax≥1 D/y, AST≥1 D/y	3 3	30 30	NA NA	Ri 0.1% in 20% dex Ri + with dex	UV-X unit
Cerman *et al*[36]	Turkey	RCS	SC TC	30/20 30/23	23.7±3.9 22.8±4.7	NA NA	Y	18	Kmax≥1 D/ 6mo, AST ≥1 D/6mo	3 3	30 30	365 365	Ri 0.1% in 20% dex Ri 0.1%+dex 20%+THAM+EDTA	Ricrolin TE
Eraslan *et al*[37]	Turkey	PCS	SC AC	18/12 18/15	15.5±1.7 15.4±1.7	6/6 7/8	Y	24	Kmax≥1 D/ 6mo, AST ≥1 D/6mo, VA↓≥1 line	3 3	30 30	365 365	Ri 0.1% in 20% dex 0.25% ri 1.2%+THAM+0.01% BZK	Vega
Kocak *et al*[38]	Turkey	PCS	SC TC	19/19 17/17	27.16±2.4 27.35±5.95	9/10 8/9	Y	12	Kmax≥1 D/ 6mo, AST ≥1 D/6mo	3 3	30 30	366-374 366-374	Ri 0.1% in 20% dex Ri 0.1%+15% dex+EDTA+THAM	CBM-X-Linker
Magli *et al*[17]	Italy	RCS	SC TC	23/19 16/11	14.75±2.1 15±4.2	14/5 8/3	Y	12	Kmax≥1 D/ 6mo, AST ≥1 D/6mo	3 3	30 30	365 NA	Ri 0.1% in 20% dex Ri 0.1%+15% dex+EDTA+THAM	Vega CBM X linker Vega
Nawaz *et al*[39]	India	RCT	SC TC	20/20 20/20	23.95±4.08 22.35±3.95	17/3 15/5	Y	6	Kmax≥1 D/y	3 3	30 30	765 765	NA	CL-UVR machine
Rossi *et al*[40]	Italy	RCT	SC TC	10/10 10/10	30.4±7.3 28±3.8	5/5 6/6	Y	12	UDVA, CDVA↓≥1 line/6mo, Kmax≥1 D/ 6mo, AST ≥1 D/6mo	3 3	30 30	370 NA	Ri 0.1% in 20% dex Ri 0.1%+15% dex+EDTA+THAM	UV-X System NA
Soeters *et al*[41]	The Netherlands	RCT	SC TC	26/26 35/26	24 24	19/7 28/7	N	12	Kmax,Kmean and/or topographic cylinder ≥0.5 D/6-12mo	3 3	30 30	365 365	Ri 0.1% in 20% dex Ri 0.1%+15% dex+EDTA+THAM	UV-X
Stojanovic *et al*[42]	Norway	RCT	SC TC	10/20 10/20	29.5	17/3	NA NA	12	AST or myopia≥1 D/ 12mo, Sim K≥1.5 D/12mo	3 3	30 30	365 365	Ri 0.5% without dextran	UV-X lamp

SC: Standard cross-linking; AC: Accelerated cross-linking; TC: Trans-epithelial cross-linking; Kmax: Maximum K value; UDVA: Uncorrected distant visual acuity; CDVA: Corrected distant visual acuity; AST: Astigmatism; SE: Spherical equivalent; CCT: Central cornea thickness; RCT: Randomized clinical trial; RCS: Retrospective case series; PCS: Prospective case series; Ri: Riboflavin; Dex: Dextran; BZK: Benzalkonium chloride; THAM: Tromethamine.

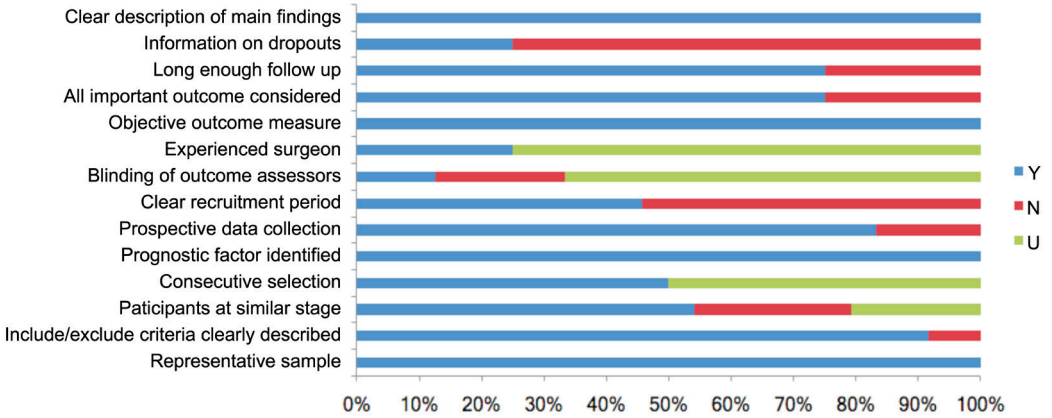

Figure 2 Evaluation of included studies Y: Yes; N: No; U: Unclear.

all 24 included studies, only two studies reported postoperative side effects. In one study, Sherif *et al*[32] mentioned that one patient had infant anterior stromal opacity for one year after SC treatment. In the other study, Shetty *et al*[33] noticed two

Table 3 Evaluation of included studies according to the checklist

First author	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Acar[35]	Y	Y	Y	U	Y	Y	N	Y	Y	Y	N	N	Y	Y
Al Fayez[16]	Y	Y	Y	U	Y	Y	N	Y	U	Y	Y	Y	Y	Y
Bouheraoua[22]	Y	Y	N	Y	Y	Y	Y	Y	U	Y	Y	N	N	Y
Cerman[36]	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	N	Y
Chow[23]	Y	Y	N	Y	Y	Y	Y	N	U	Y	Y	Y	Y	Y
Cinar[24]	Y	Y	Y	U	Y	Y	N	U	U	Y	Y	N	N	Y
Cummings[25]	Y	Y	U	Y	Y	N	Y	U	U	Y	Y	Y	N	Y
Eraslan[37]	Y	Y	Y	U	Y	Y	N	U	U	Y	Y	Y	N	Y
Hashemian 2015[26]	Y	Y	U	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Hashemian2014[27]	Y	Y	Y	U	Y	Y	N	U	U	Y	Y	Y	N	Y
Kanellopoulos[28]	Y	N	U	U	Y	Y	N	U	U	Y	Y	Y	N	Y
Kocak[38]	Y	Y	Y	Y	Y	Y	Y	N	U	Y	Y	Y	N	Y
Kymionis2016[29]	Y	Y	Y	U	Y	Y	N	U	U	Y	N	N	N	Y
Kymionis2014[30]	Y	Y	Y	U	Y	Y	N	N	Y	Y	N	N	N	Y
Magli[17]	Y	Y	Y	Y	Y	N	Y	N	U	Y	Y	Y	N	Y
Nawaz[39]	Y	N	Y	Y	Y	Y	N	U	U	Y	Y	N	N	Y
Ng 2016[18]	Y	Y	Y	Y	Y	N	Y	U	Y	Y	N	Y	N	Y
Ng 2015[31]	Y	Y	Y	Y	Y	N	Y	U	Y	Y	N	Y	N	Y
Rossi[40]	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y
Sherif[32]	Y	Y	Y	U	Y	Y	N	U	U	Y	N	Y	N	Y
Shetty[33]	Y	Y	N	U	Y	Y	N	U	U	Y	Y	Y	N	Y
Soeters[41]	Y	Y	N	Y	Y	Y	Y	U	U	Y	Y	Y	Y	Y
Stojanovic[42]	Y	Y	U	U	Y	Y	N	U	U	Y	Y	Y	N	Y
Tomita[34]	Y	Y	U	U	Y	Y	N	U	U	Y	Y	Y	N	Y

Y: Yes; N: No; U: Unclear.

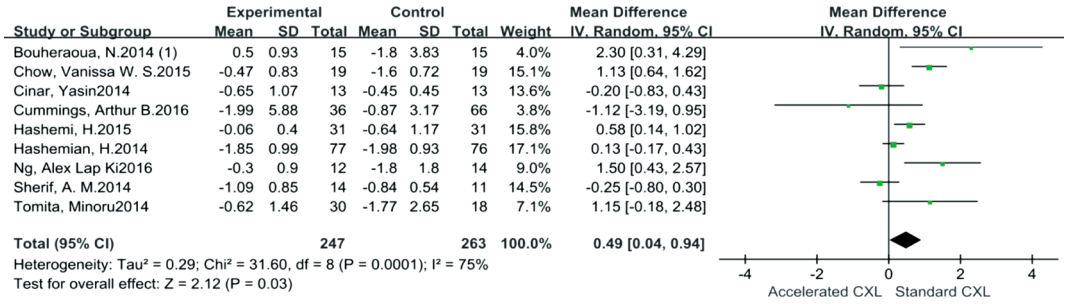

Figure 3 Forest plot for comparison of Kmax changes between AC and SC.

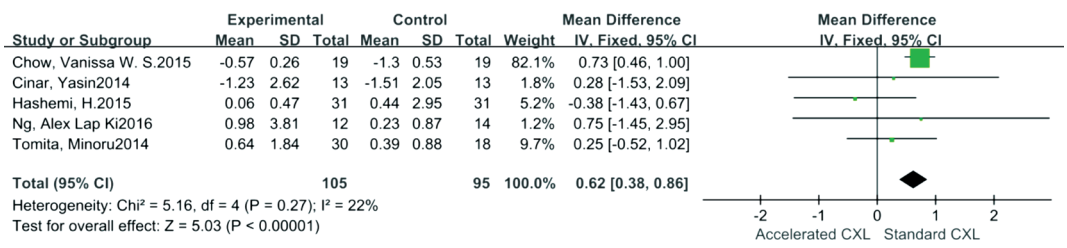

Figure 4 Forest plot for comparison of SE changes between AC and SC.

Table 4 Comparative outcomes by pooled data

Item	Sample size (Na, Ns, Nt)	Mean difference (95%CI)	Heterogeneity (I^2)	*P*	Effect-model (Ra/Fi)
Accelerated CXL *vs* Standard CXL					
Kmax	Na=247, Ns=263	0.49 (0.04, 0.94)	75%	0.03[a]	Ra
UDVA	Na=140, Ns=139	0.01 (-0.06, 0.09)	65%	0.74	Ra
CDVA	Na=167, Ns=168	-0.02 (-0.12, 0.07)	93%	0.63	Ra
SE	Na=105, Ns=95	0.62 (0.38, 0.86)	22%	<0.00001[a]	Fi
DDL	Na=98, Ns=91	-38.84 (-116.32, 38.64)	96%	0.33	Ra
CCT	Na=91, Ns=90	0.54 (-2.52, 3.06)	6%	0.73	Fi
ECD	Na=196, Ns=183	4.70 (-9.36, 18.7)	1%	0.51	Fi
Trans-epithelial CXL vs Standard CXL					
Kmax	Nt=161, Ns=161	1.15 (0.54, 1.75)	50%	0.0002[a]	Ra
UDVA	Nt=126, Ns=126	0.01 (-0.01, 0.03)	34%	0.57	Fi
CDVA	Nt=161, Ns=161	-0.01 (-0.05, 0.02)	46%	0.47	Ra
SE	Nt=130, Ns=12	-0.53 (-1.19, 0.13)	67%	0.11	Ra
DDL	Nt=56, Ns=51	-133.49 (-145.94, -121.04)	33%	<0.00001[a]	Fi
CCT	Nt=119, Ns=120	0.36 (-5.14, 5.87)	48%	0.90	Ra
ECD	Nt=67, Ns=75	-5.19 (-36.15, 25.76)	0	0.74	Fi

UDVA: Uncorrected distant visual acuity; CDVA: Corrected distant visual acuity; SE: Spherical equivalent; DDL: Depth of demarcation line; CCT: Central cornea thickness; ECC: Endothelium cell density; Na: Number of eyes for accelerated CXL; Ns: Number of eyes for standard CXL; Nt: Number of eyes for trans-epithelial CXL; Ra: Random; Fi: Fix. [a]*P*<0.05.

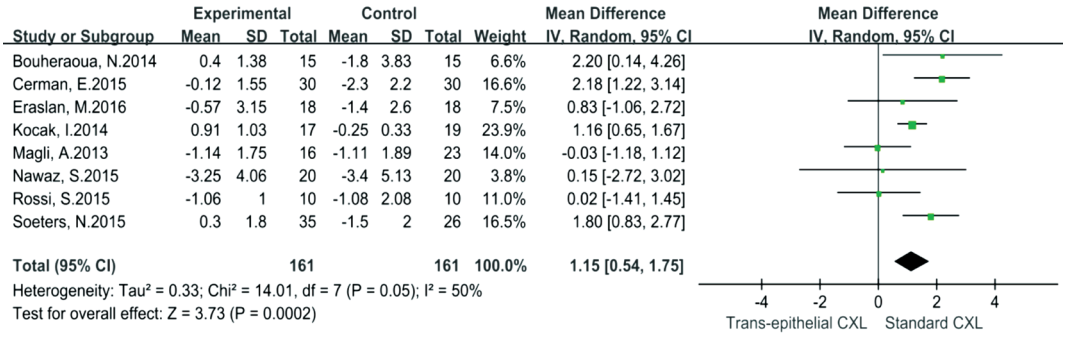

Figure 5 Forest plot for comparison of Kmax changes between TC and SC.

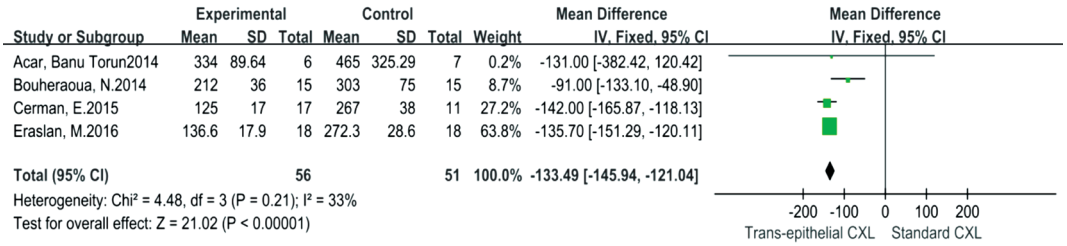

Figure 6 Forest plot for comparison of DDL between TC and SC.

patients in the SC group and four patients in the AC group had delayed epithelial healing and two patients had anterior scarring after AC.

DISCUSSION

Both SC and MCs have been proved to halt progressive keratoconus effectively by more and more studies[7-11,43-46], but whether MCs are equivalent to SC in effectiveness has remained unclear. From our Meta-analysis, pooled data showed significant inferiority for MCs relative to SC at halting Kmax deterioration in progressive keratoconus. In addition, SE and DDL showed significant differences when comparing SC with AC and TC, respectively. However, UDVA, CDVA, CCT and ECD demonstrated no significant differences in comparison of MCs and SC. These findings illustrated that SC is superior to MCs athalting progression of keratoconus, but improvements for visual acuity and safety showed equivalence between MCs and SC.

The rationale for CXL is mainly about photochemical effects generated from reactions between ultraviolet radiation and riboflavin (vitamin B2) in the cornea stroma. This procedure can lead to more covalent bond formation within cornea lamellar fibers through which the thinner part of the keratoconic cornea can be consolidated and cornea curvature could also be decreased[47-48]. Moreover, the cross-linked corneal collagen fibers can delay the progression of keratoconus *via* resisting the intraocular pressure (IOP) effectively[49].

The corneal epithelium is the critical obstacle to riboflavin permeation into the corneal stroma, and it affects CXL's effects significantly because a complete and intact epithelial layer is a tough lipophilic barrier to hydro-soluble riboflavin[11,47]. Franch *et al*[50] testified that through an enhancer used in the riboflavin solution, the concentration of riboflavin in epi-on cornea was much lower than in epi-off cornea *in vivo*. This can explain to a large extent why TC was significantly inferior to SC at halting progression of Kmax value, which was also confirmed by superficial DDL in TC caused by shallower infiltration of riboflavin and lower absorption. Similarly, Wollensak and Iomdina[51] suggested that the therapeutic effect of TC was only about one fifth that of SC. Although the corneal epithelium is also an obstacle for UVA radiation, it is not significant enough to influence CXL's effects. Bottos *et al*[52] assumed that the main obstacle caused by the cornea epithelium in TC is prevention of riboflavin penetration rather than limitation of UVA transmittance. Other authors estimated that approximately 30% of UVA radiation and approximately 80% of riboflavin could be absorbed by intact cornea epithelium[53-54].

In contrast to TC, the corneal epithelium is usually removed by mechanical scraping or excimer laser cutting in order to allow more riboflavin to permeate into the cornea stroma in AC and SC[11,47]. As a standard step for both AC and SC, the riboflavin penetration depth is greater than in TC after the epithelium is removed. In addition, the position that the reactions occur in the corneal stroma should be identical between AC and SC theoretically, because the similar procedures and riboflavin are used. Since DDL indicates the depth of riboflavin permeation and the reacted position in the cornea, this assumption is consistent with our pooled result that DDL was not significantly different between AC and SC.

Ultraviolet radiation intensity and duration are other significant factors that influence CXL's effects. Most AC protocols used in the included studies employed different combinations that had an energy dose (5.4 J/cm^2) equal to SC, such as 30 mW/cm^2 for 3min and 18 mW/cm^2 for 5min[26-27]. According to Bunsen-Roscoe's law of reciprocity that effects of CXL mainly depend on the energy absorbed by tissue[55-56], the effect of AC should be equivalent to SC through the similar radiation dose used in these studies. However, we found that it was significantly superior for SC to AC at halting progression of Kmax values by the pooled data. Paralleling to our result, Wernli *et al*[57] found that higher intensities, *e.g.* from 50 mW/cm^2 up to 90 mW/cm^2, could not reach the same stiffness effects as lower intensities did even though they complied with Bunsen-Roscoe's law. The reasons accounting for this, inferred by some authors, are limitation of intrastromal oxygen diffusion and more oxygen consumption from higher intensity UVA radiation, which could reduce the biomechanical effects of AC[58].

It is somewhat contradictory to explain that UDVA and CDVA from our pooled results for TC and AC could be comparable to SC even though they were inferior to SC at halting the progression of keratoconus. We assume that the effects generated from CXL could not exert enough impact to improve visual acuity and refractive condition dramatically, no matter what CXL protocol is used. In other words, the effects of CXL mainly reflect the biomechanical impact on stiffening the thinning cornea rather than reforming cornea shape. Even though the pooled SE showed more decrease in SC when compared to AC, we assume that the result was caused by one included study[23] that was given too much weight in the analysis.

In most cases, CCT decreases after CXL have been observed regardless of what CXL protocol was used[8-11,43-46]. Greenstein *et al*[59] explained this phenomenon by compactness of cornea fibers after CXL caused by thermal and photochemical effects, but other authors attribute this to measurement errors from different apparatus[60]. We assume that thermal and photochemical effects are relatively minor for both MCs and SC, so the CCT decrease from the three CXLs did not show any trend of significance in our pooled data. The safety of MCs and SC have been proved by pooled ECD data that indicated reactions between UVA and riboflavin had no influence on endothelial layer[18,22,31,35-37].

To the best of our knowledge, there is no published Meta-analysis comparing MCs and SC until now, but this Meta-analysis still has some unavoidable limitations. One objective limitation was that the definition criteria for progressive keratoconus, demographic baseline and follow-up period varied within the included studies. Moreover, a small sample size of participants was enrolled in most studies and all of them were single centered, consecutive case serials without randomization. Lastly, different UVA instruments, riboflavin ingredients, surgical procedures and postoperative medications were used in these studies. In the future, accompanied by more participants enrolled into multi-center randomized clinical trials and by standardization for apparatus and riboflavin ingredients, more reliable outcomes should be obtained and more confirmed conclusions could be made.

In conclusion, SC was more favorable at halting the progression of keratoconus, but visual acuity improvement showed comparable results between MCs and SC. MCs are more suitable for pediatrics regarding epithelium-on and short duration, and TC could be carried out for patients with cornea thickness less than 400 μm due to its shallower DDL.

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