Comparison of Standard Versus Accelerated Corneal Collagen Cross-Linking for Keratoconus: A Meta-Analysis

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PURPOSE. To systematically compare epithelial-off standard (SCXL) to accelerated corneal collagen cross-linking (ACXL) for the treatment of keratoconus.

METHODS. PubMed, Embase, the Cochrane Library, and the US trial registry were searched for trials comparing SCXL and ACXL for keratoconus up to October 2017. Standardized mean differences (SMDs) with 95% confidence intervals (CIs) were calculated. Primary outcomes were changes in uncorrected distance visual acuity, maximum keratometry (Kmax), and mean keratometry (mean K). Secondary outcomes were changes in corrected distance visual acuity, mean refractive spherical equivalent, central corneal thickness (CCT), and endothelial cell density (ECD).

RESULTS. Eleven trials were included. For primary outcomes, SCXL showed a greater reduction in Kmax (SMD 0.32; 95% CI 0.16, 0.48) than ACXL. For secondary outcomes, the decrease in CCT (SMD 0.32; 95% CI 0.03, 0.61) and ECD (SMD 0.26; 95% CI 0.06, 0.46) was less with ACXL than with SCXL. For the other outcomes, there were no statistically significant differences.

CONCLUSIONS. SCXL has a greater effect in terms of reduction in Kmax than ACXL, while ACXL induces less reduction in CCT and ECD than SCXL. Further well-designed randomized controlled trials comparing ACXL and SCXL are indicated.

Keywords: corneal cross-linking, keratoconus, standard, accelerated

Keratoconus is a corneal dystrophy distinguished by localized thinning of the corneal stroma with secondary ectasia.1 This results in progressive myopia and irregular astigmatism with associated progressive loss of vision and reduced quality of life.2–4 It is one of the most common corneal diseases, affecting approximately 1 in 375 individuals and occurs in all races.5

Keratoconus usually presents in adolescence and is often asymmetrical in presentation.6–8 The disease typically progresses for approximately 2 decades.9–11 What happens to affected patients later on in their life remains unknown.1,2 The pathogenesis of keratoconus is complicated and includes environmental factors, atopy, and hereditary susceptibility.13,14

Eye rubbing, contact lens wear, and ultraviolet radiation appear to be important factors.15–17 There are studies indicating higher prevalence rate in those with family history of keratoconus,18,19 and with systemic diseases including familial Mediterranean fever, Down syndrome, osteogenesis imperfecta, and inflammatory bowel disease.20–25 Management depends on the severity of the disease. In mild cases, spectacles or soft contact lenses may be adequate but with advanced disease, rigid gas permeable and scleral contact lenses are often required. Keratoplasty is usually reserved for advanced disease with suboptimal vision and impaired wearing tolerance with contact lenses.2,24–26

Corneal collagen cross-linking (CXL) was first introduced by Wollensak and colleagues27 with an ultraviolet-A (UVA) protocol of 3 mW/cm2 intensity at 370 nm over an exposure time of 30 minutes (now termed the ‘Dresden protocol’). It uses the photochemical interaction of UVA and riboflavin (vitamin B2), to induce cross-links between corneal stromal macromolecules. Studies have reported that UVA absorption coefficient has a linear correlation with the concentrations of riboflavin up to 0% to 0.5%, suggesting that different riboflavin concentrations may impact clinical outcomes.28–30 CXL has been proved in its effectiveness and safety in halting the progression of keratoconus and improving topographic and visual parameters in numerous prospective, published studies, including randomized controlled trials.31–36 However, given the prolonged irradiation time of this standard CXL (SCXL) protocol, with total treatment times in excess of 1 hour, researchers have proposed accelerated CXL (ACXL) protocols, to improve convenience and comfort for patients. These ACXL protocols have the aim of decreasing UVA exposure time by increasing UVA fluency to achieve the same overall total UVA dosage. According to the rule of Bunsen and Roscoe, a photochemical reaction is directly proportional to the total energy dose, irrespective of the time over which this dose is delivered.37 At present the ACXL protocols are carried out in a shorter period such as 3, 5, or 10 minutes by using 30, 18, or 9
mW/cm² irradiance, respectively, with a cumulative irradiation dose of 5.4 J/cm². The shorter corneal exposure time of ACXL, it has been proposed, might have the potential advantages of reducing the rate of complications such as corneal thinning, haze, infection, and melting. However, it may affect efficacy.56 Schumacher et al.59 have found equivalent biomechanical responses between standard (3 mW/cm², 30 minutes) protocols and accelerated (10 mW/cm², 9 minutes) treatment protocols. Touboul and colleagues40 have compared corneal alterations after standard and accelerated procedures (30 mW/cm² for 3 minutes) and found similar alterations in the subbasal nerve plexus and anterior stromal keratocytes. Numerous clinical studies have now been published to demonstrate the efficacy and safety of ACXL.41–49 Shajari et al.50 have compared conventional and accelerated CXL and found a significant difference in the D value (a value that involves anterior and posterior corneal elevation, corneal pachymetry, and progression of corneal thinning) with more favorable results for the conventional procedure. However, other studies have demonstrated that both procedures have a comparable effect in posterior corneal elevation, corneal pachymetry, and progression of corneal thinning.51,52 It is of note that typically both SCXL and ACXL are generally preceded with epithelial removal (epithelium-off CXL), although investigations have been conducted to explore the potential influence on clinical outcomes between epithelium-off and transepithelial (epithelium-on) procedures using both SXCL and ACXL protocols.53,54

In an attempt to try to clarify the potential benefits of CXL, we undertook this current meta-analysis to compare the effectiveness and safety of ACXL in comparison to SCXL.

**METHODS**

This systematic review with meta-analysis was conducted according to the guidelines of the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement on the quality of published trials.55

**Search Strategy**

A systematic literature review for the primary source of data up to October 2017 was conducted by two researchers (QL and BS) independently in PubMed, Embase, the Cochrane Library, and the US trial registry (ClinicalTrials.gov). The search strategy included keywords that are summarized as follows: “cross linking,” “cross linking,” “cross-link,” “cross link,” and “keratoconus.” References from pertinent studies were manually searched. The search strategy is shown in detail in Supplementary Material.

**Inclusion and Exclusion Criteria**

Two independent investigators (QL and BS) performed the article screening; any discrepancies were resolved by focused discussion or consultation with an additional investigator (RT). Trials were included when they met the following criteria:

1. Study population: patients with keratoconus;
2. Intervention: CXL with epithelium-off;
3. Comparison: SCXL versus ACXL;
4. Outcomes: studies containing preoperative and postoperative changes of these primary or secondary outcomes, which included uncorrected distance visual acuity (UDVA), mean keratometry (mean K), maximum keratometry (Kmax), corrected distance visual acuity (CDVA), mean refractive spherical equivalent (MRSE), central corneal thickness (CCT), and endothelial cell density (ECD);
5. Studies with more than 6 months follow-up.

We excluded studies that did not contain any of our defined primary or secondary outcomes mentioned above. We compared the results of the last follow-up visit.

**Outcome Measures**

Primary outcomes were change in UDVA, mean K, and Kmax after CXL. Secondary outcomes were change in CDVA, MRSE, CCT, and ECD.

**Date Extraction and Assessment of Study Quality**

We extracted information containing the author, year of publication, study design, sample size, characteristics of sample, and the outcomes at baseline and postoperatively. For data that were missing or that could not be directly obtained, we contacted the authors of trial reports. We used the risk of bias method from the Cochrane Collaboration to assess the study quality of randomized controlled trials (RCTs).55 The evaluation was conducted in terms of random sequence generation and allocation concealment (selection bias), blinding of participants and personnel (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other biases by grading with low, high, or unclear risk of bias for each study. For nonrandomized comparative studies, the methodologic index for nonrandomized studies (MINORS)56 was applied. MINORS contains 12 items, the first subscale of eight items related to noncomparative studies, whereas all 12 items were relevant to comparative studies. Each item was scored from 0 to 2 with 0 indicating that it was not reported in the article evaluated, 1 indicating that it was reported but inadequately, and 2 indicating that it was reported adequately. We gave a mark in respect of selection of patients, comparability of cohorts, and outcome measurements, amounting to 12 scales.

**Statistical Analysis**

Stata statistical software (version 13.0; Stata Corporation, College Station, TX, USA) was used to perform statistical analyses. For continuous outcomes, standardized mean differences (SMDs) with 95% confidence intervals (CIs) were calculated. Baseline demographics, and preoperative and postoperative mean values for the primary and secondary outcomes were combined by using weighted means. At the same time, a test for the heterogeneity between the included trials for each comparison was performed with the Cochrane’s Q test and I² tests.57 If the Q test showed $P < 0.05$ or if $I^2 > 50\%$, which means high heterogeneity among the included studies, the SMD values were pooled in accordance with the random effects model.58,59 Z-values represent overall effect with statistical significance at a $P$ value of $< 0.05$.60 To identify differences between different ACXL protocols, we undertook subgroup analyses and meta-regression. Further sensitivity analysis was conducted by removing studies that were not RCTs. Furthermore, Egger’s linear regression test, with visual inspection of the funnel plot, was applied to detect the potential publication bias.61,62

**RESULTS**

**Baseline Characteristics of Included Studies**

The initial literature search yielded 2182 articles. After duplicates were excluded, 1326 studies remained. Of these, 18 studies matched the inclusion criteria and an additional 3 articles were added from other reference sources as detailed in the Methods section. Eight of the 21 articles were excluded as
they did not include any primary or secondary outcome data. Ultimately 13 studies met our criteria and were included in our study (Fig. 1). Seven studies were RCTs and six were nonrandomized comparative trials. The characteristics of the 13 included studies are shown in Table 1 (no data were acquired by contacting the authors). The 13 studies included 713 eyes: 352 eyes underwent SCXL and 361 eyes underwent ACXL. There were two trials reporting ACXL procedure with 30 mW/cm² (4 minutes), whose total irradiation energy differed from the other trials, and thus we only performed descriptive analysis for these trials.

Risk of Bias Assessment

The risk of bias of the RCTs included is shown in Figure 2. All randomized trials were rated at “low risk of bias” in terms of randomization, but only 14.3% described randomization concealment techniques. Observer and participant masking of treatment type were generally poor, with 71.4% of the RCTs being rated at “unclear risk of bias” and 14.3% being rated at “high risk of bias.” In terms of attrition and reporting bias, almost all trials were rated as “low risk of bias.” With regard to nonrandomized comparative studies, the total scores of all these trials were not lower than 20 (Table 2).

Primary Outcomes

Uncorrected Distance Visual Acuity. A total of seven studies were included in our analysis. There was no statistical significant difference in the change of UDVA post CXL between SCXL and ACXL (SMD −0.18; 95% CI −0.37, 0.02) (Fig. 3A).

Mean Keratometry. Eight studies reported the relevant data. There was no significant difference in mean K in SCXL compared to ACXL (SMD 0.38; 95% CI −0.01, 0.77) (Fig. 4A).

Maximum Keratometry. All of the 12 studies reported the relevant data. SCXL appeared to flatten the Kmax to a greater extent than ACXL (SMD 0.32; 95% CI 0.16, 0.48) (Fig. 5A).

Secondary Outcomes

Corrected Distance Visual Acuity. In 10 studies with relevant data, there was no significant difference in the change of CDVA between SCXL and ACXL (SMD −0.02; 95% CI −0.31, 0.27) (Figure 6A).

Mean Refractive Spherical Equivalent. Nine studies compared the outcomes of MRSE post CXL. The results of the current meta-analysis found no statistical difference (SMD −0.06; 95% CI −0.27, 0.14) between SCXL and ACXL (Supplementary Fig. S2).

Central Corneal Thickness. We found that CCT was reduced to a greater extent post SCXL when compared with ACXL in the analysis of four studies (SMD −0.03; 95% CI −0.61) (Supplementary Fig. S3). The follow-up times were all greater than 6 months in these four trials, but not greater than 12 to 18 months, when CCT often returns to preoperative values.

Endothelial Cell Density. Seven studies reported the relevant data. Both ACXL and SCXL caused a reduction in ECD with less reduction with ACXL (SMD 0.26; 95% CI 0.06, 0.46) (Supplementary Fig. S4).

Subgroup Analysis and Meta-Regression

We divided the ACXL trials into three groups according to the difference of UVA irradiation/time. The results of subgroup analysis are shown in Supplementary Table S1. There were only 7, 2, and 3 trials in subgroups of 9 mW/cm² (10 minutes), 18 mW/cm² (5 minutes), and 30 mW/cm² (3 minutes), respectively, in the analysis. Meta-regression analysis indicated that different acceleration protocols were not a source of heterogeneity (P > 0.05).
### Table 1. The Baseline Characteristic of Trials Included in the Meta-Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Design</th>
<th>Group</th>
<th>No. of Eyes</th>
<th>UVA Irradiation Intensity, mW/cm²</th>
<th>Mean K, D, logMAR, Mean ± SD</th>
<th>Change in UVA, logMAR, Mean ± SD</th>
<th>Change in CDVA, logMAR, Mean ± SD</th>
<th>Change in Mean K, D, Mean ± SD</th>
<th>Change in MrSE, D, Mean ± SD</th>
<th>Change in CCT, μm, Mean ± SD</th>
<th>Change in ECD, Cells/mm², Mean ± SD</th>
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</thead>
<tbody>
<tr>
<td>Brittingham</td>
<td>Switzerland</td>
<td>non-RCT</td>
<td>SCXL</td>
<td>28.62 ± 10.55</td>
<td>71</td>
<td>30</td>
<td>3</td>
<td>-0.09 ± 0.11</td>
<td>-0.44 ± 0.61</td>
<td>0.55 ± 0.89</td>
<td>0.6 ± 0.89</td>
<td>-0.76 ± 2.71</td>
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<tr>
<td>2014</td>
<td></td>
<td>ACXL</td>
<td>26.14 ± 10.25</td>
<td>29</td>
<td>10</td>
<td>9</td>
<td>0.72 ± 1.5</td>
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<td>50</td>
<td>5</td>
<td>0.07 ± 0.13</td>
<td>0.11 ± 0.51</td>
<td>0.32 ± 0.86</td>
<td>0.4 ± 1.16</td>
<td>46 ± 226.5</td>
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<td>2017</td>
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<td>ACXL</td>
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<td>1.51 ± 2.05</td>
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<td>10</td>
<td>9</td>
<td>0.25 ± 0.39</td>
<td>0.19 ± 0.28</td>
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<td>-1.14 ± 2.09</td>
<td>1.23 ± 2.62</td>
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<td>27.5 ± 8.5</td>
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<td>10</td>
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<td>RCT</td>
<td>SCXL</td>
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<td>3</td>
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<td>-0.02 ± 0.2</td>
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<td>SCXL</td>
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<td>50</td>
<td>3</td>
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<td>3</td>
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<td>36.1 ± 10.7</td>
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<td>5</td>
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<td>-0.12</td>
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<td>ACXL</td>
<td>21.58 ± 5.78</td>
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<td>21.1 ± 4.5</td>
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<td>50</td>
<td>3</td>
<td>-0.1 ± 0.16</td>
<td>-0.11 ± 0.15</td>
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<td>-2.15 ± 2.6</td>
<td>0.96 ± 1.5</td>
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<td>10</td>
<td>9</td>
<td>0.21 ± 0.2</td>
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<td>Tomita</td>
<td>Japan</td>
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<td>30.83 ± 5.2</td>
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<td>50</td>
<td>3</td>
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<td>-0.10 ± 0.2</td>
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<td>-0.39 ± 0.8</td>
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</tbody>
</table>

logMAR, logarithm of the minimum angle of resolution.
Sensitivity Analysis and Publication Bias

There were six RCTs in total included in the analysis. When we removed trials that were not RCTs, the statistical results changed only in terms of CCT (SMD 0.26; 95% CI –0.16, 0.68) and ECD (SMD 0.21; 95% CI –0.01, 0.44). The other outcomes remained unchanged (Figs. 3–5B; Supplementary Figs. S5–8). The result of Egger’s test showed that publication bias was not detected (P > 0.05).

Descriptive Analysis

Sherif has found that the reduction in Kmax with ACXL (30 mW/cm² for 4 minutes) was 1.09 ± 0.85 D, and 0.84 ± 0.54 D with SCXL, and the difference between both groups was not statistically significant (P = 0.38). ACXL showed a significant reduction in CCT (from 484.18 ± 19.45 µm to 469.64 ± 20 µm) and SCXL showed no statistically significant difference from the baseline values (from 464.18 ± 29.15 µm to 451.75 ± 24.39 µm) at 12 months postoperatively. The CCT changes were comparable in both groups (P = 0.66). In terms of CDVA, both groups showed significant improvements at 12 months (P = 0.015 for ACXL and P = 0.03 for SCXL).

The changes in these parameters in the study of Toker et al. are shown in Table 1. They demonstrate that no statistically significant difference is found between SCXL and ACXL (30 mW/cm² for 4 minutes) at 12 months in the change in UDVA, CDVA, MRSE, and CCT (all P > 0.05). But they show that the ACXL group has statistically significantly less reduction in mean K and Kmax than the SCXL group (both P < 0.01).

Discussion

To our knowledge, this is the first meta-analysis to compare the efficacy and safety of SCXL and ACXL. Our study demonstrated that standard CXL appears to be more effective in stabilizing corneal topography, but ACXL may be less likely to reduce CCT and corneal endothelial cell loss.

In terms of the primary outcomes, this current systematic review and meta-analysis demonstrated that SCXL was superior to ACXL in terms of the ability to reduce Kmax (SMD 0.32; 95% CI 0.16, 0.48). Shetty et al. have compared four protocols of CXL and found that after 6 months of follow-up, SCXL (3 mW/cm² for 30 minutes) shows better flattening effect than ACXL.

In terms of visual outcomes, we found equal outcomes for SCXL and ACXL with regard to both UDVA (SMD –0.18; 95% CI –0.37, 0.02) and CDVA (SMD –0.02; 95% CI –0.31, 0.27). Similarly, Medeiros et al. have described different protocols of ACXL, and they indicate that all the different subtypes of ACXL could improve visual acuity. Interestingly, we found no differences in visual acuity between SCXL and ACXL, despite the fact that SCXL behaved superiorly in reducing Kmax. This is likely due to visual acuity being influenced by various factors, such as the transparency of the refractive system, the functional state of the retina and optic nerve, environmental and psychological factors, and not just corneal curvature.

With regard to secondary outcomes, this meta-analysis indicated that SCXL created greater ECD loss than ACXL (SMD 0.26; 95% CI 0.06, 0.46). This may imply that ACXL may be superior to SCXL in this respect because of the possible cytotoxicity caused by prolonged ultraviolet radiation or less posterior irradiation with ACXL, although it must be noted that only seven of our included studies provided data on ECD. Ozgurhan et al. have reported that after ACXL with 30 mW/cm² for 3 minutes, the mean endothelial cell density was unchanged after surgery (2726.02 ± 230.21 preoperatively and 2714.58 ± 218.26 cells/mm² at 12 months postoperatively, P = 0.086). However, Badawi has reported a decrease in ECD following ACXL with 10 mW/cm² for 9 minutes. In their nonrandomized controlled study, the ECD changes from 2633.40 ± 283.10 cells/mm² at baseline to 2610.00 ± 271.18 cells/mm² (P = 0.001) at 12 months. It is difficult to explain such conflicting results but they are likely influenced by the small sample sizes in these studies.

In terms of MRSE, this meta-analysis found that both SCXL and ACXL appear to achieve the same outcomes (SMD –0.06; 95% CI –0.27, 0.14). O’Brart et al. have performed a prospective cohort study to determine long-term efficacy and safety of SCXL (UVA for 30 minutes with 370-nm UVA radiation at 5 mW/cm²), and they found that the MRSE is significantly
Table 2. Risk of Bias Assessment Based on Methodologic Index for Nonrandomized Studies (NINORS)

<table>
<thead>
<tr>
<th>Methodologic Items for Nonrandomized Studies</th>
<th>Additional Criteria</th>
<th>in the Case of Comparative Study</th>
<th>baseline Adequate Statistical Contemporaneous Equivalence Analysis</th>
<th>inclusion of the Study of Groups</th>
<th>Follow-up Length Less Than 5%</th>
<th>Loss to Follow-up</th>
<th>prospective Calculation of the Control Group</th>
<th>prospective Collection Appropriate to the Aims of the Study</th>
<th>unbiased Assessment of the Study Endpoint</th>
<th>Consecutive Patients Stated Aim</th>
<th>A Clearly Stated Aim of the Study</th>
<th>Total Score</th>
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<tr>
<td>Total Irradiation Dose of the Study (J/cm²)</td>
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Most articles of current ACXL protocols have used only comparative studies with 18 mW/cm² for 5 minutes (two trials). These conflicting findings are probably not the result of differences in efficacy of ACXL protocol but likely due to the paucity of comparative studies, with a lack of comparative studies with 18 mW/cm² for 5 minutes (two trials). In addition, as already alluded to, small sample sizes in subgroup analyses impact the conclusions, and thus we should be cautious with the findings. Clearly there is a great need for further well-constructed randomized comparative studies of SCXL and various ACXL protocols. It is of note that in our sensitivity analysis, the result was slightly changed when we removed the non-RCTs, so clearly more RCTs in this area need to be undertaken.

Although many studies have reported that CXL is a safe and effective method in the treatment of keratoconus, it has complications, such as haze, sterile infiltrates, infectious keratitis, endothelial failure, and progression of ectasia. In our analysis, there was only one trial that reported complications. Sherif has described haze after both SCXL and ACXL, and in all cases in both groups, the haze resolved with time.

The total irradiation dose of SCXL with 3 mW/cm² for 30 minutes is 5.4 J/cm². Most articles of current ACXL protocols used the same total irradiation dose of 5.4 J/cm² but with a higher UVA power and a shorter irradiance time. However, some ex vivo studies have suggested that ACXL protocols with higher total irradiation doses may be more efficacious than ACXL protocols with a total dose of 5.4 mJ/cm². Although there is a small amount of research concerning these extended ACXL protocols with total energies of 7.2 mJ/cm² and showing good efficacy, these studies generally have small sample sizes and comparative studies with larger numbers and longer follow-up are indicated.

Apart from the varying ACXL protocols used in the comparative studies we analyzed, there were other limitations in this current meta-analysis. First, like other meta-analysis, our study results are influenced by the differences among the included trials. These differences may have potential impacts on our results, such as the difference in surgical procedures, operation techniques, and follow-up. Second, our results indicated that ACXL showed statistically less flattening in Kmax than SCXL but a comparable effect in UDVA and CDVA. We should realize that not all cases of keratoconus with the same Kmax are the same, which means different individuals behave differently in regard to these parameters. They differ not only in CCT but also in the thinnest point and location, disparate pachymetry throughout the cornea, high-order aberrations, and overall shape. These differences might potentially influence the therapeutic efficacy of CXL. Third, corneal demarcation line depth has been suggested as an
FIGURE 3. Standardized mean differences (SMDs) of change in UDVA between patients undergoing SCXL and ACXL with all studies (A) and only RCTs (B).
FIGURE 4. Standardized mean differences (SMDs) of change in mean keratometry (mean K) between patients undergoing SCXL and ACXL with all studies (A) and only RCTs (B).
FIGURE 5. Standardized mean differences (SMDs) of change in maximum keratometry (Kmax) between patients undergoing SCXL and ACXL with all studies (A) and only RCTs (B).
important parameter to assess the efficacy of CXL, but unfortunately too few relevant RCTs generally report this parameter. Four, the longest follow-up was only 15 months; further longer-term follow-up studies are required to confirm our conclusions.

In conclusion, we found that SCXL has a greater effect in terms of reduction in Kmax than ACXL, and ACXL possibly showed better ability to keep CCT and protect corneal endothelial cells. With regard to other parameters, such as UDVA and CDVA, SCXL and ACXL behaved comparably. More well-constructed randomized, controlled trials are required, however, to confirm our findings.

Acknowledgments

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