Accelerated Versus Standard Corneal Cross-Linking for Progressive Keratoconus: A Meta-Analysis of Randomized Controlled Trials

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Purpose: To compare the clinical results of accelerated corneal collagen cross-linking (ACXL) to standard corneal collagen cross-linking (SCXL) in progressive keratoconus by summarizing randomized controlled trials using a meta-analysis.

Methods: Trials meeting the selection criteria were quality appraised, and data were extracted by 2 independent authors. A comprehensive search was performed using the Cochrane methodology to evaluate the clinical outcomes of ACXL and SCXL for treating progressive keratoconus. Estimates were evaluated by weighted mean difference (WMD) and 95% confidence interval (CI) for absolute changes of the outcomes during 12-month observation periods. Postoperative demarcation line depth was also compared.

Results: We identified 6 randomized controlled trials that met the eligibility criteria for this meta-analysis. SCXL resulted in a significantly better outcome in postoperative changes in best spectacle-corrected visual acuity (WMD = −0.02; 95% CI, −0.03 to −0.01; $P < 0.0001$); however, the small differences may not be clinically significant. ACXL provided a significantly better improvement of cylindrical refraction after the 1-year follow-up (WMD = 0.15; 95% CI, 0.05–0.26; $P = 0.005$). Demarcation line depth at 1 month after SCXL was deeper than that after ACXL (WMD = −102.25; 95% CI, −157.16 to −47.35; $P = 0.0003$). No differences in the changes in maximum keratometry, central corneal thickness, uncorrected visual acuity, spherical equivalent refraction, corneal biomechanical properties, and corneal endothelial cell density were found among both groups.

Conclusions: An ACXL shows a comparable efficacy and safety profile at the 1-year follow-up, but it has less impact on improving best spectacle-corrected visual acuity when compared with the Dresden protocol. Overall, both methods similarly stop the disease progression.

Keratoconus is a progressive, frequently asymmetric, noninflammatory corneal thinning disorder characterized by changes in the structure and organization of corneal collagen.[1] It results in corneal thinning and protrusion, progressive myopia, and irregular astigmatism.

Corneal collagen cross-linking (CXL) was first introduced as a promising technique to slow or stop the progression of corneal ectasia.[2] The standard method of CXL with riboflavin and ultraviolet-A (UVA, 365 nm) (3 mW/cm^2, 30 minutes), now widely known as the "Dresden protocol," was originally developed by Wollensak et al[2] from Germany in 2003. The interaction of riboflavin and UVA leads to the formation of reactive oxygen species, which leads to the formation of additional covalent bonds between collagen molecules, with consequent biomechanical stiffening of the cornea.[3] Since the first clinical study was published by Wollensak et al,[2] there has been an increasing number of published studies reporting the safety and efficacy of the treatment in slowing down or halting the progression of keratoconus. There have been various modifications to the standard CXL (SCXL) such as increasing the intensity of UVA irradiation and shortening the exposure time [accelerated CXL (ACXL)] without altering the total energy delivered. Another modification has been to perform the CXL through an intact epithelium (transepithelial CXL) with less discomfort to the patient and reduced postoperative complications.[4] The ACXL protocol is based on the Bunsen–Roscoe law of reciprocity.[5] It claims an inverse relationship between applied intensity and illumination time. Equal photochemical effects on the cornea are expected using the same cumulative dose, meaning higher intensities in a shorter time of treatment. The shorter duration of ACXL has the advantage of shorter corneal exposure time, which may reduce the rate of complications such as corneal thinning, haze, infection, and melting; however, it may alter the efficacy. It is presently unknown whether any of this ACXL technique is as effective in treating progressive keratoconus as the SCXL technique, and there is only a scarcity of randomized controlled trials (RCTs) comparing different techniques in keratoconus within the literature.[6–11] To
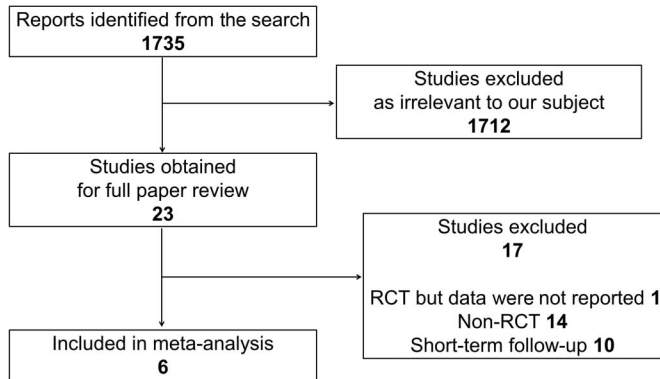
FIGURE 1. Flow chart of trial selection.

provide powerful evidence for the widespread clinical practice of these therapeutic techniques, we undertook this meta-analysis of all published RCTs to compare the clinical effects and safety of ACXL with SCXL in progressive keratoconus.

METHODS

This meta-analysis was performed in an academic medical setting in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.[12]

Study Selection

Two reviewers searched MEDLINE and the Cochrane Central Register of Controlled Trials databases for publications. Our search was performed on December 29, 2018. The keywords in our search strategy included "corneal cross-linking," "corneal collagen cross-linking," "collagen cross-linkage," and "corneal ectasia." Two reviewers (H.K. and K.T.) reviewed the titles and abstracts of the search results and retrieved full-text articles if the title or abstract appeared to meet the eligibility criteria for this review.

Inclusion and Exclusion Criteria

Studies were included if they discussed the diagnosis of progressive keratoconus.[13] We defined the progression of

keratoconus as an increase of at least 1 diopter (D) in the steepest keratometry, a degradation of visual acuity, and an increase of 1 D or more in the manifest cylinder over the preceding 12 months. We included studies that had a 1-year minimum follow-up time and followed the accelerated or standard technique. When the same trial was reported more than once we used the most recent trial report. Only studies including human research participants and published in the English language were included. We also defined the ACXL protocol as a UVA intensity of 9 mW/cm^2 or more for 10 minutes or less. We excluded animal and ex vivo studies. We also excluded studies in which CXL was performed in combination with other surgical procedures such as intracorneal segment insertion, excimer laser procedures, or iontophoresis techniques. Our meta-analysis limited selection to RCTs. All articles that we found were carefully reviewed to select those that reported original clinical data preoperatively and postoperatively. Data from previously reported cases included in different articles were omitted to avoid duplication of data.

Risk of Bias Assessment

Two review authors (H.K. and K.T.) independently assessed the risk of bias of the included studies in accordance with the Cochrane Handbook for Systematic Reviews of Interventions[14] using the following parameters: adequacy of sequence generation; allocation concealment; blinding of participants, personnel, and outcome assessors; incomplete outcome data; and selective outcome reporting.

Outcome Measures

Effective outcomes were the changes in the following parameters between baseline and 1-year follow-up:

1. Maximum keratometry value (Kmax): the steepest keratometry value obtained using topographies of a rotating Scheimpflug camera or computerized videokeratography;
2. Central corneal thickness (CCT): the thickness of the central point using Scheimpflug or ultrasound pachymetry;
3. Best spectacle-corrected visual acuity (BSCVA): the visual acuity corrected only by glasses;
4. Uncorrected distance visual acuity (UDVA): the visual acuity without correction;

TABLE 1. Characteristics of 6 RCTs Evaluating Accelerated Versus Standard CXL

| Study* (Y) | Clinical Trials Registration | Country | Follow-Up (Mo) | Treated Eyes (N) | | Mean Age (Y) | | Mean Baseline Kmax (D) | |
				ACXL	SCXL	ACXL	SCXL	ACXL	SCXL-Off
Hagem et al[6] (2017)	NCT02883478	Norway	12	20	20	N/A	N/A	58.4	57.6
Hashemi et al[7] (2015)	IRCT201207244333N1	Iran	18	31	31	25.1 (both groups)		47.89	48.77
Hashemian et al[8] (2014)	Not registered	Iran	15	77	76	22.6	22.3	54.1	53.6
Sadoughi et al[9] (2018)	Not registered	Iran	12	15	15	19.4	19.4	50.13	51.38
Sherif[10] (2014)	Not registered	Egypt	12	14	11	21.6	23.6	49.43	51.40
Shetty et al[11] (2015)	Not registered	India	12	33	36	24.2	22.8	49.4	50.5

*First author.
N/A, not available.

TABLE 2. Summary of Riboflavin Profiles of CXL Protocols

Study* (yr)	Concentration		Impregnation	
	ACXL	SCXL	ACXL	SCXL
Hagem et al[6] (2017)	0.1% riboflavin with 1.1% HPMC	0.1% riboflavin with 1.1% HPMC	For 20 min, then every 2 min during UVA	For 20 min, then every 2 min during UVA
Hashemi et al[7] (2015)	0.1% riboflavin with 20% dextran	0.1% riboflavin with 20% dextran	Every 3 min for 30 min, then every 3 min during UVA	Every 3 min for 30 min, then every 3 min during UVA
Hashemian et al[8] (2014)	0.1% riboflavin with 20% dextran	0.1% riboflavin with 20% dextran	For 30 min, then stopped	For 30 min, then stopped
Sadoughi et al[9] (2018)	0.1% riboflavin with 20% dextran	0.1% riboflavin with 20% dextran	Every 2 min for 30 min, then every 5 min during UVA	Every 2 min for 30 min, then every 5 min during UVA
Sherif[10] (2014)	0.1% riboflavin with 20% dextran	0.1% riboflavin with 20% dextran	Every 2 min for 30 min, then stopped	Every 2 min for 30 min, then every 2 min during UVA
Shetty et al[11] (2015)	0.1% riboflavin with 20% dextran	0.1% riboflavin with 20% dextran	Every 2 min for 30 min, then every 2 min during UVA	Every 2 min for 30 min, then every 2 min during UVA

*First author.
HPMC, hydroxypropyl methylcellulose.

5. Manifest refraction spherical equivalent (MRSE): the manifest subjective refraction of the spherical equivalent (SE);
6. Cylindrical refraction: the manifest subjective refraction of the cylinder.

Best-corrected visual acuity with a contact lens was not included in this analysis because the evaluation of visual acuity was limited to BSCVA or UDVA in most previous trials.

To study the biomechanical parameters of the cornea, ocular response analyzer (Reichert Technologies Inc, Depew, NY) measurements were compared: corneal hysteresis (CH) and corneal resistance factor (CRF) were recorded at 12 months after CXL.

Safety outcomes were the decrease in endothelial cell density 12 months postoperatively and the absolute values of demarcation line depth at 1 month after CXL. The number of eyes postoperatively with adverse events was assessed, but not statistically analyzed.

Data Extraction

Two reviewers (H.K. and K.T.) independently extracted data from the included trials using a standardized form. We collected the above outcome measures and details of the interventions, such as setting, sample size, age, follow-up period, mean baseline Kmax, riboflavin solutions, and UVA irradiation. We requested the unpublished data from the corresponding authors of the individual trials through email and waited for their replies for 3 months.

Heterogeneity Assessment

We planned to assess heterogeneity by looking at the clinical and methodological diversity of the included studies and by examining the forest plots and I^2 statistics as described in the Cochrane Handbook for Systematic Reviews of Interventions.[14]

Statistical Analysis

Treatment effects were evaluated as weighted mean difference (WMD) and 95% confidence interval (CI) calculated for absolute changes of the interested outcomes. For individual articles, WMD was computed by the difference of the mean change in the ACXL group and that in the SCXL group. The outcomes were measured as mean ± SD. Heterogeneity was also assessed, and an I^2 value greater than 50% was considered significant. In this instance, a random-effects model was used because it provides a conservative estimate and is less influenced by the weighting of each study than are other methods.[15] A fixed model was used when the level of heterogeneity was less than 50%. The meta-analysis was performed using RevMan software (version 5.2; Information Management Systems

TABLE 3. Summary of UVA Irradiation Profiles of CXL Protocols

Study* (yr)	UVA Irradiation Dose and Duration		Total Dose (J/Cm²)	
	ACXL	SCXL	ACXL	SCXL
Hagem et al[6] (2017)	9 mW/cm² for 10 min	3 mW/cm² for 30 min	5.4	5.4
Hashemi et al[7] (2015)	18 mW/cm² for 5 min	3 mW/cm² for 30 min	5.4	5.4
Hashemian et al[8] (2014)	30 mW/cm² for 3 min	3 mW/cm² for 30 min	5.4	5.4
Sadoughi et al[9] (2018)	9 mW/cm² for 10 min	3 mW/cm² for 30 min	5.4	5.4
Sherif[10] (2014)	30 mW/cm² for 4 min and 20 sec	3 mW/cm² for 30 min	7.8	5.4
Shetty et al[11] (2015)	30 mW/cm² for 3 min	3 mW/cm² for 30 min	5.4	5.4

*First author.

TABLE 4. Risk of Bias in Included Studies

Study* (yr)	Random Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Masked Participants and Personnel (Performance Bias)	Masked Outcome Assessment (Detection Bias)	Incomplete Outcome Data (Attrition Bias)	Selective Reporting (Reporting Bias)
Hagem et al[6] (2017)	Unclear	Unclear	High	Unclear	Low	Low
Hashemi et al[7] (2015)	Unclear	Unclear	High	Unclear	Low	Low
Hashemian et al[8] (2014)	High	High	High	Unclear	High	High
Sadoughi et al[9] (2018)	Low	Low	High	Unclear	Low	High
Sherif[10] (2014)	Low	Unclear	High	Unclear	Unclear	High
Shetty et al[11] (2015)	Unclear	Unclear	High	Unclear	Unclear	High

*First author.

Group, Cochrane Collaboration). A *P* value <0.05 was considered statistically significant using a 2-sided test.

RESULTS

Results of the Search

There were 1735 articles relevant to the search terms. After screening titles and abstracts, we excluded 1712 studies. Twenty-three articles[6–11,16–32] were initially considered potentially relevant; however, 17 of these were excluded. The RCT by Kanellopoulos[16] was excluded because it did not include any outcome measure. Fourteen[19–32] of these were also excluded because of non-RCT trials. Ten[17–26] of these were short-term follow-ups (Fig. 1). Finally, the remaining 6 RCTs involving 379 eyes were included in this meta-analysis.[6–11] We obtained

FIGURE 2. Forest plot comparing the change in the topographic result of ACXL and SCXL after the 1-year follow-up. A, Kmax (diopters), (B) CCT (μm). IV, inverse variance; Tau², tau-square statistic; df, degrees of freedom; I², I-square heterogeneity statistic; Z, Z-statistic.

A Best spectacle-corrected visual acuity

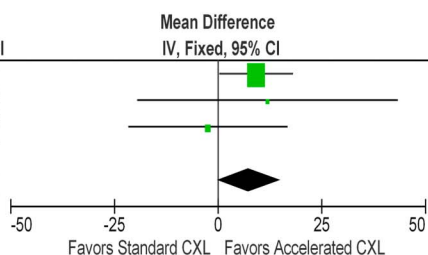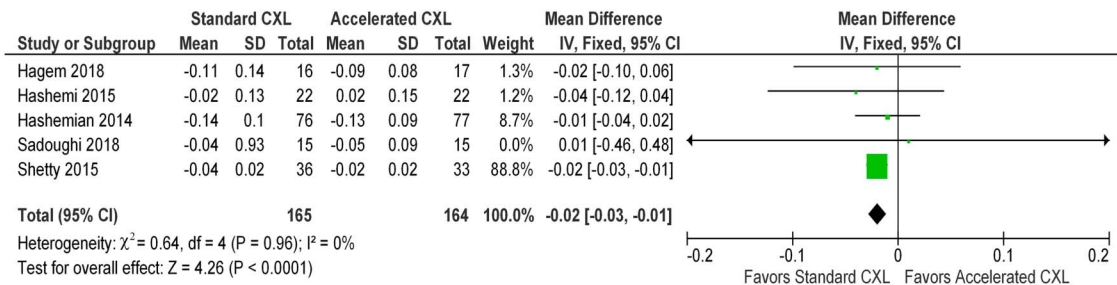| Study or Subgroup	Standard CXL			Accelerated CXL			Weight	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Hagem 2018	-0.11	0.14	16	-0.09	0.08	17	1.3%	-0.02 [-0.10, 0.06]
Hashemi 2015	-0.02	0.13	22	0.02	0.15	22	1.2%	-0.04 [-0.12, 0.04]
Hashemian 2014	-0.14	0.1	76	-0.13	0.09	77	8.7%	-0.01 [-0.04, 0.02]
Sadoughi 2018	-0.04	0.93	15	-0.05	0.09	15	0.0%	0.01 [-0.46, 0.48]
Shetty 2015	-0.04	0.02	36	-0.02	0.02	33	88.8%	-0.02 [-0.03, -0.01]
Total (95% CI)			165			164	100.0%	-0.02 [-0.03, -0.01]

Heterogeneity: χ^2 = 0.64, df = 4 (P = 0.96); I^2 = 0%
Test for overall effect: Z = 4.26 (P < 0.0001)

B Uncorrected distance visual acuity

Study or Subgroup	Standard CXL			Accelerated CXL			Weight	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Hagem 2018	-0.06	0.2	16	-0.16	0.25	17	27.1%	0.10 [-0.05, 0.25]
Hashemi 2015	-0.04	0.15	22	-0.07	0.39	22	24.0%	0.03 [-0.14, 0.20]
Hashemian 2014	-0.22	0.2	76	-0.12	0.2	77	43.4%	-0.10 [-0.16, -0.04]
Sadoughi 2018	-0.04	0.13	15	-0.04	0.93	15	5.6%	0.00 [-0.48, 0.48]
Total (95% CI)			129			131	100.0%	-0.01 [-0.13, 0.11]

Heterogeneity: Tau² = 0.01; χ^2 = 6.76, df = 3 (P = 0.08); I^2 = 56%
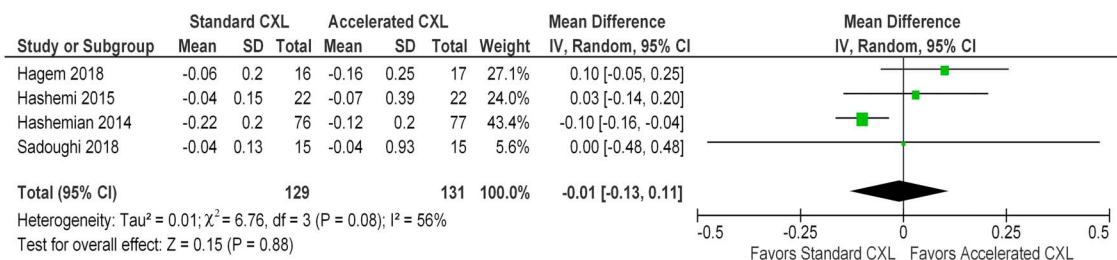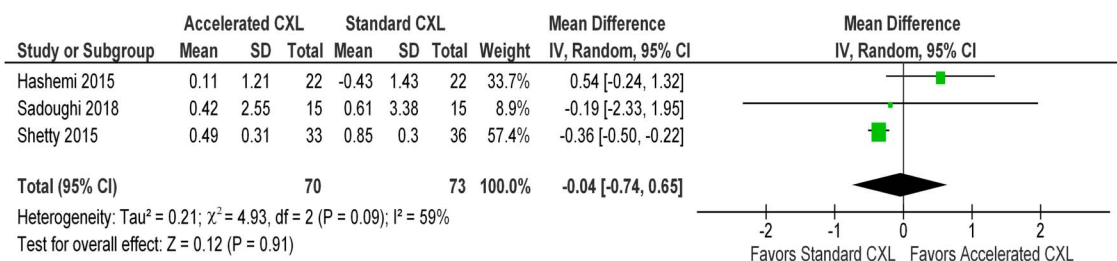Test for overall effect: Z = 0.15 (P = 0.88)

FIGURE 3. Forest plot comparing the change in visual acuity of ACXL and SCXL after the 1-year follow-up. A, BSCVA (LogMAR), (B) uncorrected visual acuity (LogMAR). IV, inverse variance; Tau², tau-square statistic; df, degrees of freedom; I², I-square heterogeneity statistic; Z, Z-statistic.

each parameter as unpublished information from the RCT by Hashemi et al.[7] We did not receive any unpublished data for Sherif,[10] despite inquiries.

Characteristics of the Included Studies

Table 1 shows the main characteristics of the 6 included RCTs. Six studies that reported on 190 eyes in the ACXL group and 189 eyes in the SCXL group

A Manifest refraction spherical equivalent

Study or Subgroup	Accelerated CXL			Standard CXL			Weight	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Hashemi 2015	0.11	1.21	22	-0.43	1.43	22	33.7%	0.54 [-0.24, 1.32]
Sadoughi 2018	0.42	2.55	15	0.61	3.38	15	8.9%	-0.19 [-2.33, 1.95]
Shetty 2015	0.49	0.31	33	0.85	0.3	36	57.4%	-0.36 [-0.50, -0.22]
Total (95% CI)			70			73	100.0%	-0.04 [-0.74, 0.65]

Heterogeneity: Tau² = 0.21; χ^2 = 4.93, df = 2 (P = 0.09); I^2 = 59%
Test for overall effect: Z = 0.12 (P = 0.91)

B Cylindrical refraction

Study or Subgroup	Accelerated CXL			Standard CXL			Weight	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Hashemi 2015	0.15	0.94	22	-0.01	1	22	3.4%	0.16 [-0.41, 0.73]
Hashemian 2014	1.31	0.12	77	1.15	0.47	76	95.5%	0.16 [0.05, 0.27]
Sadoughi 2018	0.27	1.7	15	0.85	1.11	15	1.1%	-0.58 [-1.61, 0.45]
Total (95% CI)			114			113	100.0%	0.15 [0.05, 0.26]

Heterogeneity: χ^2 = 1.97, df = 2 (P = 0.37); I^2 = 0%
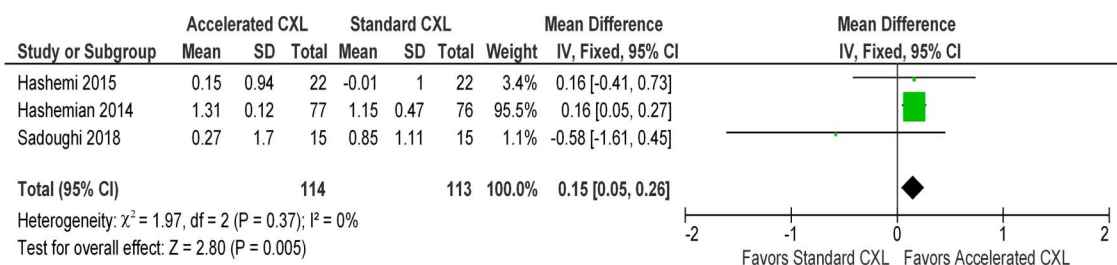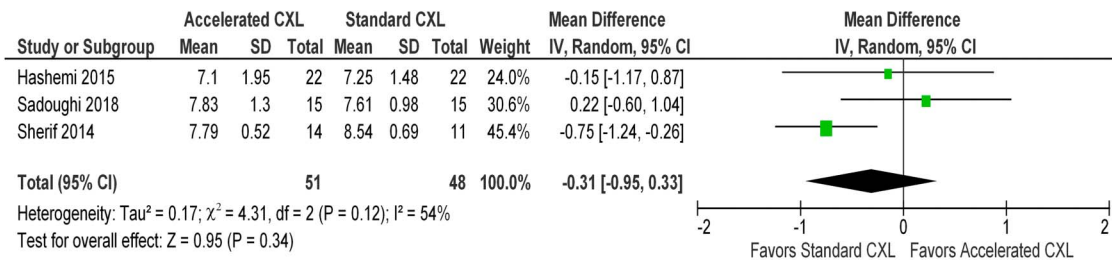Test for overall effect: Z = 2.80 (P = 0.005)

FIGURE 4. Forest plot comparing the change in manifest refraction of ACXL and SCXL after the 1-year follow-up. A, MRSE (diopters), (B) cylindrical refraction (diopters). IV, inverse variance; Tau², tau-square statistic; df, degrees of freedom; I², I-square heterogeneity statistic; Z, Z-statistic.

A Corneal hysteresis

Study or Subgroup	Accelerated CXL Mean	SD	Total	Standard CXL Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Hashemi 2015	7.1	1.95	22	7.25	1.48	22	24.0%	-0.15 [-1.17, 0.87]
Sadoughi 2018	7.83	1.3	15	7.61	0.98	15	30.6%	0.22 [-0.60, 1.04]
Sherif 2014	7.79	0.52	14	8.54	0.69	11	45.4%	-0.75 [-1.24, -0.26]
Total (95% CI)			51			48	100.0%	-0.31 [-0.95, 0.33]

Heterogeneity: Tau² = 0.17; χ² = 4.31, df = 2 (P = 0.12); I² = 54%
Test for overall effect: Z = 0.95 (P = 0.34)

Mean Difference
IV, Random, 95% CI

Favors Standard CXL   Favors Accelerated CXL

B Corneal resistance factor

Study or Subgroup	Accelerated CXL Mean	SD	Total	Standard CXL Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Hashemi 2015	6.39	1.61	22	6.62	1.79	22	30.6%	-0.23 [-1.24, 0.78]
Sadoughi 2018	6.68	1.48	15	6.54	0.93	15	39.6%	0.14 [-0.74, 1.02]
Sherif 2014	7.16	0.88	14	7.68	1.54	11	29.8%	-0.52 [-1.54, 0.50]
Total (95% CI)			51			48	100.0%	-0.17 [-0.73, 0.39]

Heterogeneity: χ² = 0.94, df = 2 (P = 0.63); I² = 0%
Test for overall effect: Z = 0.60 (P = 0.55)

Mean Difference
IV, Fixed, 95% CI

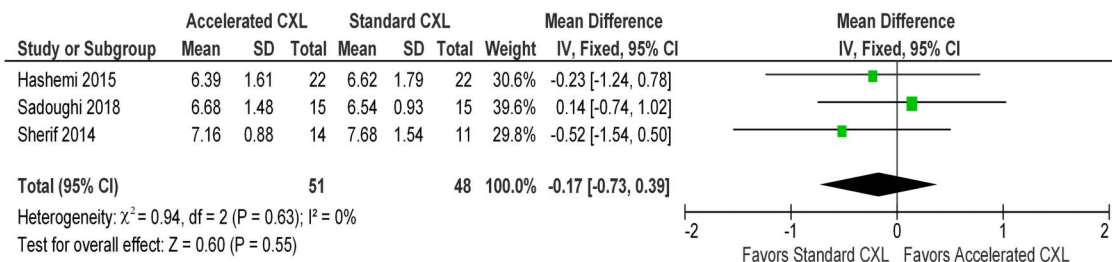Favors Standard CXL   Favors Accelerated CXL

FIGURE 5. Forest plot comparing the change in corneal biomechanics of ACXL and SCXL after the 1-year follow-up. A, CH (mm Hg), (B) CRF (mm Hg). IV, inverse variance; Tau², tau-square statistic; df, degrees of freedom; I², I-square heterogeneity statistic; Z, Z-statistic.

provided data for our meta-analysis. Table 2 and Table 3 show the summary of riboflavin profiles and UVA irradiation of both CXL protocols in the 6 included trials, respectively. ACXL protocols are shown in greater detail, demonstrating a heterogeneous group of 4 different ACXL procedures. As the RCT by Shetty et al had 3 different ACXL protocols, our meta-analysis included the 30 mW/cm² for 3 minutes group because we chose the higher irradiance of UVA.

Quality of the Evidence

The risk of bias in the included studies is summarized in Table 4. No disagreements were observed between the 2 reviewers. All 6 trials were at high risk of bias for blinding study participants and personnel. Masking of the investigators collecting the postoperative data was unclear for all trials.

Topographic Results

Kmax data were reported by all 6 studies that qualified for inclusion in our study. The Kmax forest plots showed no significant difference in the change after the 1-year follow-up between the 2 groups (WMD = −0.45; 95% CI, −1.08–0.17, P = 0.15) (Fig. 2A). Similar results were found when comparing the CCT. There was no difference between the 2 groups after the 1-year follow-up (WMD = 7.41; 95% CI, −0.29–15.11, P = 0.06) (Fig. 2B).

Visual Acuity and Refractive Outcomes

BSCVAs were reported by 5 of the 6 studies that qualified for inclusion in our study. Treated eyes in the SCXL group significantly improved in BSCVA in comparison with the ACXL group after the 1-year follow-up (WMD = −0.02; 95% CI, −0.03 to −0.01; $P < 0.0001$) (Fig. 3A).

Endothelial cell density

Study or Subgroup	Accelerated CXL Mean	SD	Total	Standard CXL Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Hagem 2018	-54	245	17	-112	302	16	5.8%	58.00 [-130.31, 246.31]
Hashemi 2015	-160.1	313.59	22	-192.81	320.69	22	5.9%	32.71 [-154.72, 220.14]
Hashemian 2014	3	58	77	-11	66	76	35.0%	14.00 [-5.70, 33.70]
Sadoughi 2018	1	132	15	-40	101	15	17.9%	41.00 [-43.11, 125.11]
Shetty 2015	-215	37	33	-166	36	36	35.4%	-49.00 [-66.25, -31.75]
Total (95% CI)			164			165	100.0%	0.18 [-49.36, 49.72]

Heterogeneity: Tau² = 1726.18; χ² = 25.28, df = 4 (P < 0.0001); I² = 84%
Test for overall effect: Z = 0.01 (P = 0.99)

Mean Difference
IV, Random, 95% CI
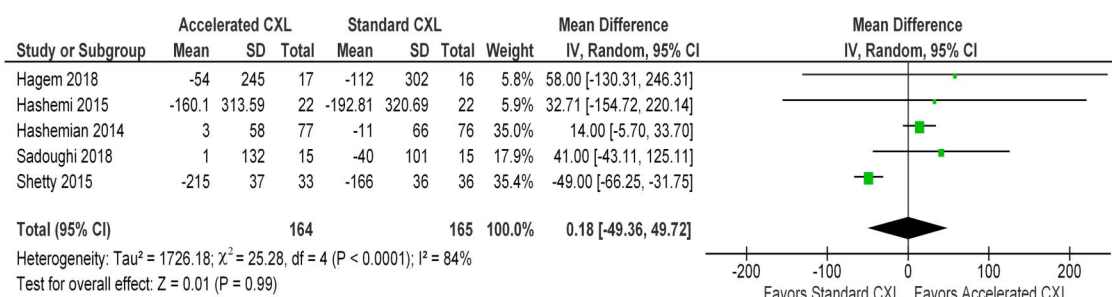
Favors Standard CXL   Favors Accelerated CXL

FIGURE 6. Forest plot comparing the change in endothelial cell density (cells/mm²) of ACXL and SCXL after the 1-year follow-up. IV, inverse variance; Tau², tau-square statistic; df, degrees of freedom; I², I-square heterogeneity statistic; Z, Z-statistic.
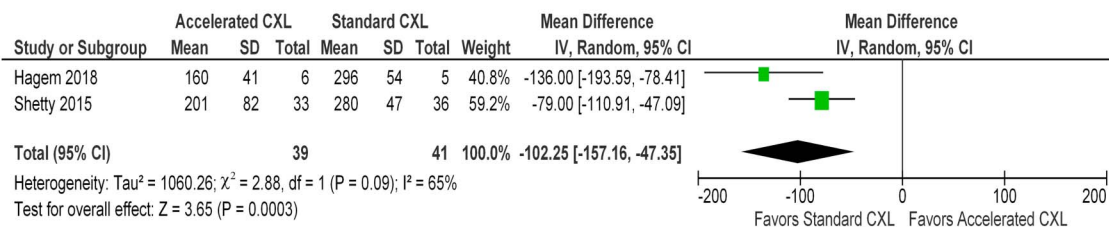
Demarcation line depth

FIGURE 7. Forest plot comparing demarcation line depth (μm) of ACXL and SCXL after the 1-month follow-up. IV, inverse variance; Tau², tau-square statistic; df, degrees of freedom; I², I-square heterogeneity statistic; Z, Z-statistic.

UDVAs were reported by 4 of the 6 studies that qualified for inclusion in our study. The change in UDVA was not significantly different between the 2 groups after the 1-year follow-up (WMD = 0.01; 95% CI, −0.13 to 0.11; P = 0.88) (Fig. 3B).

MRSE and cylindrical refraction data were reported by 3 of the 6 studies that qualified for inclusion in our study. The change in the MRSE did not differ significantly between the 2 groups after the 1-year follow-up (WMD = −0.04; 95% CI, −0.74 to 0.65; P = 0.91) (Fig. 4A). However, ACXL provided a significant improvement of cylindrical refraction after the 1-year follow-up (WMD = 0.15; 95% CI, 0.05–0.26; P = 0.005) (Fig. 4B).

Corneal Biomechanics

Corneal biomechanics data were reported by 3 of the 6 studies that qualified for inclusion in our study. The change in the CH did not significantly differ between the 2 groups after the 1-year follow-up (WMD = −0.31; 95% CI, −0.95 to 0.33; P = 0.34) (Fig. 5A). Similar outcomes were obtained in the change in the CRF (WMD = −0.17; 95% CI, −0.73 to 0.39; P = 0.55) (Fig. 5B).

Safety Outcomes

Corneal endothelial cell density data were reported by 5 of the 6 studies that qualified for inclusion in our study. The change in corneal endothelial cell density was not significantly different statistically in both groups (WMD = 0.18; 95% CI, −49.36 to 49.72; P = 0.99) (Fig. 6). The demarcation line depth was reported by 2 of the 6 studies that qualified for inclusion in our study. Demarcation line depth at 1 month after SCXL was significantly deeper than that after ACXL (WMD = −102.25; 95% CI, −157.16 to −47.35; P = 0.0003) (Fig. 7). Table 5 shows the adverse events in the included studies.

DISCUSSION

In this meta-analysis, we observed changes in topographic, visual, and refractive outcomes after ACXL and compared these same outcome measures with those of a group of patients who had undergone SCXL treatment for progressive keratoconus. To our knowledge, this is the first meta-analysis based on RCTs to compare the efficacy and safety of SCXL and ACXL. The 2 previous meta-analyses included comparative and retrospective studies, which may lack evidence.[33,34] The meta-analysis by Wen et al[33] in 2018 included population-based prospective and retrospective studies. They did not match the follow-up time. Shajari et al[34] included 22 studies with 1158 eyes and reviewed

TABLE 5. Summary of Adverse Events of ACXL and SCXL After the 1-Year Follow-Up

Study* (yr)	No. Adverse Events		Case Presentation
	ACXL	**SCXL**	
Hagem et al[6] (2017)	N/A	N/A	Not reported
Hashemi et al[7] (2015)	N/A	N/A	Not reported
Hashemian et al[8] (2014)	N/A	N/A	Not reported
Sadoughi et al[9] (2018)	N/A	N/A	Not reported
Sherif[10] (2014)	10	11	Ten eyes developed low to moderate haze in ACXL at the 1-mo follow-up. Ten eyes and 1 eye developed low to moderate and severe haze in SCXL at the 1-mo follow-up, respectively.
Shetty et al[11] (2015)	2	0	One eye had delayed epithelial healing (≥5 d). One eye developed progression at the 12-mo follow-up.

*First author.
N/A, not available.

not only RCTs but also prospective nonrandomized studies and retrospective studies. Therefore, based on RCTs, our study could provide a lower level of bias supporting the use of the 2 CXL techniques in the management of keratoconus.

Kmax data were reported by all studies that qualified for inclusion in our study. Kmax is arguably the most popular parameter when considering keratoconus progression although it is not very reproducible. We found equal outcomes for SCXL and ACXL regarding Kmax at 12 months of follow-up. We observed evidence of significant statistical heterogeneity between the 6 studies in Kmax as indicated by an I^2 of 92%. We assume that the heterogeneity may be attributable to the differences in baseline patient characteristics such as the mean baseline Kmax and corneal thickness.

This meta-analysis showed that at the postoperative 12-month visit, the decrease in CCT of the ACXL group did not differ from that of the SCXL group. This change might not be clinically meaningful because the WMD (7.41 μm) was small and is within typical test–retest variability.

Visual acuity and subjective refraction are clinically important because these parameters may reflect patients' satisfaction with the treatment. Comparing the postoperative 12-month follow-up results, SCXL showed a better improvement in BSCVA, whereas UDVA was equally improved with both techniques. Because the WMD (0.02) in BSCVA is less than a line on an eye chart, it is unknown whether this statistically significant difference has an impact on clinical decision-making in the treatment of keratoconus. The study by Shetty et al[11] yielded 88.8% of the weight in the meta-analysis because of a smaller SD than the other studies. In the current study, we observed evidence of no significant statistical heterogeneity in BSCVA as indicated by an I^2 of 0%. For corrected visual acuity, ACXL showed a poor potential for improving vision when compared with regular SCXL.

For MRSE, this meta-analysis found that both SCXL and ACXL appear to achieve the same outcomes. We have found that there is a hyperopic shift in MRSE with both ACXL and SCXL, except for 1 study using the SCXL protocol by Hashemi et al.[7] By contrast, at the 12-month follow-up, improvement in cylindrical refraction was greater with ACXL. The study by Hashemian et al[8] yielded 95.5% of the weight in the meta-analysis because of a larger sample size and smaller SD than the other 2 studies.

CH and CRF are measurements of corneal stiffness and biomechanics. In the current meta-analysis, CH and CRF did not differ between the 2 groups. According to the law of Bunsen–Roscoe, a photochemical reaction is directly proportional to the total energy dose, irrespective of the time over which this dose is delivered.[5] Hammer et al[35] compared the effect of CXL with 3 irradiances on the corneal stiffness in porcine corneas. They observed that corneas treated with 3 mW/cm^2 for 30 minutes had the highest increase in Young's modulus (an indicator of corneal stiffness), followed by 9 mW/cm^2 for 10 minutes. They concluded that the stiffening effect of the CXL decreases with increasing irradiance and decreased treatment times.[35] Their results indicate that the Bunsen–Roscoe law is inapplicable for CXL.

Our meta-analysis showed that at the postoperative 12-month visit, the decrease in endothelial cell density of the ACXL group did not differ from that of the SCXL group, suggesting that neither longer UVA exposition nor higher UVA irradiation intensity induced pronounced endothelial cell damage. Significant heterogeneity between the 5 studies in endothelial cell density was found as indicated by an I^2 of 84%. This heterogeneity may be induced by the variability of measurements.

The demarcation line depth is useful to ascertain the corneal CXL treatment depth. It marks the area of elongated or apoptotic keratocytes due to exposure to riboflavin and UVA light.[36] Overall, both studies included in our meta-analysis reported ACXL to result in a shallower demarcation line depth.[6,11] Possibly because of reduced soak time, the occurrence of demarcation lines was less with ACXL.[6] We assume that SCXL results in higher volume of cross-linked stroma than ACXL and, thus, in higher impact on the eyes with keratoconus.

Because only 2 studies of our meta-analysis described any adverse events, we assume both procedures to be safe in the treatment of progressive keratoconus. The results by Sherif[10] demonstrated that transient haze was noted in 71% of the ACXL cases and in 91% of the SCXL group. This finding is consistent with other previous reports.[37,38]

Regarding CXL procedures, we confirmed various impregnations of riboflavin and UVA irradiation in each trial. In our meta-analysis, the study by Hagem et al[6] used riboflavin with hydroxypropyl methylcellulose in both treatment groups. Hydroxypropyl methylcellulose increases the diffusion rate of fluorescein and facilitates diffusion of riboflavin into the cornea.[39] We found that the irradiation of UVA varied among the included studies in ACXL technique. In THE ACXL procedure, studies conducted by Hagem et al[6] and Sadoughi et al[9] used 9 mW/cm^2 irradiation for 10 minutes, whereas the studies conducted by Hashemian et al[8] and Shetty et al[11] used 30 mW/cm^2 irradiation for 3 minutes and Hashemi et al[7] used 18 mW/cm^2 irradiation for 5 minutes. The total irradiation dose was 5.4 J/cm^2 in their studies. However, Sherif[10] performed 30 mW/cm^2 irradiation for 4 minutes and 20 seconds, which was regarded as equivalent to 7.8 J/cm^2 of the total irradiation dose. Therefore, the intensity and cumulative dose of UVA on the cornea varied in ACXL technique. The heterogeneity between the included trials might be attributed to those discrepancies in ACXL protocols as shown in Tables 2 and 3.

This meta-analysis has at least 3 limitations that should be considered. First, the small number of cases per trial and the total number of cases in this meta-analysis give these analyses low power. It is unknown whether 6 RCTs were adequate for comparing the 2 techniques. Nevertheless, our study provides more powerful evidence than the individual reports alone, and we are unaware of any other similar systematic reviews. It is reported that heterogeneity between small studies is larger than that between larger studies in meta-analysis.[40] A further study with greater numbers of RCT is required to confirm our findings. Second, we could only include data from the published articles, and bias could be introduced if studies with small or different effects exist but have not been published. Third, long-term results with longer follow-ups are necessary and might still reveal differences in

clinical efficacy of the 2 procedures as might be conceivable from the different depth of the demarcation line after ACXL and SCXL.

In summary, overall, ACXL and SCXL seem to provide comparable results and safety profile in halting keratoconus at the 1-year follow-up. Although SCXL showed superiority over ACXL by exhibiting a better corrected visual acuity after the 1-year follow-up, the difference may not be clinically significant.

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