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REVIEW

Safety and efficacy of epithelium removal and transepithelial corneal collagen crosslinking for keratoconus

Z Shalchi[1], X Wang[2] and MA Nanavaty[3]

Abstract

This review aims to assess the efficacy and safety of epithelial removal (ER) and transepithelial (TE) corneal collagen crosslinking (CXL) for the treatment of keratoconus. We used MEDLINE to identify all ER and TE CXL studies on keratoconic eyes ($n \geq 20$, follow-up ≥ 12 months). *Ex vivo* and studies for non-keratoconus indications or in conjunction with other procedures were excluded. Data on uncorrected (UDVA) and corrected (CDVA) distance visual acuity, refractive cylinder, maximum keratometry (Kmax), and adverse events were collected at the latest follow-up and 1 year. Only one randomised controlled trial (RCT) qualified inclusion. Forty-four ER and five TE studies were included. For logMAR UDVA, CDVA, mean spherical equivalent, refractive cylinder and Kmax, at latest follow-up 81, 85, 93, 62, and 93% ER studies *vs* 66.7, 80, 75, 33, and 40% TE studies reported improvement, respectively. Whereas at 1 year, 90, 59, and 91% ER studies *vs* 80, 50, and 25% TE studies reported improvement, respectively. The majority of studies showed reduced pachymetry in both groups. Treatment failure, retreatment rates, and conversion to transplantation were reported to be up to 33, 8.6, and 6.25%, respectively, in ER studies only. Stromal oedema, haze, keratitis, and scarring were only reported in ER studies, whereas endothelial cell counts remained variable in both groups. Both ER and TE studies showed improvement in visual acuity, refractive cylinder but Kmax worsened in most TE studies. Adverse events were reported more with ER studies. This review calls for more high quality ER and TE studies with comparable parameters for further assessment of safety and efficacy.

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Introduction

Keratoconus is the most common corneal ectatic disease. It is a chronic progressive eye condition in which the cornea deforms to a more conical shape causing visual impairment.[1] For the age group 10–44 years, the prevalence of keratoconus is 57 per 100 000 in Caucasians, but over four-fold higher in people originating from the Indian subcontinent. Conventionally spectacles, contact lenses, and corneal transplantation are the mainstay of treatment. The expected lifetime cost of management of keratoconus is $25 168 per patient.[2] The factor that most influences health-care cost is the risk of initial corneal transplantation.

In 2003, Wollensak *et al*[3] published a seminal article on corneal collagen crosslinking (CXL) describing the use of CXL to arrest the progression of keratoconus. They described a case series of patients with progressing keratoconus who had undergone epithelial removal (ER) CXL with riboflavin and ultraviolet A (UVA).[3] In the 10 years since this paper, many investigators have reproduced these findings.[4–8] In brief, this CXL procedure leads to photo-oxidation leading to additional covalent bonds between and within collagen fibrils of the cornea, which increases corneal stiffness, stabilises the keratoconus and, in some cases, improves refractive and topographic features.[9–11] In this regard, riboflavin penetration into the corneal stroma is essential as this molecule absorbs UVA to achieve

[1]Department of Ophthalmology, Queen Mary's Hospital, King's College Hospital NHS Foundation Trust, London, UK

[2]Cochrane Eyes and Vision Group, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

[3]Sussex Eye Hospital, Brighton and Sussex University Hospitals NHS Trust, Brighton, UK

Correspondence:
MA Nanavaty, Sussex Eye Hospital, Brighton and Sussex University Hospitals NHS Trust, Eastern Road, Brighton, Sussex BN6 5BF, UK
Tel: +44 (0)7947166134;
Fax: +44 (0)1342414106;
E-mail: mayank.nanavaty@bsuh.nhs.uk

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crosslinking and shields the underlying endothelium from its harmful effects. CXL is a relatively safe technique; however, complications related to epithelium removal and bandage contact lens use (such as corneal infiltrates,[12–14] corneal melting,[15,16] infection,[17–21] and scar formation[22]) have been reported.

The CXL technique has evolved rapidly over the last decade. There are studies reporting the use of pharmacological agents to loosen the epithelium before instillation of riboflavin,[23–30] iontophoretic experiments to enhance the riboflavin permeability,[31,32] partial disruption of epithelium,[28,33,34] and even CXL with intact epithelium.[27,29,30] As epithelial debridement is reported to be an essential step in the CXL reaction involving UVA and hydrophilic riboflavin,[3] we performed this systematic review to analyse the differences in the safety and efficacy profiles of ER and transepithelial (TE) CXL techniques in the management of progressive keratoconus.

Materials and methods

We conducted a systematic review of studies in which CXL was used to treat progressing keratoconus. We aimed at including randomised controlled trials (RCTs) comparing the techniques ER or TE CXL. In the absence of any RCTs with direct comparison between the techniques, we decided to include RCTs comparing either ER or TE techniques with no treatment, as well as case series in which a minimum of 20 eyes were treated with either ER or TE technique and at least 12-month follow-up. These parameters were chosen to ensure only high quality studies were included. We accepted peer-reviewed articles of human studies only and included articles in any language. Conventional as well as accelerated treatments were included. Articles published online ahead of print were also included. We excluded animal and *ex vivo* studies, as well as studies investigating non-keratoconus corneal ectatic pathologies such as pellucid marginal degeneration and post-refractive surgery ectasia. 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.

We performed a MEDLINE search for articles published to 26 January 2014 without stipulating any conditions on date or language of publication. We used the following search strategy:

1. 'crosslinking' OR 'cross-linking' OR 'crosslinkage' OR 'cross-linkage' OR 'cxl' (48 663 results)
2. 'cornea' OR 'corneal' (84 214 results)
3. 'collagen' AND 'keratoconus' (453 results)

We then combined 1 AND 2 OR 3, producing 773 studies.

We assessed the titles and the abstracts resulting from the searches. We considered full-text copies of all possibly relevant studies to see whether they met the inclusion criteria. We extracted the data using a form developed by us on an Excel 2010 spreadsheet (Microsoft, Redmond, WA, USA) outlining efficacy and safety parameters. One review author entered the data on the spreadsheets. Any disagreements for inclusion or exclusion of the studies were resolved by discussion among us. There were no exclusions based on the randomisation methods in RCTs as long as the trial design was suitable for the conditions and procedures being studied. Publications in a language other than English were translated using Google Translate (Mountain View, CA, USA). Authors forming research teams were grouped together in tables to identify redundant articles. Redundant articles, in which identical data are published in a different language, were treated such that only one article was tabulated.

We predicted studies to have varying follow-up in each arm and so decided to present the data at their latest follow-up visit and the data on change in logMAR CDVA, change in refractive cylinder, and change in Kmax at 1 year for better comparison between ER and TE groups.

Statistical analysis was performed with SPSS Statistics 17.0 (IBM Corporation, Armonk, NY, USA) and utilised medians rather than means to overcome methodological problems involving redundant studies. All visual acuity data were converted to logMAR if presented in Snellen or decimal formats.

Results

We identified 45 ER[4–11,35–71] and 6 TE[27–30,36,72] studies satisfying our entry criteria (Tables 1 and 2; Figure 1). Of the included studies, only one was an RCT comparing ER and TE crosslinking.[36] The study designs of all included studies are described in Tables 1 and 2. The TE studies were all published in English, but five of the ER studies[56,59,73–75] were published in German. Three[73–75] of these were excluded as they were redundant articles presenting data identical to an included English article. A further redundant article in English was excluded,[76] as was a large study that failed to present the sample size at follow-up.[77] The analysis includes a total of 1990 eyes in the ER group and 215 eyes in the TE group. Excluded studies[3,51,73,74,76–94] are listed in Table 3, together with the reason for their exclusion. As there was only one RCT comparing ER *vs* TE, meta-analysis was not possible.

Crosslinking efficacy

Tables 1 and 2 present the crosslinking efficacy data for ER and TE studies, respectively. Articles are listed by

Table 1 Systematic review of efficacy of epithelial removal (ER) corneal collagen crosslinking

Lead Author	*Year*	*Study design*	*Eyes at latest follow-up (n)*	*Age (years) (mean ± SD) (range)*	*Latest follow-up (month) (mean ± SD) (Range)*	*Mean UDVA change (logMAR)*	*Mean CDVA change (logMAR)*	*MSE change (D)*	*Cylinder change (D)*	*K max change (D)*	*Pachymetry change (microns)*	*Failure (%)*	*Retreatment (%)*	*DALK (%)*
Agrawal V[9]	2009	CS[a]	37	16.9 ± 6.35 (12–39)	12	—	−0.09	—	−1.20	−2.47	—	8.1	—	—
Arora R[70]	2013	CS	30	16 (12–18)	12	−0.18[b]	−0.12[b]	—	—	0.4[b]	−66.46[b]	—	—	—
Asri D[69]	2011	CS	64	24.12 ± 7.58	12	0.00	−0.01	—	+0.07	−0.49	−11	9.8	—	6.25
Caporossi A[4]	2010	CS	44	10–40	48	−0.37	−0.14	+2.15	−0.55	−2.26	+0.6	—	—	—
Caporossi A[68]	2012	CS	77	10–18	36	−0.15	−0.09	—	—	−0.72	—	—	—	—
Ghanem R[67]	2013	CS	42	22.4 ± 5.6 (14–34)	24	−0.24	−0.12	0.39	0.46	−0.9	—	—	—	—
Greenstein S[66]	2010	CS	31	32.3 ± 10.3 (15–52)	12	—	—	—	—	—	—		—	—
Greenstein S[71]	2011	CS	54	No data	12	—	—	—	—	—	−12.1	—	—	—
Greenstein S[7]	2012	CS	64	No data	12	—	—	—	—	—	—	—	—	—
Greenstein S[65]	2012	CS	46	No data	12	—	—	—	—	—	—	—	—	—
Greenstein S[64]	2012	CS	66	No data	12	−0.08	−0.10	—	—	−1.60	—	—	—	—
Grewal D[63]	2009	CS	102	25.6 ± 4.5 (18–31)	12	—	−0.02	+1.43	−0.17	—	−3.7	—	—	—
Guber I[62]	2013	CS	33	26.36 ± 7.62 (13–40)	12	—	−0.04	—	0.73	−0.16	−11.33	—	—	—
Hashemi H[61]	2013	CS	40	22.45 ± 5.48 (16–35)	60	−0.02	−0.12	0.41	0.65	−0.24	2	—	—	—
Hassan Z[60]	2013	CS	38	29.36 ± 9.7 (16–42)	36	−0.17	−0.09		−0.55	—	—	—	—	—
Hersh P[10]	2011	CS	49	No data	12	−0.05	−0.14	+0.85	−0.08	−2.00	—	—	—	—
Hoyer A[59]	2009	CS	35	27.92 ± 17.15	36	—	−0.14	—	−1.64	−2.73	—	8.6	8.6	—
Ivarson A[58]	2013	CS	28	12–38	22 ± 8 (10–43)	—	−0.07	—	—	1.1	−0.52	—	—	—
Jordan C[57]	2013	CS	38	21.9 ± 6.0	12	—	—	—	—	—	—	—	—	—
Kampik D[56]	2011	CS	46	33.5 ± 9.9	24	—	−0.05	—	—	−1.23	−21.6	—	—	—
Kontadakis G[55]	2013	CS	24	25 ± 4.7 (20–36)	24	—	—	—	—	—	—	—	—	—
Kranitz K[11]	2012	CS	25	29.92	12	−0.13	−0.09	+1.32	−0.49	−1.68	−31	—	—	—
Kymionis G[54]	2010	CS	55	24.4 ± 4.1 (18–36)	12	—	—	—	—	—	—	—	—	—
Lamy R[53]	2013	CS	68	24.4 (18–33)	24	—	−0.16	—	—	−0.99	—			
Legare M[52]	2013	CS	39	26.8 ± 10.3 (15–56)	15.8	0.18 (12 months)[c]	0 (at 24 months)[c]	1.55 (at 24 months)[c]	1.30 (at 24 months)[c]	—	−15.58 (at 24 months)	—	—	—
Magli A[51]	2013	Comparative CS (ER *vs* TE)	23	14.75 ± 2.1 (12–18)	12	−0.01	0.01	—	0.11	−1.14	−1.98	—	—	—
Mastropasqua L[36]	2013	RCT (ER *vs* TE)	20	23 ± 2.5 (16–23)	12	—	—	—	—		37	—	—	—
Mazzotta C[49]	2008	CS	44	No data	36	—	—	—	—	—	—	—	—	—
Mazzotta C[50]	2012	CS	44	No data	12	−0.19	−0.11	—	—	−0.30	+14.5	—	—	—
Mencucci R[48]	2012	CS	54	26.2 ± 7	12	—	—	—	—	—	+1	—	—	—
O'Brart D[8]	2011	RCT (ER *vs* observation)	24	29.6 (21–42)	18	−0.08	+0.06	+0.82	−0.5	−0.62	+3.4	—	—	—
O'Brart D[47]	2013	CS	30	26.3 (12–40)	53.3 (48 to 72)	0.03	0.05	0.82	0.28	—	3			
Poli M[46]	2013	CS	45	26 ± 7.3 (15–46)	21.7 ± 6.14	−0.2 (at 12 months)	−0.23 (at 36 months)	—	—	−0.14 (at 2 years)	−0.24	—	—	—
Raiskup-Wolf F[44]	2008	CS	33	30.04 ± 10.46	36	—	−0.15	—	−1.45	−2.57	—	33.3	5.4	—
Raiskup F[45]	2009	CS	163	31.53 ± 8.58	12	—	0.05	—	—	−0.75	—	—	—	—
Raiskup F[5]	2011	CS	32	27.4 ± 9.4	12	—	−0.04	—	—	−0.7	—	—	—	—
Rechichi M[43]	2013	Comparative CS (Fellow eye with no treatment as control)	28	28.8 (18–41 years)	12	0.25	−0.05	0.96	0.99	—	−15	—	—	—

Table 1 (Continued)

Lead Author	*Year*	*Study design*	*Eyes at latest follow-up (n)*	*Age (years) (mean ± SD) (range)*	*Latest follow-up (month) (mean ± SD) (Range)*	*Mean UDVA change (logMAR)*	*Mean CDVA change (logMAR)*	*MSE change (D)*	*Cylinder change (D)*	*K max change (D)*	*Pachymetry change (microns)*	*Failure (%)*	*Retreatment (%)*	*DALK (%)*
Sloot F[42]	2013	CS	53[b]	21.5 (12–49)	12	—	−0.13[b]	—	—	−1.5[b]	−9[b]	9% (5 of 53)[b]		
Spoerl E[41]	2011	CS	50	29.4 ± 9.3 (16–45)	12	—	—	—	—	—	—	—	—	—
Toprak I[40]	2013	CS	59	28.7 ± 9.0	12	—	−0.13	—	—	−0.84	—	—	—	—
Vinciguerra P[37]	2009	CS	28	24–52	24	−0.24	−0.15	+0.81	−0.34	−1.35	−8.1	—	—	—
Vinciguerra P[38]	2009	CS	28	24–52	12	−0.20	−0.14	+0.41	−0.26	−6.16	−14.9	—	—	—
Vinciguerra P[39]	2010	CS	24	15–36	12				—	−0.73	+11.0	—	—	—
Vinciguerra P[6]	2012	CS	40	14.2 ± 1.7 (9–18)	24	−0.21	−0.19	+1.57	−1.31	−1.27	+14.0	—	—	—
Wittig-Silva C[35]	2014	RCT (ER *vs* observation)	46	25.6 ± 6.2	36	−0.15	−0.09	−0.61	−0.90	−1.03	5.86			

Abbreviations: CDVA, Corrected Distance Visual Acuity; DALK, deep anterior lamellar keratoplasty; ER, epithelial removal; K, keratometry; MSE, mean spherical equivalent; RCT, randomised controlled trial; SD, standard deviation; TE, transepithelial removal; UDVA, uncorrected visual acuity.
[a]Case series.
[b]Mean of all eyes in all groups.
[c]Extrapolated from graphical data.

Figure 1 Study flow diagram.

alphabetical order as per first author and those by the same author listed together to highlight the possibility of data redundancy. ER articles were published from 2008 onwards, while TE studies were published from 2010 onwards. ER studies in general included a larger number of eyes and had longer follow-up (range: 12–72 months) *vs* TE studies (range: 12–24 months). The included RCT[36] reported only pachymetry out of the included study parameters.

Uncorrected distance visual acuity At the last follow-up visit 21 ER studies[4,6,8,10,11,35,37,38,43,46,47,50–52,60,61,64,67–70] out of 45 studies reported uncorrected distance visual acuity (UDVA) (Table 1).
Seventeen[4,6,8,10,11,35,37,38,46,50,51,60,61,64,67,68,70] of these 21 ER studies (81% of studies) showed a median improvement of −0.17 logMAR UDVA (range: −0.37 to −0.01 logMAR), 3 studies[43,47,52] showed median worsening of 0.18 logMAR UDVA (range: 0.03–0.25 logMAR) and 1 study[69] showed no change in UDVA.

Three TE studies[28,29,72] out of six reported UDVA (Table 2). Only two studies[28,29] out of these three (66.7% of studies) showed a median improvement of −0.27 logMAR (range −0.23 to −0.30) and one study[76] showed worsening by 0.08 logMAR.

Corrected distance visual acuity Thirty-three ER studies[4–11,35,37,38,40,42–47,50–53,56,58–63,67–70] out of 45 reported corrected distance visual acuity (CDVA) (Table 1). Twenty-eight[4–7,9–11,35,37,38,40,42–44,46,50,53,56,58–63,67–70] these 33 studies (85% of studies) showed a median improvement of −0.09 logMAR (range: −0.23 to −0.01 logMAR), 4 studies[8,45,47,51] showed median worsening of 0.05

Table 2 Systematic review of efficacy of transepithelial (TE) corneal collagen crosslinking

Lead Author	*Year*	*Study design*	*Eyes at latest follow-up (n)*	*Age (years) (mean ± SD) (Range)*	*Latest follow-up (months)*	*UIDVA change (logMAR)*	*CDVA change (logMAR)*	*MSE change (D)*	*Cylinder change (D)*	*K max change (D)*	*Pachymetry change (microns)*	*Failure*	*Retreatment (%)*	*DALK (%)*
Caporossi A[72]	2013	CS	26	22 (11–26 years)	24	0.08	0	0	0	1.55	−32	—	—	—
Filippello M[29]	2012	CS	20	27 (12–42 years)	18	−0.23	−0.11	—	—	−1.17	−4.00	0	—	—
Koppen C[27]	2012	CS	37	24.02 ± 7.29 (12–46 years)	12	—	−0.04	+0.21	+0.04	1.33	−8.06	—	—	—
Leccisotti A[30]	2010	CS	51	26.9 ± 6.3 (18–39 years)	12	—	−0.04	+0.36		0.51	—	—	—	—
Mastropasqua L[36]	2013	RCT (ER *vs* TE)	20	23 ± 2.5 (16–23 years)	12	—	—	—	—	—	0.51	—	—	—
Stojanovic A[28]	2012	CS	61	32 ± 10 (15–52 years)	12	−0.30	−0.12	+0.74	−1.15	−0.57	+9.00	—	—	—

Abbreviations: CDVA, corrected distance visual acuity; CS, case series; DALK, deep anterior lamellar keratoplasty; ER, epithelial removal; K, keratometry; MSE, mean spherical equivalent; RCT, randomised controlled trial; SD, standard deviation; TR, transepithelial removal; UDVA, uncorrected visual acuity.

logMAR (range: 0.01–0.05) and 1 study[52] did not show any change in CDVA.

Similarly, five TE studies[27,28,30,75,76] out of six reported CDVA (Table 2). Four TE studies[27–30] of these five (80% of the studies) showed a median improvement of −0.08 logMAR (range: −0.12 to −0.04 logMAR) and one study[72] showed no change in CDVA.

Mean myopic spherical equivalent Fourteen ER studies[4,6,8,10,11,35,37,38,43,47,52,61,63,67] of 45 reported spherical equivalent (Table 1). Thirteen studies[4,6,8,10,11,37,38,43,47,52,61,63,67] of these fourteen (93% of studies) showed a reduction in mean myopic spherical equivalent (median 0.85D, range 0.39–2.15D) and one study[35] showed a −0.61D worsening.

Four TE studies[27,28,30,72] out of six reported spherical equivalent (Table 2). Three[27,28,30] of these four studies (75% of studies) showed a reduction in mean myopic spherical equivalent (median 0.36D, range 0.21 to +0.74D) and one study[72] showed no change.

Refractive astigmatism Twenty-one ER studies[4,6,8–11,35,37,38,43,44,47,51,52,59–63,67,69] out of forty-five reported refractive astigmatism (Table 1). Thirteen[4,6,8–11,35,37,38,44,59,60,63] of these twenty-one ER studies (62% of studies) showed a reduction in refractive astigmatism (median −0.55D, range −1.64 to −0.08D) and eight ER studies[43,47,51,52,61,62,67,69] showed increased astigmatism (median 0.56D, range: 0.07–1.30 D).

Only three TE studies[27,28,72] reported data on refractive astigmatism (Table 2). One study each reported reduced (−1.15D) (33% of the studies),[28] increased (0.04D),[27] and no change[72] in refractive astigmatism post-crosslinking.

Maximum keratometry Twenty-nine ER studies[4–11,35,37–40,42,44–46,50,51,53,56,58,59,61,62,67–70] out of forty-five showed reported data on maximum keratometry (Kmax) (Table 1). Twenty-seven studies[5–7,9–11,35–39,41,43–45,47,50,52,54,57,60,62,63,69–72] of these twenty-nine (93% of the studies) showed reduction (median −1.01D, range −0.14 to −6.16D) and two[59,73] out of twenty-nine studies showed an increase in Kmax (median 0.75D, range 0.4–1.1D).

Five TE studies[27–30,72] out of six reported data on Kmax (Table 2). Two[27,30,72] of these five TE studies (40% of the studies) reported reduction in Kmax (median −0.87D, range −1.17 to −0.57D) and three TE studies[28,29] reported an increase in Kmax (median 1.33D, range 0.51–1.55D).

Pachymetry In the included RCT,[36] corneal thickness increased in both TE and ER at 12 months but more after TE crosslinking (Tables 1 and 2). Twenty-four ER studies[4,6,8,11,35,37–39,42,43,46–48,50–52,56,58,61–63,69–71] out of

Table 3 Prominent corneal collagen crosslinking trials not included in systematic review and reason for exclusion

Lead Author	*Year*	*Reason for exclusion*
Caporossi A[93]	2006	Case series too small
Caporossi A[77]	2011	Case series size at follow-up not stated
Coskunseven E[92]	2009	Case series too small
Croxatto J[90]	2010	Case series too small
Derakhshan A[89]	2011	Follow-up too short
Doors M[88]	2009	Case series too small
Goldich Y[87]	2012	Case series too small
Greenstein S[94]	2013	No separate data for keratoconus presented
Greenstein S[76]	2011	Redundant article
Hafezi F[86]	2009	Case series too small
Holopainen J[85]	2011	Follow-up too short
Hoyer A[73]	2010	Redundant article
Jankov M[84]	2008	Follow-up too short
Koller T[82]	2011	Not exclusively keratoconus
Koller T[83]	2009	Not exclusively keratoconus
Kymionis G[81]	2012	Case series too small
Magli A (Transepithelial arm)[51]	2013	Case series too small
Mazzotta C[80]	2007	Follow-up too short
Raiskup F[74]	2010	Redundant article
Salman A[91]	2013	Follow-up too short
Tu K[79]	2009	Case series too small
Wittig-Silva C[78]	2008	Case series too small
Wollensak G[3]	2003	Case series too small

forty-five reported data on pachymetry (Table 1). Fifteen[11,37,38,42,43,46,51,52,56,58,62,63,69–71] of these twenty-five ER studies (60% of the studies) reported reduction in pachymetry (median change: $-11.33\,\mu$m, range -66.46 to $-0.24\,\mu$m) and 9 ER studies[4,6,8,35,39,47,48,50,61] showed an increase in pachymetry (median change: $4.63\,\mu$m, range 0.6–37 μm).

Four TE studies[27–29,72] out of six reported data on pachymetry (Table 2). Three[27,29,72] of these (75% of the studies) showed reduction in pachymetry (median change: $-8.06\,\mu$m, range -32 to $-0.4\,\mu$m) and one study[28] showed increase in pachymetry ($9\,\mu$m).

Treatment failure Only five ER studies[9,42,44,59,69] out of six reported treatment failure (median percentage of eye: 8.6%; range: 8.1–33.3%) (Table 1), and where this was done, the definitions were not consistent. Only one[29] (out of six) TE studies reported 0% treatment failure (Table 2).

Retreatment rates Only two ER studies reported retreatment rates of 5.4%[44] and 8.6%[59] (Table 1), whereas no TE study reported any retreatment rates (Table 2).

Conversion to deep anterior lamellar keratoplasty Only one ER study reported 6.25%[69] of patients progressing to deep anterior lamellar keratoplasty (DALK) and no TE study reported any conversion to DALK (Tables 1 and 2).

Crosslinking safety

Tables 4 and 5 present the safety data for the ER and TE studies, respectively. Overall, the ER studies reported more adverse events than TE studies, although reporting was haphazard in almost all studies. The included RCT[36] reported outcomes on stromal oedema and change in endothelial counts only.

Failure to re-epithelise Nine ER studies[5,8,38,50–52,54,56,59] reported data on this and showed no reports of failure to re-epithelise (Table 4). By definition, TE studies did not show any problems in this category (Table 5).

Stromal oedema The included RCT[36] reported 1.68% stromal oedema with ER compared with 0% with TE crosslinking at 12 months.

Six ER studies[4,5,51,68–70] reported data on stromal oedema with the median percentage of 17.5% (range: 0–70%) after treatment (Table 4) whereas no TE study (except the included RCT[36]) reported on stromal oedema (Table 5).

Sterile infiltrates Only six TE studies[5,35,42,59,67,70] reported data on sterile infiltrate with median percentage of eyes of 2.5% (range: 2–4%). Hoyer *et al*[59] noted sterile infiltrates which resolved on treatment with topical steroids (no percentage of eyes mentioned) (Table 4). None of the TE studies reported sterile infiltrate (Table 5).

Golden striae Golden striae were reported by two ER studies from the same group in 43.5%[38] to 62.0%[6] of eyes (Table 4). There were no eyes with this complication in the TE group (Table 5).

Stromal haze Twelve[4–6,8,38,45,49,56,66,68–70] of forty-five ER studies reported data on stromal haze as a phenomenon that was responsive to topical steroid treatment (median percentage of eyes: 9.8%; range: 0–100%). One[66] of these twelve ER studies reported haze in their own grading system and hence it was not possible to include their stromal haze data in the calculations (Table 4).

Four TE studies[27–30] reported data on stromal haze (median percentage of eyes: 0%; range: 0–100%) (Table 5).

Corneal scar formation Only 5 TE studies[5,8,62,68,69] out of 45 reported corneal scar formation (median percentage eyes: 0%; range: 0–6%) (Table 4).

Four TE studies[27–30] reported data 0% scar formation (Table 5).

Incidence of microbial keratitis Seven ER studies[5,8,42,46,52,59,68] out of forty-five reported data on microbial keratitis (median percentage of eyes: 0%; range: 0–3%). One[46] of these seven ER studies did not report microbial keratitis data specifically in eyes with keratoconus and hence the keratitis data from this study were not considered for calculation (Table 4).

Four TE studies[27–30] out of six reported data 0% incidence of microbial keratitis (Table 5).

Loss of CDVA Six ER studies[9,47,56,58,62,69] of forty-five reported data on loss of CDVA (median percentage of eyes: 12.4%; range: 0–27%) (Table 4).

Whereas only two TE studies[27,30] out of six reported data (0% eyes with loss of CDVA) (Table 5).

Changes in endothelial cell count The included RCT[36] did not show significant difference in endothelial cell counts after ER or TE crosslinking.

Thirteen ER studies[4,6,35,37–39,43,46,50,51,56,69,70] of forty-five reported on endothelial cell counts. Two[46,50] of these fourteen ER studies reported no change in endothelial cell counts, whereas nine ER studies[4,6,35,37–39,43,51,69] reported reduction in endothelial cell counts (median: -24 cells/mm^2; range: -131 to -12 cells/mm^2) and two[56,70] of these fourteen ER studies reported a small increase in endothelial cell counts (median: 29.5 cells/mm^2; range: 4–55 cells/mm^2) (Table 4).

Three TE studies[28–30] out of six reported data on endothelial cell counts. One[36] of these four TE studies reported no change, two[28,29] reported reduction in endothelial cell counts (median: -82 cells/mm^2; range: -130 to -34 cells/mm^2) and one[30] reported an increase in cell counts (27 cells/mm^2) (Table 5).

Comparison of mean change in logMAR CDVA, refractive cylinder, and Kmax at 1 year

Thirty-three ER studies[4–7,9–11,35,37–40,42–45,47,48,50–54,56,59–63,67–70] out of forty-five and five TE studies[27–30,72] out of six reported one or more of these parameters at 1 year (Table 6).

LogMAR CDVA at 1 year Thirty ER studies[4–7,9–11,35,37,38,40,42–45,47,50–53,56,59–63,67–70] out of these thirty-three reported this parameter. Twenty-seven[4–7,9–11,35,37,38,40,42–44,50,52,53,56,59–63,67–70] out of these thirty ER studies (90% of the studies) showed a median improvement of -0.09 logMAR CDVA (range: -0.58 to -0.01 logMAR) and the remaining three ER studies[45,47,51] showed a median worsening of 0.05 logMAR CDVA (range, 0.01–0.05 logMAR) (Table 6).

Four TE studies[27–30] out of five (80% of the studies) reported a median improvement of -0.07 logMAR CDVA (range: -0.12 to -0.04 logMAR) at 1 year (Table 6).

Refractive cylinder at 1 year Seventeen ER studies[4,9–11,35,37,44,47,59,60] out of thirty-three reported this parameter at 1 year. Ten ER studies[4,9–11,35,37,43,44,47,51,52,59–62,67,69] out of these 17 (59% of the studies) reported a median reduction of -0.65D refractive cylinder (range: -1.02 to -0.02D) whereas remaining seven studies[43,51,52,61,62,67,69] reported a median worsening of refractive cylinder (median: 0.25D; range: 0.07–0.99D) (Table 6).

Only two TE studies out of five reported data on refractive cylinder: one[28] reported improvement of -1.15D (50% of the studies) and other[27] reported worsening by 0.04D at 1 year (Table 6).

Kmax at 1 year Twenty-two ER studies[5,7,9–11,35,37,39,40,42,44,45,50,51,53,59,61,62,67–70] out of thirty-three at 1 year reported this parameter. Twenty[5,7,9–11,35,37,39,40,42,44,45,50,51,59,61,62,67–69] of these twenty-two ER studies (91% of the studies) showed a median reduction in Kmax by -0.82D (range: -6.26 to -0.16D) and only two studies[53,70] showed a median worsening of Kmax by 0.48D (range: 0.4–0.56D) (Table 6).

Four TE studies[27,28,30,72] of five reported data on this parameter at 1 year and three[27,30,72] of these (75% of the studies) showed a median worsening of 0.60D Kmax (range: 0.51–1.33D) and one study[28] showed a reduction of -0.57D in Kmax at 1 year.

Table 4 Systematic review of safety of epithelium removal (ER) corneal collagen crosslinking

Lead Author	*Year*	*Eyes at latest follow-up (n)*	*Latest follow-up (months)*	*Failure to re-epithelialise (%)*	*Stromal oedema (%)*	*Sterile infiltrate (%)*	*Golden striae (%)*	*Haze (%)*	*Scar (%)*	*Infection (%)*	*Loss of CDVA (%)*	*ECC change (/mm²)*
Agrawal V[9]	2009	37	12	—	—	—	—	—	—	—	18.9 (7 of 37 eyes at 1 year)	—
Arora R[70]	2013	30	12	—	27 (8 of 30 eyes)[a]	3 (1 of 30 eyes)[a]	—	3 (1 of 30 eyes)	—	—	—	4 (at 1 year)
Asri D[69]	2011	64	12	—	1.56 (1 of 64 eyes at 1 month)	—	—	4.8% (5 of 104 eyes at 3 months) 1.9% (2 of 104 eyes at 6 months) 1.5% (1 of 64 eyes at 1 year)	0.96% (1 of 104 eyes at 1 month)	—	7.8% (5 of 64 eyes at 1 year)	−110 (at 1 year)
Caporossi A[4]	2010	44	48	—	70 (31 of 44 eyes within 6 weeks)	—	—	9.8% (4 of 44 eyes within 3 months)	—	—		−19 (at 2 years) (mean loss of 2% per year)
Caporossi A[68]	2012	152	36	—	55	—	—	9.80	0	0	—	—
Ghanem R[67]	2013	42	24	—	—	2% (1 of 42 eyes)	—	—	—	—	—	—
Greenstein S[66]	2010	31	12	—	—	—	—	Unable due to author's own haze grading system	—	—	—	—
Greenstein S[71]	2011	54	12	—	—	—	—	—	—	—	—	—
Greenstein S[7]	2012	64	12	—	—	—	—	—	—	—	—	—
Greenstein S[65]	2012	46	12	—	—	—	—	—	—	—	—	—
Greenstein S[64]	2012	66	12	—	—	—	—	—	—	—	—	—
Grewal D[63]	2009	102	12	—	—	—	—	—	—	—	—	—
Guber I[62]	2013	33	12	—	—	—	—	—	6 (2 of 33 eyes)	—	6 (2 of 33 eyes)	—
Hashemi H[61]	2013	40	60	—	—	—	—	—	—	—	—	—
Hassan Z[60]	2013	38	36	—	—	—	—	—	—	—	—	—
Hersh P[10]	2011	49	12	—	—	—	—	—	—	—	—	—
Hoyer A[59]	2009	35	36	0	—	No data but seen in few eyes		—	—	3% (1 of 35eyes)	—	—
Ivarson A[58]	2013	28	22 ± 8 (10–43)	—	—	—	—	—	—	—	0	—
Jordan C[57]	2013	38	12	—	—	—	—	—	—	—	—	—
Kampik D[56]	2011	46	24	0% (46 eyes at 1 week)	—	—	—	100% (46 eyes within 3 months)	—	—	27% (12 of 46 eyes at 2 years)	55 (at 2 years)
Kontadakis G[55]	2013	24	24	—	—	—	—	—	—	—	—	—
Kranitz K[11]	2012	25	12	—	—	—	—	—	—	—	—	—
Kymionis G[54]	2010	55	12	0 (0 of 55 eyes)	—	—	—	—	—	—	—	—
Lamy R[53]	2013	68	24	—	—	—	—	—	—	—	—	—
Legare M[52]	2013	39	24	0	—	—	—	—	—	0	—	—
Magli A[51]	2013	23	12	0	8 (2 of 23)	—	—	—	—	—	—	−24 (at 1 year)

Table 4 (Continued)

Lead Author	*Year*	*Eyes at latest follow-up (n)*	*Latest follow-up (months)*	*Failure to re-epithelialise (%)*	*Stromal oedema (%)*	*Sterile infiltrate (%)*	*Golden striae (%)*	*Haze (%)*	*Scar (%)*	*Infection (%)*	*Loss of CDVA (%)*	*ECC change (/mm²)*
Mastropasqua L[36]	2013	20	12	—	1.68	—	—	—	—	—	—	No significant change-
Mazzotta C[49]	2008	44	36	—	—	—	—	11.4% (5 out of 44 eyes. Four within first 3 months and one after 6 months)	—	—	—	—
Mazzotta C[50]	2012	44	12	0 (0 of 44 eyes)	—	—	—	—	—	—	—	0 (at 12 months)
Mencucci R[48]	2012	54	12	—	—	—	—	—	—	—	—	—
O'Brart D[8]	2011	24	18	0% (24 eyes at 1 week)	—	—	—	100% (24 eyes within 6 months)	0% (at 18 months)	0% (at 18 months)	—	—
O'Brart D[47]	2013	30	48–72	—	—	—	—	—	—	—	17% (5 of 29 eyes)	
Poli M[46]	2013	45	21.7 ± 6.14	—	—	—	—	—	—	Specific data in keratoconic eyes not reported (2 eyes in entire study had microabcess)	—	No significant change
Raiskup-Wolf F[44]	2008	33	36	—	—	—	—	—	—	—	—	—
Raiskup F[45]	2009	163	12	—	—	—	—	8.6% (14 of 163 eyes at 1 year)	—	—	—	—
Raiskup F[5]	2011	32	12	0	0	0	—	0	0	0	—	—
Rechichi M[43]	2013	28	12	—	—	—	—	—	—	—	—	− 15 (at 1 year)
Sloot F[42]	2013	53[a]	21.5 (12–49)	—	—	2% (1 of 53)[a]	—	—	—	2% (1 of 53)[a]	—	—
Spoerl E[41]	2011	50	12	—	—	—	—	—	—	—	—	—
Toprak I[40]	2013	59	12	—	—	—	—	—	—	—	—	—
Vinciguerra P[37]	2009	28	24	0	—	—	—		—	—	—	− 53 (at 1 year) − 131 (at 2years)
Vinciguerra P[38]	2009	28	12	—	—	—	43.5% (12 of 28 eyes at 1 year)	12.7 (4 of 28 eyes at 1 year)	—	—	—	− 53 (at 1 year)
Vinciguerra P[39]	2010	24	12	—	—	—	—	—	—	—	—	− 22 (at 1 year)
Vinciguerra P[6]	2012	40	24	—	—	—	62.0 (25 of 40 eyes)	6.9 (3 of 40 eyes)	—	—	—	− 32 (at 1 year) − 12 (at 2 years)
Wittig-Silva C[35]	2014	50	36	—	—	4% (2 of 46 eyes)	—	—	—	—	—	28 (at 1 year) 13 (at 2 years) − 35 (at 3 years)

Abbreviations: CDVA, corrected distance visual acuity; ECC, endothelial cell count.
— indicates data not provided in published article.
[a]Mean of all eyes in all groups.

Table 5 Systematic review of safety of transepithelial (TE) corneal collagen crosslinking

Lead Author	*Year*	*Eyes at latest follow-up (n)*	*Latest follow-up (months)*	*Failure to re-epithelialise (%)*	*Stromal oedema (%)*	*Sterile infiltrate (%)*	*Golden striae (%)*	*Haze (%)*	*Scar (%)*	*Infection (%)*	*Loss of CDVA (%)*	*ECC change (/mm²)*
Caporossi A[72]	2013	26	24	n/a	—	—	—	—	—	—	—	—
Filippello M[29]	2012	20	18	n/a	—	—	—	0 (0 of 20 eyes)	0 (0 of 20 eyes)	0 (0 of 20 eyes)	—	−34 (at 1.5 years)
Koppen C[27]	2012	37	12	n/a	—	—	—	0 (0 of 37 eyes)	0 (0 of 37 eyes)	0 (0 of 37 eyes)	0 (0 of 37 eyes)	—
Leccisotti A[30]	2010	51	12	n/a	—	—	—	4 (2 eyes 51)	0 (0 of 51 eyes)	0 (0 of 51 eyes)	0 (0 of 51 eyes)	+27 (at 1 year)
Mastropasqua L[36]	2013	20	12	—	0	—	—	—	—	—	—	No significant change
Stojanovic A[28]	2012	61	12	n/a	—	—	—	0 (0 of 61 eyes)	0 (0 of 61 eyes)	0 (0 of 61 eyes)	—	−130 (at 1 year)

Abbreviations: CDVA, corrected distance visual acuity; ECC, endothelial cell count.
— indicates data not provided in published article.

Discussion

Our systematic review highlights that although there is a paucity of TE studies in comparison with existing ER studies and follow-up remains relatively short in TE trials, the majority of eyes have improved visual acuity and reduced myopic spherical equivalent after ER or TE CXL. Nevertheless, although TE CXL has fewer complications, it is less effective, particularly in stabilising or improving Kmax.

The main conclusions of this review are listed below:

1. Majority of the studies in ER (17 out of 21 studies = 81%) and TE (2 out of 3 studies = 66.7%) groups at the latest follow-up showed improvement in logMAR UDVA (Tables 1 and 2).
2. Majority of the studies in ER (28 out of 33 studies = 85%) and TE (4 out of 5 studies = 80%) groups showed improvement in logMAR CDVA (Tables 1 and 2). This was similar at 1-year follow-up in ER (27 out of 30 studies = 90%) and TE (4 out of 5 studies = 80%) (Table 6).
3. Majority of the studies in ER (13 out of 14 studies = 93%) and TE (3 out of 4 studies = 75%) groups showed reduction in mean myopic spherical equivalent (Tables 1 and 2).
4. Over half of the studies in ER group (13 out of 21 studies = 62%) and a third of the studies in TE group (1 out of 3 studies = 33%) showed reduction in refractive cylinder (Tables 1 and 2). This was similar at 1-year follow-up in ER (10 out of 17 studies = 59%) and TE (1 out of 2 studies = 50%)(Table 6).
5. Majority of the studies in ER (27 out of 29 studies = 93%) showed reduction in Kmax whereas with TE, majority (3 out of 5 studies = 75%) showed worsening in Kmax (Tables 1 and 2). This was similar at 1-year follow-up in ER (20 out of 22 studies = 91%) showing improvement in Kmax and TE (3 out of 4 studies = 75%) studies showing worsening (Table 6).
6. Equal proportion of studies in ER (15 out of 25 studies = 60%) and TE (3 out of 5 studies = 60%) showed reduced pachymetry following CXL (Tables 1 and 2).
7. Treatment failure (although this was defined variably in many studies), retreatment rates, and conversion to DALK were reported to be up to 33, 8.6, and 6.25%, respectively, in studies of ER group only (Tables 1 and 2). This may be due to significantly less number of TE studies reported until January 2014.
8. Stromal oedema, haze, scarring, and risk of microbial keratitis were only seen in ER studies. Endothelial cell counts were variable in both ER and TE groups (Tables 4 and 5).

Table 6 Systematic review of efficacy of epithelial removal (ER) and transepithelial corneal collagen crosslinking: change in CDVA, cylinder and maximum keratomtery at 12 months

		LogMAR CDVA change at 1 year	*Cylinder (diopters) change at 1 year*	*Maximum keratometry (Kmax) change at 1 year*
Epithelium removal technique				
Agrawal V[9]	2009	−0.09	−1.2	−2.47
Arora R[70]	2013	−0.12	—	0.4
Asri D[69]	2011	−0.01	0.07	−0.49
Caporossi A[4]	2010	−0.30	−0.52	—
Caporossi A[68]	2012	−0.09	—	−0.72
Ghanem R[67]	2013	−0.12	0.42	−0.8
Greenstein S[64]	2012	−0.10	—	−1.60
Grewal D[63]	2009	−0.02	—	—
Guber I[62]	2013	−0.04	0.73	−0.16
Hassan Z[60]	2013	−0.04	−0.78	—
Hashemi H[61]	2013	−0.11	0.25	−0.16
Hersh P[10]	2011	−0.14	−0.08	−2.00
Hoyer A[59]	2009	−0.07	−0.90	−1.35
Kampik D[56]	2011	−0.09	—	—
Kranitz K[11]	2012	−0.09	−0.49	−1.68
Kymionis G[54]	2012	—	—	—
Lamy[53]	2013	−0.14	—	0.56
Legare[52]	2013	−0.02	0.2	—
Magli[51]	2013	0.01	0.11	−1.14
Mazzotta C[50]	2012	−0.11	—	−0.30
Mencucci R[48]	2012	—	—	—
O'Brart D[47]	2013	0.05	−0.02	—
Raiskup-Wolf F[44]	2008	−0.08	−0.93	−1.43
Raiskup F[45]	2009	0.05	—	−0.75
Raiskup F[5]	2011	−0.04	—	−0.7
Rechichi M[43]	2013	−0.05	0.99	—
Sloot F[42]	2013	−0.13	—	−1.5
Toprak I[40]	2013	−0.13	—	−0.84
Vinciguerra P[37]	2009	−0.14	—	—
Vinciguerra P[38]	2009	−0.14	−0.26	−6.26
Vinciguerra P[39]	2010	—	—	−0.73
Vinciguerra P[6]	2012	−0.58	—	—
Wittig-Silva C[35]	2014	−0.09	−0.85	−0.72
Transepithelial				
Caporossi A[72]	2013	—	—	0.60
Filippello M[29]	2012	−0.09	—	—
Koppen C[27]	2012	−0.04	0.04	1.33
Leccisotti A[30]	2010	−0.04	—	0.51
Stojanovic A[28]	2012	−0.12	−1.15	−0.57

— indicates data not provided in published article.

Since the publication of the first seminal study 10 years ago,[3] CXL has revolutionised the treatment of keratoconus. Although many established therapies, such as rigid gas-permeable contact lenses and corneal transplantation, are effective in improving patient vision, no known therapy other than CXL is successful in halting the progression of disease. The work of the Dresden group revolutionised the field by showing that CXL could not only do this, but in some cases also leads to an improvement in many anatomical and refractive indices in keratoconus. However, despite the value of CXL in halting the progression of keratoconus, several investigators have raised concerns about its significant vision-threatening complications. These include corneal infiltrates,[12–14] melting,[15,16] infection,[17–21] and scar formation,[22] all of which may lead to a reduction in CDVA.

Encouraged by the efficacy of ER CXL, some investigators concluded that CXL would prove significantly safer if the epithelium could be left *in situ*.[95] This raised the problem of how riboflavin, a hydrophilic molecule, could be transported across the hydrophobic corneal epithelium. Several methods have now been shown to be helpful in achieving this, including the use of benzalkonium chloride[23,24,96] EDTA,[25] gentamicin,[26] iontophoresis,[31,32] as well as minimal trauma (through epithelial poke marks) to the epithelium.[33]

Our review sought to answer the question of whether the new TE form of CXL is as effective as the standard ER form, and whether it is truly safer. This review certainly shows TE crosslinking lacks many of the significant complications of ER CXL. Despite lower numbers of TE studies published to date, the efficacy of ER and TE techniques appears to be comparable for most parameters with majority of the studies showing improvement of UDVA, CDVA, myopic spherical equivalent, and refractive astigmatism (Tables 1 and 2). However, whereas 93.1% (27 of 29 studies) showed Kmax to be stable or better with ER CXL, this figure was only 40.0% (2 of 5 studies) for TE CXL. This is of concern as Kmax is arguably the most important parameter when considering keratoconus progression, and hence, treatment failure. The greater efficacy of ER than TE CXL may be related to the deeper demarcation line observed after treatment.[29]

The TE CXL studies considered here had different surgical methodologies, with altogether disparate treatment effects. Most TE studies were able to achieve results that are comparable to ER studies.[27–30,36,72] Filippello *et al*[29] used EDTA and trometamol as epithelial permeation enhancers, as well as a silicone corneal ring to help create a pool of enhanced riboflavin solution 30 min before UVA irradiation. This resulted in improvement of UDVA and CDVA by −0.23 and −0.11, respectively, and mean Kmax reduction of 1.17D. Moreover, Stojanovic *et al*[28] used riboflavin solution without dextran, together with BAK, gentamicin and proparacaine as well as a polyvinyl alcohol sponge to increase epithelial permeability and riboflavin uptake. This led to significant improvements in UDVA and CDVA, as well as reduced mean myopic MSE by 0.74D and reduced mean Kmax by 0.57D.

This review has important strengths and limitations. It is, to our knowledge, the first systematic review of the safety and efficacy of CXL for the treatment of progressing keratoconus, and as it included both ER and TE treatments, helps summarise the published evidence to date. Our analysis had clear inclusion and exclusion criteria to collect specific and relevant data, and included trials published in languages other than English to ensure no relevant data were omitted. The analysis, however, is limited by the quality of reporting of study outcomes, which was inconsistent in many cases as is evident from the many gaps in our efficacy and safety tables (Tables 1, 2, 4, and 5). Furthermore, our work is completely reliant on the publication of conducted studies, and is therefore subjected to publication bias. Our review also makes significant assumptions where it compares studies with unequal follow-up durations, particularly between ER and TE CXL. However to address this, we identified three important parameters (change in CDVA, refractive astigmatism, and Kmax) and compared 12-month data of ER and TE CXL studies where these data were available (Table 6). The paucity of TE studies included also has significant potential for type II (beta) error, which is to overlook significant treatment effect due to a small sample size. Moreover, it was hard to analyse the data between the two groups categorising it as paediatric and adult. As evident from Tables 1 and 2, there were few studies where paediatric patients were involved and few of these had a heterogeneous age group consisting of paediatric and adult population.

A systematic review-based upon meta-analysis using the Cochrane Collaboration's trusted and well-established methods would provide the ideal way to compare the efficacy and safety of ER and TE CXL. Unfortunately, this was not possible due to the paucity of RCTs comparing the two treatment modalities head-to-head. Furthermore, although two RCTs exist that compare ER CXL with observation alone,[8,35] there are currently no RCTs comparing TE CXL with observation. As a result of this, as well as the different study sizes and follow-up intervals, we employed medians and ranges to give the best statistically sound method of comparing treatment effects.

Our systematic review has important implications for research. We have highlighted the paucity of high-quality TE studies in the literature, as well as their relatively short follow-up. Techniques for TE CXL clearly need further modification and standardisation comparable to ER studies. We have demonstrated the inconsistency between CXL trials in reporting of important measures of efficacy and safety, and we recommend that all future trials report findings in terms of the headings used to assess the efficacy and safety in this review to aid standardisation. The variations in the treatment protocols of TE studies are envisaged to complicate the safety and efficacy data further as many researchers have now started questioning the standard Dresden protocol for TE and ER CXL and are employing permutation and combinations of settings to attain equivalent outcomes (an example of this is the recent introduction of rapid crosslinking protocols[97,98]).

In summary, our study has significant implications for current clinical practice. It has shown that although further research is required in the field of ER and TE CXL to assess the efficacy and safety. A multitude of studies already testify to the efficacy of ER CXL in halting the progression of keratoconus, and recommending it as the standard of care. Additionally, our work has systematically brought together safety data on the treatment, such that patients may be counselled about complication rates to make informed decisions about their care.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

ZS contributed to data collection, analysis and manuscript drafting. XW contributed to statistical analysis and interpretation. MN contributed to concept and design, analysis, manuscript editing, drafting, and critical review.

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