Clinical science

Repeat corneal collagen cross-linking after failure of primary cross-linking in keratoconus

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ABSTRACT

Background Primary corneal collagen cross-linking (CXL) stabilises 96% of progressive keratoconus. There is limited evidence for the treatment of choice when this fails. We present 10 years of repeat CXL and compare with our published experience of primary CXL to (1) identify perioperative risk factors of primary CXL failure and (2) demonstrate the safety and efficacy of repeat CXL.

Methods Patients undergoing repeat accelerated epithelium-off CXL at St James's University Hospital, Leeds, UK January 2012–August 2022 were identified through electronic patient record, and compared with a previously published cohort of primary CXL patients at the same site.

Results Twenty-one eyes underwent repeat CXL. The mean interval between primary and repeat CXL treatments was 47.1 months (SD 22.5). Twenty (95%) eyes stabilised after repeat CXL at a mean follow-up of 29.9 months. These cases were compared with 151 cases of primary CXL from our previous study. Patients failing primary CXL were significantly younger (21.3 years (SD 7.0) vs 26.7 years (SD 6.5), p=0.0008). Repeat CXL and primary CXL induced a similar amount of flattening of Kmax (−1.2 D (SD 3.9) vs −0.7 D (SD 4.4), p=0.22). A small, but clinically insignificant, improvement in best-corrected visual acuity was found in the repeat CXL group (−0.04 (SD 0.17) vs −0.05 (SD 0.13), p=0.04). No complications of repeat CXL were noted.

Conclusion Younger age may be associated with failure of primary CXL. Repeat CXL is an effective and safe treatment for progressive keratoconus despite primary CXL.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Primary corneal collagen cross-linking (CXL) stabilises the majority of progressive keratoconus. There is limited evidence for the treatment of choice when this fails, but case reports and small case series suggest repeat CXL may be effective.

WHAT THIS STUDY ADDS

⇒ Repeat CXL is an effective and safe treatment for progressive keratoconus despite primary CXL. Younger age and lack of corneal flattening postoperatively may be associated with failure of primary CXL.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Repeat CXL should be considered for cases of progressive keratoconus where primary CXL has failed. Postoperative monitoring of topography is essential to predicting stabilisation.

INTRODUCTION

Corneal collagen cross-linking (CXL) is a procedure aimed at preventing the progression of corneal ectasia, most commonly keratoconus. In the most widely approved method (known as 'epi-off'), the corneal epithelium is removed, riboflavin applied and the cornea then irradiated with ultraviolet A light (UV-A). Corneal stiffness is hence increased by the induction of covalent cross-links between the collagen fibrils in the corneal stroma, preventing further deformation and resultant irregular astigmatism. Alternatively, some choose to apply riboflavin directly to intact epithelium, known as 'epi-on'. As for the irradiation step, two sequences also exist: the original Dresden protocol (3 mW/cm for 30 min, dose 5.4 J/cm) and accelerated protocols (with several variations giving the same overall dose of irradiation).[1] Epi-off accelerated protocol is successful in halting keratoconus progression in more than 90% of eyes and has an excellent safety profile.[2–5] As a result, CXL is first-line treatment for progressive keratoconus. However, no consensus exists on the optimal management for those eyes that progress after initial successful primary CXL. Risk factors for CXL failure are reported to include a high preoperative maximal keratometry (Kmax), paediatric patients and the presence of atopy.[6] Keratoplasty may be considered as the next treatment of choice, especially if best-corrected visual acuity (BCVA) becomes unsatisfactory.[7]

Experimental studies of repeat CXL showed limited benefit. In a biomechanical study of 30 human corneas ex vivo, no significant difference in corneal stiffness was found between those that underwent CXL once, twice and thrice.[8] This may have been due to biomechanical tissue changes occurring postmortem. However, a subsequent study of 12 mouse corneas in vivo also demonstrated no difference in stiffness after repeat CXL.[9] In this study, repeat CXL was performed 3 days after the first treatment, which may have been too soon to allow stabilisation. Individual case reports of repeat CXL in clinical practice were published thereafter,

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in which the interval between treatments was measured in months to years.[10 11]

Small case series of repeat CXL have since been published, the largest comprising 12 eyes with keratoconus, in which Kmax stabilised and/or regressed in 10 (83%) following repeated CXL 7–42 months after initial treatment.[12] Follow-up was 6–58 months and no complications were observed. Furthermore, within a randomised controlled trial of epi-off versus epi-on CXL, five eyes underwent repeated CXL for keratoconus, 10–33 months after initial treatment.[13] One year after, four eyes showed decreased Kmax and the last eye was lost to follow-up.

Last, a case series of seven eyes, four of which had intracorneal ring segments (ICRS) implanted, showed all of them remained stable 1 year after repeat CXL with no complications.[14] In this study, six eyes had keratoconus and one had post-LASIK ectasia. Repeat CXL for post-LASIK ectasia had previously been shown to stabilise keratometry and BCVA in a single case report, 1 year after retreatment.[15]

In our tertiary centre, repeat CXL is the standard treatment for corneal ectasia that has progressed despite primary CXL in patients with corneal thickness >400 µm. We therefore present the largest study to date of eyes that have undergone repeat CXL for keratoconus over a 10-year period, to evaluate the subsequent changes in visual acuity and keratometry and compare them to our previously published cohort of keratoconus receiving primary CXL.[4]

We aim to:

- Define tomographical characteristics associated with failure of primary CXL.
- Investigate if repeat CXL is effective and safe.
- Compare the efficacy and safety between primary CXL and repeat CXL.

METHODS

For this retrospective observational study, we searched the operative records for episodes of repeat CXL at St. James's University Hospital, Leeds, from January 2012 to August 2022.

Surgical technique

All patients underwent repeat epithelium off accelerated CXL with UV-A Irradiation time 4 min; total energy—7.2 J/cm^2; UV power—30 mW/cm^2; treatment mode—pulse mode (1 s off and 1 s on) (Avedro KXL System, Avedro). The central 8 mm of corneal epithelium was debrided with 18% alcohol applied for 30 s. In some cases, ICRSs were implanted either before or after primary CXL. In such cases, the KeraRing (Haag-Streit) was sized and implanted according to manufacturer's recommendations.

Clinical assessment

We reviewed the medical records and the Galilei tomography (G4 Galilei tomographer, Zeimer) for each patient. Along with standard tomography parameters (K1, K2, Kmax, pachymetric thinnest value), BCVA after subjective refraction in units of logMAR (Logarithm of the Minimum Angle of Resolution) was recorded prior to first CXL, as close to 3 months after first CXL as possible, prior to second CXL, and as close to 3 months after second CXL as possible. Tomography at the latest follow-up was then recorded. Failure of primary CXL was defined as either of the following over 12 months, with baseline tomography taken at 3 months post primary CXL:

- >1.5 D increase in Kmax.
- >1.5 D increase in K2 (or Steep K).
- >1.5 D increase in refractive astigmatism.
- > Two-line loss of BCVA.

A similar tomographic definition for progression was shown by Brunner *et al* to give a 95% confidence of true keratoconus progression when accounting for technician interobserver variability.[16] We compared our repeat CXL data with the previously published Leeds experience of 186 patients who underwent the same protocol for CXL.[4] Of these, requisite tomography data were available for 151, so the present analysis was therefore restricted to these cases.

Descriptive statistics were then calculated in STATA V.17.0 (StataCorp). The Shapiro-Wilk test was used to determine normality, along with histogram inspection. The t-test was then used for parametric data, and the Mann-Whitney U test for non-parametric data. χ^2 tests were used to compare categorical data. Testing was two tailed and effects were considered significant if a $p<0.05$ was observed.

Table 1 Comparing baseline demographics for the present cohort of eyes that underwent repeated corneal collagen cross-linking (CXL) with those of the previously published leeds experience of primary CXL.

		Repeat CXL (present study, n=21)	Single CXL (previous study, n=151)	P value
Right laterality (n, %)		9 (43)	94 (50)	0.39
Mean K1 in D (mean, SD)		45.9 (4.3)	46.4 (4.3)	0.52
Mean K2 in D (mean, SD)		50.5 (6.4)	50.2 (5.1)	0.90
Mean Kmax in D (mean, SD)		57.9 (6.1)	55.3 (6.4)	0.20
Thinnest pachymetry in µm (mean, SD)		459.1 (40.9)	454.1 (41.0)	0.71
Age in years (mean, SD)		21.3 (7.0)	26.7 (6.5)	0.0008*
Male sex (n, %)		15 (71)	126 (68)	0.73
Ethnicity (n, %)	Caucasian	7 (33)	89 (48)	0.45
	South Asian	10 (48)	70 (38)	
	Other or non-declared	4 (18)	27 (15)	

Asterisks represent the attainment of statistical significance. SD: standard deviation.

RESULTS

Demographics

Out of the 1535 eyes that underwent CXL during the study period, 21 (1.37%) eyes of 20 consecutive patients underwent repeat CXL for progressive keratoconus, 6 eyes of whom belonged to females (29%). Twelve of the cases were left eyes (57%). Ethnicity was recorded as 'white' in 7 (33%), 'Pakistani' in 6 (29%), 'Indian' in 3 (14%), 'black' in 2 (10%) and 'Bangladeshi' in 1 (5%). The remaining cases were either listed as 'other' or 'not given'. Eye rubbing was documented after primary CXL in four cases (19%). Demographics are detailed in table 1.

Failed primary CXL

Seven eyes had ICRS implanted prior to first CXL (33%). Prior to primary CXL, the mean Kmax was 57.9 D (SD 6.1), the mean K1 was 45.9 D (SD 4.3) and the mean thinnest pachymetry was 459.1 µm (SD 40.9). Mean baseline BCVA was 0.22 (SD 0.20). The mean age at primary CXL was 21.3 years (SD 7.0). Three months after the primary CXL, mean BCVA increased to 0.16 (SD 0.16). The mean Kmax at this stage was 57.3 D (SD 5.5), the mean K1 was 45.8 D (SD 3.8) and mean thinnest pachymetry was 451.1 µm (SD 35.2). One eye had ICRS implanted in the interval between CXL treatments (5%).

Preoperative tomography was missing for 7 eyes (33%) and preoperative BCVA for 8 (38%). Three months after first CXL,

Table 2 Summary descriptive statistics for tomography and best-corrected visual acuity (BCVA) of 21 eyes that underwent repeat corneal collagen cross-linking (CXL) within a period of 10 years

	Pre first CXL	Post first CXL (3 months)	Change from first CXL	Pre second CXL	Post second CXL (3 months)	Post second CXL (latest)	Change from second CXL
K1 (D)	45.9 (4.3)	45.8 (3.8)	−0.3 (2.7)	48.2 (5.4)	47.9 (5.1)	46.9 (5.1)	−1.3 (1.9)
K2 (D)	50.5 (6.4)	50.3 (4.0)	−0.5 (3.5)	52.6 (5.9)	52.3 (5.4)	51.3 (5.9)	−1.3 (2.1)
Kmax (D)	57.9 (6.1)	57.3 (5.5)	−0.01 (2.4)	60.7 (5.7)	60.4 (4.5)	59.5 (5.4)	−1.2 (3.9)
Thinnest pachymetry (µm)	459.1 (40.9)	451.1 (35.2)	−5.3 (23.3)	436.2 (44.3)	426.8 (35.8)	413.6 (50.6)	−22.6 (47.4)
BCVA (logMAR)	0.22 (0.20)	0.16 (0.16)	−0.09 (0.19)	0.32 (0.17)	0.25 (0.22)	N/A	−0.04 (0.17)

All figures represent means, followed by SD in parentheses. All figures are rounded to 1 decimal place except for BCVA, which is rounded to 2. Changes (the grey columns) are calculated from pre-CXL and post-CXL.
N/A, not available.

tomography was missing for 3 eyes (14%) and BCVA for 2 (10%).

Repeat CXL

The mean interval between CXL treatments was 47.1 months (SD 22.5). Prior to repeat CXL, the mean Kmax was 60.7 D (SD 5.7), mean K1 48.2 D (SD 5.4), mean thinnest pachymetry 436.2 µm (SD 44.3) and mean BCVA 0.32 (SD 0.17). This represents a mean difference in Kmax of 3.4 D from 3 months after primary CXL. The mean age at second CXL was 25.2 years (SD 7.5). Three months after the repeated CXL, the mean Kmax was 60.4 D (SD 4.5), mean K1 47.9 D (SD 5.1), mean thinnest pachymetry 426.8 µm (SD 35.8) and mean BCVA 0.25 (SD 0.22). The changes in these parameters 3 months after repeat CXL were compared with the changes 3 months after primary CXL, but no differences were found to be statistically significant (K1 p=0.31, K2 p=0.29, Kmax p=0.20, thinnest pachymetry p=0.06, BCVA p=0.70). Tomographic statistics are detailed in table 2.

The mean follow-up period from repeat CXL was 29.9 months (SD 20.5). At latest follow-up tomography, the mean Kmax was 59.5D (SD 5.4). Twenty of 21 eyes have remained clinically stable (95%).

No immediate postoperative complications were observed secondary to primary or repeat CXL in this cohort. Corneal haze was not objectively measured, but no clinically significant corneal haze was noted in any of the patients that had undergone repeat CXL. After primary CXL, no patients had a recorded decrease in BCVA. After repeat CXL, one patient lost more than two Snellen lines of BCVA (5%). This patient's BCVA remained unchanged 3 months after first CXL (0.48 logMAR) but dropped from 0.6 to 0.9 units of logMAR after second CXL due to refractive changes despite successful treatment. Her baseline Kmax was 75.67 D which decreased to 71.83 D 3 months after first CXL. Thirty months after first CXL, Kmax had increased to 76.36 D. Second CXL was therefore performed resulting in a Kmax of 71.32 D at latest follow-up 16 months later. Her keratoconus, therefore, remains stable. No corneal haze or corneal scarring was noted.

Prior to repeat CXL, tomography was available for all eyes but BCVA was missing for 7 (33%). Three months after second CXL, tomography was missing for 2 (10%) and BCVA for 4 (19%). At latest follow-up, tomography was available for all patients.

Comparison of failed primary CXL with previous Leeds study

We then compared the results of the present study with the previously published Leeds experience of CXL (tomography available n=151). We first compared baseline demographics to ensure a valid comparison (table 1). The mean age was significantly younger in those that failed primary CXL (21.3 years (SD 7.0) vs 26.7 years (SD 6.5), p=0.0008). Kmax was, however, not significantly different in the two cohorts (57.9 D (SD 6.1) vs 55.3 D (6.4), p=0.20). The sex ratio was similar between studies, with 32% female in the previous study compared with the present 29%. As expected, this difference was not statistically significant (p=0.73). Ethnicity proportions appeared slightly different, with 48% Caucasian and 38% South Asian in the previous study (ie, the present study comprised a higher proportion of South Asians by 10%). However, this difference was not statistically significant (p=0.45). Last, the difference in eye laterality percentages between the two studies was also not significant (p=0.39). Whether eye rubbing was documented for each patient was not recorded in the previous study so a comparison could not be made here. We therefore demonstrated the two study groups to be similar in all but age and so resumed our comparison.

No episodes of repeat CXL were included in the previous study. The first CXL treatments of six eyes in the present study were included in the cohort of the previous study due to overlapping time periods, but these eyes had not yet progressed to requiring repeat CXL at the prescribed time of follow-up. These cases were, therefore, not removed from the present analysis to avoid introducing retrospective bias.

We compared the results of primary CXL in the present study with primary CXL of the previous study. We first calculated the difference in tomographic parameters and BCVA from before to after first CXL, then compared these changes to the same changes in the previous study. No statistically significant differences were found for tomography (K1 p=0.64, K2 p=0.42, Kmax p=0.40, thinnest pachymetry p=0.90). However, the difference between the mean reductions in BCVA was found to be statistically significant (−0.09 (SD 0.19) vs −0.05 (SD 0.13), p=0.005).

Comparison of repeat CXL with previous Leeds study

Baseline characteristics are described above.

Repeated CXL stabilised 95% of eyes compared with 96% of eyes stabilising after primary CXL in the previous study. The postoperative tomography and BCVA were then compared with preoperative measurements for both studies. These differences in parameters, for example, postoperative reduction in Kmax, had already been calculated for the previously published data and are listed below. For the present study, we calculated the change in these parameters from the latest follow-up to the measurements recorded prior to second CXL, then compared these changes to those calculated in the previous study. This allowed us to compare the effects of a successful second CXL with the previously published effects of successful first CXL.

First, the difference between the mean age at second CXL in the present study compared with the mean age in the previous study was not statistically significant (25.2 years (SD 7.5) vs 26.7 years (SD 6.5), p=0.57).

Second, no significant difference was found between repeat CXL and primary CXL in the previous Leeds study for the mean reduction in Kmax (−1.2 D (SD 3.9) vs −0.7 D (SD 4.4), p=0.22). However, a significantly larger flattening affect was found for K2 in repeat CXL (−1.3 D (SD 1.9) vs −0.4 D (SD 2.1), p=0.03). A larger reduction in thinnest pachymetry was also observed in repeat CXL (−22.6 µm (SD 47.4) vs −7.7 µm (SD 24.7), p=0.00001). A statistically significant, but likely visually insignificant, smaller improvement in BCVA was found in the repeat CXL group (−0.04 (SD 0.17) vs −0.05 (SD 0.13), p=0.04). For a summary of these descriptive statistics, see online supplemental table 1.

DISCUSSION

In Leeds, Caucasians make up 77% of the population and those of South Asian origin make up 7.7%.[17] Despite this 10-fold discrepancy, South Asians were overrepresented in our repeat CXL patients at 48%. This proportion was similar to that of our cohort of successful first CXL cases from our previous study, that is, 38%. Our study is not the first to show this ethnic group is more likely to develop keratoconus.[18] For example, a Leicester study in 2000 showed those of Asian origin had a significantly higher incidence and severity of keratoconus than Caucasians.[19] In contrast, we did not find a statistically significant difference between our repeat CXL patients and successful primary CXL patients.

In the present study, we found that repeat CXL stabilised keratoconus in 95% of 22 eyes, which, to our knowledge, is the largest study of repeat CXL to date. Our results were consistent with the previous small case series and single case reports, which also demonstrated high rates of stabilisation.[10–15]

Another strength of our study is the ability to compare our experience of repeat CXL with the previously published experience of primary CXL in Leeds, which can thereby serve as a baseline. In the previous study, primary CXL stabilised keratoconus in 96% of 186 patients.[4] No complications were observed, as in the present study. Our patients who required second CXL in the present study were significantly younger at first CXL than those who required only one CXL treatment in the previous study, in concordance with previous findings.[6]

In the previous Leeds study (tomography available for 151 patients), mean Kmax decreased to 54.7 D at 12 months following primary CXL, a reduction of 0.7 D from the preoperative mean. This is the same reduction as was found in the Cochrane review of CXL efficacy.[20] In the present study, a mean reduction in Kmax of 1.2 D was observed demonstrating that a similar significant flattening is found after repeat CXL. However, we observed greater reduction in corneal thickness after repeat CXL than found in the previous Leeds study or than is reported in the literature. Therefore, perhaps repeat CXL should be approached with caution in patients with thin corneas. Our practice is to perform CXL or repeat CXL only for patients with corneas >400 µm immediately prior to UV-A light exposure.

With similar success rates and flattening, this may suggest that failure of primary CXL, when it occurs, may be more likely in younger patients due to a lack of flattening. This idea is supported by the minimal change in Kmax after failed primary CXL found in the present study (−0.01 D), although this change was not found statistically significant compared with the change after repeated CXL, perhaps due to type 2 error from a small underpowered sample size. Most important is the consideration of visual function, and the repeat CXL improved the mean BCVA by 0.04 units of logMAR. This is comparable to successful primary CXL, as the corresponding figure was 0.05 units in the previous study.

The main limitation of our study was access to retrospective data. However, enough data were available to judge clinical stability for each case, such that the effects of repeated CXL could at least be assessed through either BCVA or topography, if not both. Reviewing the clinical documentation also allowed confirmation of stability. Such limitations are inherent in a retrospective study and point to the need for a randomised controlled trial. Unfortunately, the effectiveness of primary CXL means that an adequate sample size for such a study would likely be difficult to attain. In the same vein, the small sample size of the present study also meant it was likely underpowered to detect any differences between the change after first CXL and the change after second CXL.

This study shows that younger age and lack of flattening post primary CXL may be associated with failure. Repeat CXL after failure of primary CXL is a safe and effective treatment for progressive keratoconus despite primary CXL. Corneal haze was not objectively measured in this study. However, no clinically significant haze was documented after repeat CXL. Further studies may objectively measure changes in corneal haze after repeat treatment to determine whether there is any significant difference from primary treatment.

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Contributors DM is the guarantor. The following authors were responsible for conception and design of the work as well as the acquisition, analysis, and interpretation of data for the work: DM, AO and SA. The following authors were responsible for drafting the work and revising it critically for important intellectual content: DM, AO, SA, SH, CO and AD. The following authors were responsible for final approval of the version to be published: DM, AO, SA, SH, CO and AD. The following authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: DM, AO, SA, SH, CO and AD.

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