REVIEW

The efficacy of standard versus accelerated epi-off corneal cross-linking protocols: a systematic review and sub-group analysis

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Abstract

Purpose To compare the one-year efficacy of accelerated and standard 5.4 J/cm^2 protocols of cross-linking (CXL) in the treatment of progressive keratoconus.

Methods In this systematic review, two members of the research team searched Scopus, Pubmed, ISI, Ovid, Science Direct, and Cochrane databases independently for publications between January 2010 and December 2016. The majority of retrieved studies were not randomized clinical trials (RCT), or the second arm of the RCT was either untreated or customized CXL. The outcomes of interest were uncorrected distance visual acuity, corrected visual acuity, manifest refraction spherical equivalent, maximum keratometry in the central 3 mm, minimum keratometry in the central 3 mm, and corneal thickness in the apex or thinnest point at baseline and 1 year after CXL.

Results Of the 453 papers found in the preliminary search, 23 papers were included in the final analysis. Analysis of variance of one-year changes showed that longer irradiation times were associated with a greater corneal flattening effect, although there was no difference in terms of improvement in vision or refraction.

Conclusions In other words, efficacy is comparable among different CXL protocols, so it is recommended to use the standard method in cases where maximum flattening is expected, such as young people and severe cases.

Keywords Standard cross-linking · Accelerated cross-linking · Systematic review

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Introduction

Keratoconus, which is characterized by corneal protrusion, local stroma thinning, and increased corneal curvature [1], is associated with increased irregular

astigmatism and visual loss [2]. Wollensak et al. [3] developed corneal cross-linking (CXL) to halt disease progression, and the procedure received approval of the Food and Drug Administration (FDA) in 2016. Since 2010, accelerated methods of CXL have been introduced in which irradiation time is reduced by increasing the intensity to maintain 5.4 J/cm^2 radiant exposure. Although studies have shown the efficacy of these methods [4–8], there are still debates about the efficacy of accelerated methods compared to the standard approach. Some suggest that better corneal flattening is achieved with the standard protocol than accelerated CXL [9–11], and some have reported that results are similar in this regard [8, 12, 13]. Studies on different accelerated protocols also report inconsistent results. Some allow for procedure times as short as 2 min [14, 15], while ex vivo experiments indicate that procedures shorter than 10 min lack sufficient efficacy [6]. In light of these contradictions, the present systematic review was carried out to examine and compare the effects of 3-min (30 mW/cm^2), 5-min (18 mW/cm^2), 10-min (9 mW/cm^2), and standard 30-min (3 mW/cm^2) CXL protocols.

Subjects and methods

Search strategy

Two members of the research team independently searched Scopus, Pubmed, ISI, Ovid, Science Direct, and Cochrane databases for publications between 1/1/2010 and 30/30/2016 using the search term (corneal crosslinking or cross-linking or cross linking) AND (visual acuity or keratometry or spherical equivalent or corneal thickness) NOT (pediatric). In the initial search, 453 articles were retrieved. Of these, 112 duplicate articles were eliminated. The reference lists of the remaining articles were also reviewed to find relevant articles. This step was completed in 3 months.

Main measures

The summary measure in this study was the effectiveness of CXL protocols in over 18-year-old patients. Outcomes included one-year change in uncorrected distance visual acuity (UDVA), corrected visual acuity (CDVA), manifest refraction spherical

equivalent (MRSE), maximum keratometry in the central 3 mm (Kmax-3 mm), minimum keratometry in the central 3 mm (Kmin-3 mm), and corneal thickness (CT) in the apex or thinnest point.

Quality assessment of the study

Two members of the research team (MM, SA) independently evaluated the quality of the selected articles using the Crow Critical Appraisal Tool (CCAT, V1.4). In this form, a score is given on a scale of 0–5 for the items presented in eight categories, and these eight category scores are ultimately used to calculate the total score (maximum of 40) and the percentage of total. Compared to informal appraisal, CCAT has been shown to have good repeatability [16] and acceptable reliability [17].

Statistical analysis

Since comparative studies were limited, especially in accelerated groups, sub-group analysis was used instead of meta-analysis to compare the effectiveness of the protocols. For this purpose, pooled mean ± SD of one-year changes in each of the study indices was calculated in 3-min, 5-min, 10-min, and 30-min subgroups and compared using analysis of variance and post hoc tests for pooled data. These tests were also used to compare baseline values. A significance level of 5% was considered.

Results

Study selection

Of the 112 non-redundant publications identified in the initial search, we excluded non-English papers, as well as articles that had any of the words "ectasia," "surface ablation," "keratoplasty," "transepithelial," "laser in situ keratomileusis," "photorefractive keratectomy," "review," "case report" in the title, abstract, or keywords. Also, those that contained the word "ring" in the title or the phrase "hypo-osmolar" or "hypoosmolar" or "hypo osmolar" in the abstract were excluded. Studies were conducted with the epi-on method, those that included a minimal CT less than 400 μm, and in vitro studies were also eliminated. Eventually, 23 articles remained. Therefore, included

articles were studies that reported one-year vision, refraction, and topography results of CXL (without combination therapy) in patients with progressive keratoconus. Figure 1 illustrates the selection process.

Twenty-three articles published between January 2010 and December 2016 that included a total of 1275 eyes of patients with a mean age of 25.04 ± 3.00 years underwent quality assessment. Among these publications, there were 2, 4, and 2 studies on the 3-min, 5-min, and 10-min protocols, respectively, and 21 studies on the 30-min approach. Sixteen studies were before–after and 7 were RCT studies. Twenty studies were prospective in design and 3 were retrospective. Table 1 summarizes the full characteristics of the articles. Also, Table 2 presents baseline and one-year values to facilitate comparisons between different CXL protocols.

Mean one-year change in UDVA was $- 0.12 \pm 0.20$ logMAR in the 3-min group (1 study, $n = 77$ eyes), $- 0.07 \pm 0.17$ logMAR in the 5-min group (2 papers, $n = 64$ eyes), $- 0.13 \pm 0.18$ logMAR in the 10-min group (1 article, $n = 16$ eyes), and $- 0.09 \pm 0.10$ logMAR in the 30-min group (13 articles, $n = 538$ eyes); the overall inter-group difference was of borderline significance ($P = 0.058$) due to the only borderline significant difference which was between the 3- and 5-min groups. Mean baseline UDVA was significantly different between the 3- and 5-min groups ($P < 0.001$) as well as the 5- and 30-min groups ($P < 0.001$).

Mean one-year change in CDVA was $- 0.11 \pm 0.12$ logMAR in the 3-min group (2 studies,

Fig. 1 Flow diagram of study selection for one-year results of corneal cross-linking in progressive keratoconus

$n = 110$ eyes), $- 0.05 \pm 0.09$ logMAR in the 5-min group (4 papers, $n = 122$ eyes), $- 0.07 \pm 0.65$ logMAR in the 10-min group (2 papers, $n = 52$ eyes), and $- 0.09 \pm 0.09$ logMAR in the 30-min group (20 articles, $n = 860$ eyes); the overall inter-group difference was statistically significant ($P = 0.028$) due to the only significant difference which was between 3- and 5-min groups ($P = 0.029$). Mean baseline CDVA was significantly different between the 3- and 5-min groups ($P < 0.001$) as well as the 5- and 30-min groups ($P < 0.001$).

Mean change in MRSE at one year was -0.49 ± 1.80 D in the 3-minute group (1 study, $n = 33$ eyes), $- 0.54 \pm 1.37$ D in the 5-min group (3 articles, $n = 80$ eyes), $- 0.77 \pm 1.65$ D in the 10-min group (2 papers, $n = 52$ eyes), and $- 0.62 \pm 0.95$ D in the 30-min group (16 articles, $n = 645$ eyes); the overall inter-group difference was not statistically significant ($P = 0.604$). Mean baseline MRSE was not significantly different between any two groups either.

Mean change in Kmax-3 mm at one year was $- 0.18 \pm 1.44$ D in the 3-min group (1 study, $n = 33$ eyes), $- 0.35 \pm 1.03$ D in the 5-min group (3 papers, $n = 97$ eyes), $- 0.46 \pm 1.23$ D in the 10-min group (2 papers, $n = 79$ eyes), and $- 0.95 \pm 1.36$ D in the 30-min group (9 papers, $n = 333$ eyes); the overall inter-group difference was statistically significant ($P < 0.001$), and the post hoc test showed that the difference was significant between the 3- and 30-min groups ($P = 0.006$), the 5- and 30-min groups ($P = 0.004$), and also between the 10- and 30-min groups ($P = 0.013$). There was no significant difference between other groups. Baseline Kmax-3 mm was significantly higher in the 30-min group (50.46 ± 5.12 D) than the 5-min group (48.75 ± 3.51 D; p?) and the 10-min group (48.85 ± 1.51 D; p?).

Mean change in Kmin-3 mm at 1 year was $- 0.15 \pm 1.05$ D in the 3-min group (1 study, $n = 33$ eyes), $- 0.22 \pm 0.81$ D in the 5-min group (3 papers, $n = 97$ eyes), $- 0.37 \pm 1.28$ D in the 10-min group (2 papers, $n = 52$ eyes), and -0.68 ± 1.25 D in the 30-min group (11 articles, $n = 392$ eyes); the overall inter-group difference was statistically significant ($P < 0.001$), and the post hoc test showed that differences were significant between the 3- and 30-min groups ($P = 0.046$) and the 5- and 30-min groups ($P = 0.003$); there were no significant
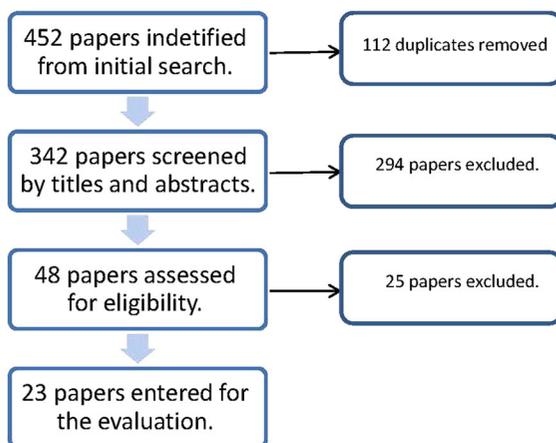
Table 1 Summary of articles that reviewed one-year cross-linking results in patients with progressive keratoconus

Author, country	Study design	CXL protocol (min)	No of eyes at baseline	No of eyes after 1 year	Mean age	Main results	CCAT score
Hashemian, Iran-2014	RCT	3	77	77	22.6	Improvement of UDVA and CDVA, decrease in MRSE and Kmax-8 mm	33 (82.5%)
		30	76	76	22.3	Improvement of UDVA and CDVA, decrease of MRSE and Kmax-8 mm	
Shetty, India-2015	RCT	3	33	33	24.2	Improvement of CDVA, decrease of MRSE, Kmax-3 mm, Kmin-3 mm and CT in all groups	29.5 (73.7%)
		5	33	33	19.9		
		10	36	36	23.1		
		30	36	36	22.8		
Hashemi, Iran-2016[a]	RCT	5	31	22	25.13	Improvement of UDVA, decline of CDVA, increase of MRSE, decrease of Kmax-3 mm, Kmin-3 mm and CT	34 (85.0%)
		30	31	22	25.13	Improvement of UDVA, decline of CDVA, decrease of MRSE, Kmax-3 mm, Kmin-3 mm and CT	
Chan, China-2015	Before–after	5	25	25	30.2	Decline of CDVA, increase of MRSE, decrease of Kmax-8 mm and CT	30 (75%)
Kurt, Turkey-2016	Retrospective	5	42	42	24.3	Improvement of UDVA and CDVA, decrease of Kmax-8 mm, Kmax-3 mm, Kmin-3 mm and CT	33.5 (83.7%)
Elbaz, Canada-2014	Retrospective	10	16	16	24.9	Improvement of UDVA and CDVA, decrease of MRSE, Kmax-8 mm, Kmax-3 mm and Kmin-3 mm	38 (95%)
Goldich, Canada-2014	Before–after	30	17	Not reported	27.3	Improvement of UDVA and CDVA, decrease of MRSE, Kmax-8 mm, increase of CT	35 (87.5%)
Viswanathan, Australia-2013	Before–after	30	51	Not reported	24.2	Improvement of CDVA, decrease of MRSE, Kmax-8 mm and CT	37 (92.5%)
Goldich, Canada-2010	Before–after	30	14	Not reported	28.2	Decline of UDVA, Improvement of CDVA, decrease of MRSE, Kmax-8 mm, Kmin-3 mm, increase of CT	34.5 (86.2%)
Henriquez, Peru-2011	Before–after	30	10	10	29.7	Improvement of UDVA and CDVA, increase of MRSE, Kmax-3 mm, Kmin-3 mm and decrease of CT	31.5 (78.7%)
Soeters, Netherlands-2014	Before–after	30	56	Not reported	Range: 18–26	Improvement of UDVA and CDVA, decrease of Kmax-8 mm, Kmin-3 mm and CT	32.5 (81.2%)
De Bernardo, Italy-2015	Before–after	30	57	Not reported	22.5	Improvement of CDVA, decrease of MRSE, Kmax-8 mm and CT	33.5 (83.7%)
Kranitz, Hungary-2012	Before–after	30	40	40	29.9	Improvement of UDVA and CDVA, decrease of MRSE, Kmax-3 mm, Kmin-3 mm and CT	37 (92.5%)
Ghanem, Brazil-2011	Before–after	30	42	42	22.4	Improvement of UDVA and CDVA, decrease of MRSE, Kmax-8 mm and Kmax-3 mm	35.5 (87.8%)

Table 1 continued

Author, country	Study design	CXL protocol (min)	No of eyes at baseline	No of eyes after 1 year	Mean age	Main results	CCAT score
Sloot, Netherlands-2013	Retrospective	30	53	53	21.5	Improvement of CDVA, decrease of Kmax-8 mm and CT	30 (75.0%)
Kymionis, Greece-2014	Before–after	30	25	25	27.9	Improvement of UDVA and CDVA, decrease of MRSE, Kmax-3 mm, Kmin-3 mm and CT	38.5 (96.2%)
Guber, Switzerland-2013	Before–after	30	33	33	26.4	Improvement of CDVA, decrease of MRSE, Kmax-8 mm, Kmin-3 mm and CT	34.5 (86.2%)
Wittig-Silva, Australia-2014	RCT	30	50	46	25.6	Improvement of UDVA and CDVA, increase of MRSE, decrease of Kmax-8 mm, Kmin-3 mm and CT	37.5 (93.7%)
Seyedian, Iran-2015	RCT	30	52	52	25.6	Improvement of CDVA, increase of MRSE, decrease of Kmax-3 mm, and CT	32.5 (81.2%)
Seiler, Germany-2016	RCT	30	40	38	25.9	Improvement of CDVA, decrease of Kmax-8 mm and CT	38 (95.0%)
Khan, Pakistan-2015	Before–after	30	71	71	19.8	Improvement of UDVA and CDVA, decrease of MRSE, Kmax-8 mm and CT	31.5 (78.7%)
Greenstein, USA-2012	Before–after	30	66	66	Note reported	Improvement of UDVA and CDVA, decrease of Kmax-8 mm	35.5 (88.7%)
Hersh, USA-2011	RCT	30	49	49	> 14	Improvement of UDVA and CDVA, decrease of MRSE, Kmax-8 mm, Kmax-3 mm and Kmin-3 mm	30.5 (76.2%)

[a]One-year data were unpublished

differences between other groups. Baseline Kmin-3 mm was higher in the 3-min group (48.50 ± 3.60 D) than the other three groups (all $P < 0.001$).

Mean change in CT at 1 year was -7.00 ± 8.79 μm in the 3-min group (1 study, $n = 33$ eyes), -8.99 ± 8.79 μm in the 5-min group (4 papers, $n = 122$ eyes), -19.00 ± 18.37 D in the 10-min group (1 article, $n = 36$ eyes), and -12.61 ± 10.87 D in the 30-min group (15 articles, $n = 617$ eyes); the overall inter-group difference was statistically significant ($P < 0.001$), and the post hoc test showed significant differences between all groups except between the 3- and 5-min groups ($P = 0.802$). Baseline CT was higher in the 5-min group (468.78 ± 35.75 μm) than the 10-min group (450.00 ± 0.18) and the 30-min group (458.01 ± 35.25) ($P < 0.001$). Baseline CT differences were not statistically significant between other groups.

Discussion

The efficacy of accelerated and standard CXL protocols has been shown through single-group and comparative clinical studies [4, 18–24]. The main common indicators in these studies are visual acuity, refraction, keratometry, and corneal thickness. Visual acuity has been expressed with various units in different studies, and we converted them all into logMar before the analysis. According to the results, there was a borderline significant difference in UDVA

Table 2 Comparison of baseline and one-year values of indices between different cross-linking protocols

	No of eyes	Pre-operative	P value[a]	One-year change	P value[b]
UDVA					
3 min	77	0.97 ± 0.33	< 0.001	− 0.12 ± 0.20	0.058
5 min	64	0.59 ± 0.38		− 0.07 ± 0.17	
10 min	16	0.78 ± 0.51		− 0.13 ± 0.18	
30 min	538	0.89 ± 0.44		− 0.09 ± 0.10	
CDVA					
3 min	110	0.58 ± 0.43	< 0.001	− 0.11 ± 0.12	0.028
5 min	122	0.41 ± 0.40		− 0.05 ± 0.09	
10 min	52	0.56 ± 0.65		− 0.07 ± 0.65	
30 min	860	0.32 ± 0.34		− 0.09 ± 0.09	
MRSE					
3 min	33	− 4.17 ± 4.58	0.157	− 0.49 ± 1.80	0.604
5 min	80	− 4.06 ± 3.47		− 0.54 ± 1.37	
10 min	52	− 3.64 ± 3.45		− 0.77 ± 1.65	
30 min	605	− 3.37 ± 2.99		− 0.62 ± 0.95	
Kmax-3 mm					
3 min	33	49.40 ± 4.20	< 0.001	− 0.18 ± 1.44	< 0.001
5 min	97	48.75 ± 3.51		− 0.35 ± 1.03	
10 min	79	48.85 ± 1.51		− 0.46 ± 1.23	
30 min	333	50.46 ± 5.12		− 0.95 ± 1.36	
Kmin-3 mm					
3 min	33	48.50 ± 3.60	< 0.001	− 0.15 ± 1.05	< 0.001
5 min	97	45.21 ± 2.76		− 0.22 ± 0.81	
10 min	52	45.37 ± 2.77		− 0.37 ± 1.28	
30 min	392	45.97 ± 3.89		− 0.68 ± 1.25	
CT					
3 min	33	460 ± 36	0.006	− 7.00 ± 8.79	< 0.001
5 min	122	468.78 ± 35.75		− 8.99 ± 10.74	
10 min	36	450.0 ± 0.18		− 19.00 ± 18.37	
30 min	617	458.01 ± 35.25		− 12.61 ± 10.87	

UDVA Uncorrected distance visual acuity, *CDVA* corrected distance visual acuity, *MRSE* manifest refraction spherical equivalent, *CT* corneal thickness

[a]Comparison of baseline values

[b]Comparison of one-year change between 4 CXL protocols

improvement among accelerated protocols and also compared with the standard protocol, and this difference was due to the difference between the 3- and 5-min groups. In a meta-analysis of 24 studies, Liu et al. [25] showed that UDVA improvement in the pool of modified CXLs was similar to standard CXL. Comparative clinical studies [11, 26, 27] also suggest that UDVA improvement is similar in accelerated and standard protocols. CDVA improvement was similar between 5-min, 10-min, and 30-min approaches. In the 3-min protocol, mean CDVA improvement was higher than the 5-min protocol. The difference between the 3- and 5-min protocols in terms of UDVA and CDVA outcomes could be related to the baseline values of these indices. In studies with almost similar sample sizes, baseline UDVA and CDVA were significantly worse in the 3-min groups than in the 5-min groups. Therefore, based on the hypothesis that the patients with worse visual acuity experience better improvement after CXL [28–30], the difference observed in outcome of studies is quite expected. But regarding 5-min and 30-min protocols, due to different sample sizes, it is not possible to comment on this issue with certainty. Overall, due to the negligible differences in UDVA and CDVA (Table 2), it might be said that various accelerated CXL methods and the standard method offer the same level of safety, and there is no difference between them in this regard.

In terms of MRSE, there was no difference between the studied groups. In the study by Liu et al. [25], unlike our study, there was a greater reduction in SE in the standard group than the pool of modified CXLs. Since they analyzed accelerated and customized protocols together, their results should not be compared to our study. But clinical studies have reported similar results for SE after different accelerated protocols [11, 26, 27]. McAnena et al. [31] reviewed one-year results of standard CXL with the transepithelial approach in children in 13 studies, and they showed that MRSE remained similarly unchanged in both study groups. Although their study was conducted on children, their findings in terms of MRSE are similar to ours which concerns adults older than 18 years of age and epi-off approach.

In the present study, the standard protocol was associated with a greater reduction in Kmax than all accelerated protocols. Among accelerated protocols, although higher irradiation times were associated with an increased flattening effect, the differences were not significant. One reason for this lack of significance can be the small sample size of these groups. In the study by Liu et al. [25], there was greater Kmax reduction in the standard group than modified groups. Chunyu et al. [32], who conducted a meta-analysis of one-year CXL results in 23 articles, reported a Kmax reduction with the standard protocol as well. In contrast, McAnena et al. [31] reported no significant changes in Kmax after CXL in under 18 year olds. One reason for the difference in younger age groups is lesser corneal stiffness and higher risk of progression in these individuals [33]. The role of age on CXL results has been discussed previously [33]. Younger patients may even be more likely to require retreatment in the long term. Studies have reported different reductions in Kmax, ranging from less than 1.0 D [34] to more than 2.0 D [35], and the average is about 1.0–2.0 D [36–38]. The rearrangement of the corneal lamella and its surrounding matrix can lead to a variety of results [39]. The same trend is observed with Kmin results. The standard protocol was associated with greater decrease in central Kmin than accelerated methods. Baseline values of Kmax and Kmin did not seem to be relevant to the amount of change at one year after CXL. For example, although baseline Kmax in the standard group was similar to the 3-min group (50.46 vs. 49.40 D, $P = 0.250$), their changes were significantly different (− 0.95 vs. − 0.18 D, $P = 0.006$). Also,

mean baseline Kmin in the 3-min group was higher than the 5-min group (48.50 vs. 45.21, $P < 0.001$), but the decrease was similar in these two groups (− 0.15 vs. − 0.22 D, $P = 0.810$).

CT decrease was not significantly different between the 3- and 5-min protocols, but results were more pronounced with the 10-min approach than both other accelerated methods. With the 30-min protocol, changes were less than the 10-min approach. There can be two causes for reduced CT. One is disease progression and the failure of CXL and the other is the different change in compactness of the cross-linked cornea. The greater CT decrease in the 10-min group compared to the standard group may be attributed to disease progression in a number of cases in the former group, especially that baseline the difference was not significant between the two groups. Despite available histological studies, no conclusion can be drawn in this regard. Touboul et al. [40] and Bouheraoua et al. [41] showed that the corneal nerve and anterior keratocyte densities are lower after accelerated CXLs than the standard, but appear to be similar at 6 months after surgery. Another notable point is the 19 μm reduction in the 10-min group is due to one study with 36 eyes [27], and the 12.6 μm decrease is related to 15 studies with 617 eyes. The decrease in the 30-min group was significantly more than the 10-min group in a randomized clinical trial study as well [27]. Perhaps our study has less accurate results for the 10-min protocol than the standard.

Although accelerated CXLs are more comfortable for patients and more attractive to clinicians on account of shorter procedure time, laboratory studies show that reducing the irradiation time beyond a certain limit will not provide the same results. For example, the in vitro study by Wernli et al. [14] showed that there is no corneal stiffening effect with 50–90 mW/cm^2 intensities. Hammer et al. [15] also showed that decreasing the duration reduces the amount of cross-linking, and no more cross-linking occurs beyond 30 mW/cm^2 intensity. Therefore, based on in vitro studies, lesser therapeutic effects should be expected as CXL duration is reduced, and despite its limitations, the present systematic review confirms this hypothesis. Future studies can examine these results further.

Although the number of studies and sample sizes were small due to the defined criteria in accelerated protocols and given the limited number of

comparative studies, it was not possible to carry out meta-analysis and to determine the heterogeneity of the studies, and according to our findings, different protocols could have similar effects in terms of vision and refraction improvement for keratoconus patients. But compared to accelerated protocols, the standard protocol is more effective in reducing the keratometry and provides better flattening. Therefore, it is recommended to use the standard method in cases where most flattening is needed, such as younger individuals or more severe cases. Given the changes in CT, it may be possible to use accelerated protocols for cornea that are 350–400 μm thick pre-CXL.

Compliance with ethical standards

Conflict of interest   All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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