

Pain mechanisms and management in corneal cross-linking: a review

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ABSTRACT

Though corneal collagen cross-linking (CXL) is an increasingly available and effective treatment for keratoconus, few reports have considered its impact on pain-related physiology in depth. This comprehensive narrative review summarises mechanisms underlying pain in CXL and clinical care possibilities, with the goal of future improvement in management of CXL-related pain. Postoperative pain associated with CXL is largely due to primary afferent nerve injury and, to a smaller extent, inflammation. Chronification of pain after CXL has not been reported, even as long-term nerve damage without regeneration following standard CXL treatment is frequently observed. The lack of pain chronification may be due to the minimally invasive nature of the procedure, with its rapidly recovering superficial corneal wound, and to the positive anti-inflammatory changes of the tear film that have been described after CXL. Different CXL approaches have been developed, with the transepithelial epithelial-on technique (epi-on) associated with less postsurgical pain than the gold standard, epithelial-off technique (epi-off). After the first few days, however, the difference in pain scores and need for analgesics between epi-on and epi-off disappear. Patients experience relatively high-intensity pain the first few days post-CXL, and many strategies for acute pain control following CXL have been studied. Currently, no method of pain management is considered superior or universally accepted. Acute pain following CXL is a recognised and clinically significant side effect, but few CXL studies have systematically investigated postoperative pain and its management. This review aims to improve patient pain outcomes following this increasingly common procedure.

INTRODUCTION

Corneal collagen cross-linking (CXL) is an effective and widely used surgical treatment for keratoconus patients.¹ CXL uses ultraviolet-A (UVA) light and riboflavin as a photosensitizer to induce photochemical damage by releasing oxygen radicals. This leads to cross-linking of the collagen fibres in the corneal stroma, thereby stabilising the cornea. Unlike any other keratoconus treatments, CXL is effective at slowing or halting disease progression with preservation of vision-related and health-related quality of life.^{2–4}

Unfortunately, CXL causes acute postsurgical pain to the eye which can be intense even with aggressive pain management, particularly for the first few days.^{5,6} This is especially problematic for paediatric and developmentally delayed populations which are increasingly undergoing CXL.^{7,8} The size of the corneal epithelial defect only partially contributes to the amount of postoperative pain, which is likely influenced by other unknown factors.⁹ Different perioperative and postoperative approaches have been explored to attempt pain reduction after CXL, but no method is universally accepted.^{6,10}

A better understanding of the pathophysiological processes of corneal pain in CXL may help develop innovations in acute and postoperative pain management in corneal surgical procedures. This review aims to obtain insight into mechanisms underlying CXL pain and clinical care possibilities, with the goal of improving CXL-related pain management.

METHODS

Studies cited were obtained through a systematic literature search in PubMed, Embase and the Cochrane Library. Different terms and synonyms for *pain* (*pain**) and *corneal cross-linking* (*collagen crosslink**, *collagen cross link**, *collagen cross-link**, *corneal plexus*, *CXL*, *C3R*, *KXL*, *CCL*) were used. All articles on the pathophysiology, epidemiology, assessment and/or management of pain in CXL were considered. All articles looking at pain following CXL were summarised ([table 1](#)). Language was limited to English and French articles. Expert consultation was obtained.

RESULTS

Twenty-one papers on post-CXL pain were identified, with all but one about treating keratoconus (online supplemental table). Pain measurement methods varied, but acute pain within 24 hours of CXL was substantial in the studies and peaked during the first postoperative day and night ([table 2](#)). Pain levels decreased rapidly after the first few days,



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Table 1 Summary table of 12 key studies obtained in literature search

Reference	Trial type (if applicable)	CXL method	Patients	Eyes	Lat
5		Epi-off	135 (31F)	178	M
6		Epi-off	52 (15F)	20	M
9		Epi-off	34	68	B
10	Ketorolac 10 mg q8h×3d	Epi-on A	10	NR	NR
	Gabapentin 300 mg q8h×3d	Epi-on A	7	NR	NR
	Ketorolac 10 mg q8h×3d	Epi-off A	12	NR	NR
	Gabapentin 300 mg q8h×3d	Epi-off A	8	NR	NR
43		Iontophoresis	15 (6F)	NR	M
		Epi-off	23 (3F)	NR	M
47		Epi-on A*	11 (4F)	NR	NR
		Epi-off A	16 (6F)	NR	NR
48		Epi-off	22	22	U
		Epi-off†	22	22	U
50	Cooled 4°C riboflavin 0.1% every 2 min for 10 min	Epi-off A	50	100	B
	Room temperature riboflavin 0.1% every 2 min for 10 min	Epi-off A	48	96	B
52	No RGTA	Epi-off A	30 (13F)	30	U
	RGTA gtt (Cacicol20)	Epi-off A	30 (9F)	30	U
53		Epi-off	18 (4F)	18	B
54		Epi-off	41	30	M
55		Epi-on A	21 (9F)	21	B
		Epi-off A	21 (9F)	21	B

*With epithelial flap.

†With Epi-Bowman Keratectomy.

B, bilateral; CXL, corneal collagen cross-linking; Lat, laterality; M, mixed; NR, not reported; RGTA, ReGeneraTing Agents; U, unilateral.

and no studies reported persistent clinically significant pain 1 year after CXL. Reported pain was consistently lower with the epithelial-on (epi-on) CXL technique compared with other techniques, including the conventional epithelial-off (epi-off) technique. This difference in pain scores between epi-on and epi-off disappeared after the first few days. Reported pain levels were higher in accelerated versions of CXL. Perioperative and postoperative pharmacological management after CXL differed widely, but typically consisted of local anaesthetic eye-drops during the procedure followed postoperatively by a topical steroid and antibiotic. Roughly half of the studies reported the use of oral painkillers, often combined with bandage contact lenses (online supplemental table).

DISCUSSION

Pathophysiology

Ocular pain can be categorised as nociceptive, inflammatory and/or neuropathic.¹¹ Nociceptive eye pain is due to the noxious stimulation of trigeminal afferent nociceptors, which can later cause inflammation. When nerves are damaged, the resulting abnormal population of ion channels results in erratic impulse firing, which can lead to neuropathic pain.^{12 13} As defined by the International

Association for the Study of Pain, neuropathic pain is a direct consequence of a lesion or disease affecting the somatosensory system through the peripheral or central nervous system.¹⁴ Post-CXL pain is presumably largely due to primary afferent nerve injury and, to a smaller extent, to inflammation. Corneal afferents reside in the sub-basal nerve plexus underlying the corneal epithelium, well within the area impacted by CXL.

Corneal primary afferents can be divided into three classes based on their ability to detect environmental energy changes.¹² Polymodal nociceptor neurons comprise about 70% of corneal neurons. They produce several quick impulses in response to mechanical, chemical, and thermal stimuli and are mediated by many types of transduction channels that transduce stimuli into nociceptive signals. The second subpopulation of corneal sensory neurons is mechanonociceptor neurons, which comprise 10%–15% of corneal neurons and respond to mechanical stimuli with short phasic nerve impulses. Lastly, 10%–15% are cold thermoreceptor neurons which increase nerve impulse firing rate in response to small temperature reductions.

In response to harmful stimuli, damaged cells release factors that activate immune cells, which in turn release

Table 2 Postoperative pain ratings in studies with reports

Reference	Pain scale	Pain rated									
		D0	D1	D2	D3	D4	D5	D6	D7	D15	D30
5	FACES 0–5	2.8±1.7	2.1±1.7	1.4±1.5	0.7±1.1	0.3±0.7	0.1±0.5				
6*	VAS 0–10			6.6±3.9							
9	VRS 0–5	2.2	1.5		1.2				0.3		
10	NRS 0–10		7.7	5.3	3.1	2.1	1.6				
	NRS 0–10		8.4	4.6	2.7	2.3	2.2				
	NRS 0–10		7.7	5.3	3.1	2.1	1.6				
	NRS 0–10		8.4	4.6	2.7	2.3	2.2				
43	VAS 0–10	5.3±2.8	3.6±2.3	2.1±1.9	0.5±0.5	0.9±1.3	0.6±1.1	0.4±0.9	0.3±0.8	0.5±1.1	0.2±0.6
	VAS 0–10	5.3±3.4	3.9±2.7	2.7±2.7	0.5±0.5	0.9±1.8	0.5±1.2	0.3±0.9	0.2±0.6	0.1±0.4	0±0
47	NRS 0–4	2.3±0.4	1.4±0.5	0.9±0.4	0.5±0.5						
	NRS 0–4	3.0±0.8	2.1±0.6	1.8±0.6	1.1±0.5						
48	FACES 0–10	4.5±1.5			1.1±0.8						
	FACES 0–10	2.7±1.2			0.4±0.4						
50	VAS 0–10	3.8±3.0	2.8±3.1	2.5±2.4	1.3±1.7	0.5±0.8	0.1±0.3				
	VAS 0–10	8.1±2.2	4.9±3.3	4.0±2.4	2.0±1.7	1.2±1.7	0.5±1.4				
52	VAS 0–10	7.8	6.9	2.3	1.2						
	VAS 0–10	7.5	5.9	4.1	1.9						
53*	0–4	3.3	2.1	0.6	0.2	0.2					
54*	VRS 0–5			2.9±0.6							
55	VRS 0–5		3.7±1.0	2.1	0.6						
	VRS 0–5		3.0±0.6	2	1.3						

*Ratings averaged across postoperative treatment groups.^{6 53 54}

FACES, Wong-Baker FACES pain rating scale; NR, not reported; NRS, Numeric Rating Scale; VAS, Visual Analogue Scale.

inflammatory cytokines. Inflammatory cytokines augment the activity of various transduction channels and sensitise polymodal nociceptors. Mechanonociceptors may also have augmented activity in response to inflammation, but this mechanism is not well understood. Additionally, cold thermoreceptors are desensitised, as inflammatory cytokines inhibit their specific channels.^{12 13} Increased sensitivity of nociceptors can lead to ectopic activity resulting in spontaneous pain. Inflammation subsides through the removal of activated inflammatory cells and cell apoptosis. Continued tissue damage may lead to chronic persistent inflammation, wherein cells attract more immune cells and start an inflammatory cascade, resulting in sensitisation that leads to chronic pain.

Furthermore, during corneal surgery procedures, incisions can damage corneal sensory axons without damaging tissue, which would normally incite the inflammatory response. When axon severance occurs, the nerve terminals containing transduction channels undergo Wallerian degeneration and disappear within hours, causing reduced or complete loss of sensitivity to stimuli. Neuronal regeneration then occurs with varying results. Some neurons regain their original ion channel populations, whereas others have an abnormal distribution of

channels, resulting in spontaneous impulse firing and subsequent pain.^{12 13}

While peripheral afferents contribute to transduction of noxious stimuli and peripheral neuropathic activity, the experience of pain only manifests after central nervous system processing. Multiple cortical and subcortical brain networks are responsible for processing sensory, affective and cognitive aspects of pain.¹⁵ Some of the brain areas related to processing pain include the insula, anterior cingulate cortex, primary and secondary somatosensory cortex, amygdala, basal ganglia, thalamus and periaqueductal grey. Neuropathic pain can arise from maladaptive neuroplasticity within these central pathways.¹⁶

Animal studies on corneal nociception

Animal models have also been studied to better understand the mechanisms behind acute ocular pain. In murine models, corneal inflammation produced by topical 0.2% benzalkonium chloride induces activation of neurons and the microglial p38 MAPK pathway within the sensory trigeminal complex in the central nervous system.¹⁷ Both chemical and mechanical corneal injury resulted in corneal hypersensitivity, increased spontaneous activity of the ciliary nerve, and faster response of the ciliary nerve to chemical stimulation.¹⁸ Similarly,

a rodent model of photokeratitis using acute UV irradiation demonstrated transient sensitisation of neurons in trigeminal subnucleus caudalis, including enhanced nociceptive behaviour.¹⁹ These changes in intracellular signalling may contribute to the sensitisation of ocular brainstem circuits and therefore ocular pain development downstream.

Pain-related symptoms and complications

To our knowledge, no cases of chronic pain after CXL have been reported in the literature. A study on CXL outcomes for keratoconus and ectasia patients found no changes in reported pain between pre-CXL and 1-year post-CXL follow-up.⁴ Thus, pain following CXL is an acute problem that does not appear to become chronic. However, few studies on CXL consider the delayed onset of persistent pain, which can develop 1–24 months following ocular surgeries such as laser-assisted in situ keratomileusis (LASIK).^{20 21} Notably, pain is rarely the focus of reports on CXL outcomes, and methods of reporting pain in CXL literature are widely variable. To make cross-study comparisons more valid, standardisation of experimental and pain metrics should be considered, such as (1) using a Visual Analogue Scale for reporting pain intensity (0–10), (2) collecting reports of pain intensity for maximum and average daily pain, (3) daily tracking of postoperative pain intensity until it resolves, (4) including a natural history group for studies investigating postoperative pain management, (5) tracking and reporting numbers of male and female participants, and (6) consistent long-term follow-up beyond 3 months postoperatively.

Chronic pain can occur following other forms of corneal damage, such as trauma, cataract surgery and excimer laser procedures such as photorefractive keratectomy (PRK) and LASIK. With LASIK, corneal nerves are mechanically severed in the peripheral cornea and rare but severe cases on post-LASIK neuralgia are reported.^{12 22–26} As the number of worldwide LASIK procedures performed per year greatly surpass those of CXL,^{27 28} further investigation into the lack of chronic pain after CXL is warranted.

Other corneal procedures and pathologies frequently involve long-lasting symptoms of dry eye, including photophobia and foreign body sensation,^{12 24 27 29} but are not mentioned in CXL literature. Dry eye is a known side effect of PRK, which involves a very similar ocular surface procedure to CXL, but without the photochemical damage. The lack of these symptoms after CXL is somewhat unexpected. Furthermore, the cornea is one of the most densely innervated structures in the body, yet chronic pain after corneal surgery is not reported at the levels seen after other non-corneal surgeries (such as groin hernia repair or thoracic surgery), in which chronic postsurgical pain is estimated to occur in 10%–50% of patients.¹¹

Extensive damage is inflicted on the corneal primary afferent nerves in CXL. In vivo corneal confocal

microscopy (IVCM) studies have shown the subepithelial nerve plexus is significantly reduced and corneal nerves are essentially obliterated immediately after conventional and accelerated CXL.^{30 31} Mixed results are reported on corneal nerve recovery after CXL. An IVCM study with 24 patients showed virtually no regeneration of nerve fibres after 6 months,³⁰ while another with 38 patients showed complete regeneration of the sub-basal nerve plexus by 12 months postoperatively.³² Another IVCM study with 8 patients showed no detectable sub-basal plexus 1 year postoperatively, but some sparse nerve regrowth after 3 months.³³ Although the evidence is ambiguous, there appears to be difficulty in nerve regeneration after CXL. As nerve damage can lead to neuropathic pain in other procedures and disorders,^{12 13 34} it is unclear why chronic pain does not develop after CXL. Moreover, keratoconus is characterised by a pathological sub-basal nerve pattern, which did not change positively after CXL in a 5-year follow-up IVCM study.³⁵ This discrepancy between clinical outcome and research findings is notable, particularly because the intense postoperative pain suggests that nociceptors remain somewhat functionally intact.

One possible explanation for the lack of chronic pain is that CXL only involves removal of the epithelium. The cross-linking effect reaches the anterior 200–340 µm of the cornea, which impacts the sub-basal nerve plexus and anterior stroma but not deeper structures such as the posterior stroma and endothelium.^{31 33} There is also no incisional component. Compared with more invasive corneal procedures, CXL recovery is relatively quick, has fewer complications, and less chance of pain chronification. This suggests that damage to deeper nociceptive afferents may contribute to chronic pain, but damage to the sub-basal nerve plexus does not.

Another possible explanation is that compared with LASIK and PRK, CXL patients undergo the procedure more often at a younger age.^{7 8} Communication with young children can introduce potential challenges in obtaining accurate pain reports. Moreover, an older age might be a greater risk factor for development of postsurgical neuropathic pain, where tissue damage in younger patients might recover sooner. Next to age difference, there is a higher prevalence of developmentally delayed patients receiving CXL, which can also present with barriers in accurate communication.

Although corticosteroid-containing eye drops are used in the acute management of inflammation in CXL, the long-term homeostasis and inflammation of the cornea may be due to the changes in tear film quality. There are positive changes in the tear film after CXL treatment, and inflammatory biomarkers decrease.³⁴ The tear film is essential to corneal wound healing and preventing evaporation of tears,^{35 36} so the regenerative role of the tear film may contribute to fast wound healing and the lack of increased dry eye symptoms after CXL. In a study of 30 eyes in 16 patients, CXL had no impact on dry eye syndrome parameters 3 and 6 months postoperatively.²⁹ Additionally, local inflammation affects the

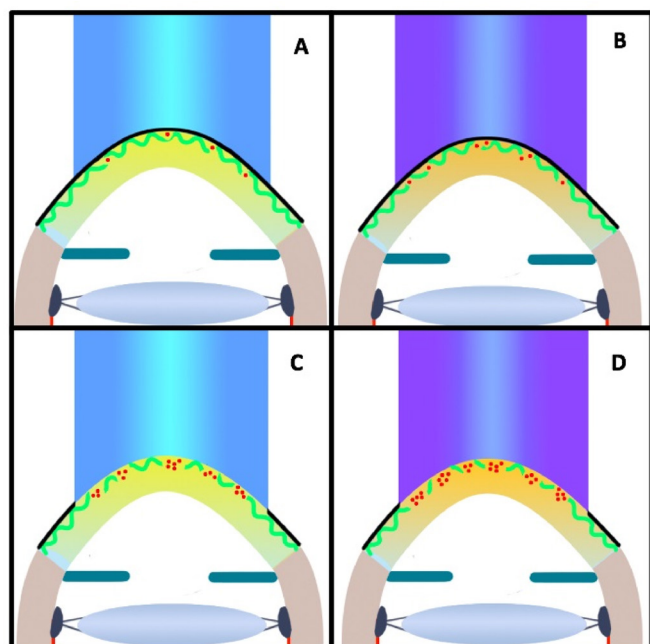


Figure 1 Impact of different CXL techniques to the corneal epithelium (black line) and sub-basal nerve plexus (wavy green line). Red dots show the CXL-induced photochemical reaction and toxic effect with the release of free radicals leading to oxidative stress and nerve damage. (A) epi-on; (B) epi-on accelerated; (C) epi-off; (D) epi-off accelerated. Illustration by Emilie S. van der Valk Bouman. CXL, corneal collagen cross-linking.

development of (chronic) ocular pain,^{12 13} therefore, the anti-inflammatory effects of CXL on the tear film could preclude the development of chronic pain.

Another possibility for chronic neuropathic pain not to develop is because certain immune cells cannot access the cornea. Perhaps the cornea as an immune-privileged site reduces the immigration of specific immune factors related to pain, thus reducing the likelihood that neuropathic pain is established.^{37 38} However, note that following refractive surgery, the cornea can feature chronic inflammatory changes and microneuromas with neuropathic corneal pain.³⁹

Different CXL approaches

Many CXL techniques have been developed (figure 1). The difference in pain between the conventional epi-off and the epi-on technique has been studied extensively, and there has been much debate over which technique is preferable.

In 2003, the Dresden protocol established epi-off CXL as the gold standard, which was then approved by the US Food and Drug Administration in 2016.⁴⁰ With the epi-off technique, the central epithelium is removed to get faster and deeper absorption of the riboflavin into the corneal stroma. With epi-on, the epithelial layer is left intact, thereby avoiding severance of the sub-basal nerve plexus, making the approach less invasive and time consuming.

Several studies have shown that patients experience less pain after epi-on, both in intensity and duration (online supplemental table, online supplemental material). This difference can be explained by the absence of de-epithelialisation and damage to corneal nerves. Other advantages of epi-on are faster postoperative recovery and less risk of complications such as infection and corneal haze.⁴¹ However, the significant advantage of epi-off is deeper and more effective therapy due to enhanced riboflavin and UV absorption with lower risk of keratoconus progression. In a systematic review in 2017 comparing epi-off to epi-on, epi-off more effectively halted the progression of keratoconus.⁴² In a study that measured postoperative CXL pain after 30 days, pain in epi-off compared with epi-on was not significantly different.⁴³ It may be concluded that the pain difference disappears after the first several postoperative days.

Different CXL approaches have unique impacts on the corneal layers (figure 1). Although epi-on CXL does not cause direct mechanical damage to the sub-basal nerve plexus, CXL-induced release of free radicals does lead to oxidative stress and nerve damage.⁴⁴ On the other hand, epi-off directly severs nociceptors in the plexus in addition to the photochemical damage. Accelerated versions of epi-off and epi-on CXL use higher intensity UV light and riboflavin concentrations, which save time while producing similar results.^{45 46} These accelerated versions do seem to result in greater pain levels, presumably due to the higher impact of the procedure to the cornea (table 2, figure 1).

Studies on other CXL methods showed significantly lower pain levels with the use of Epi-Bowman keratectomy and a technique with a subepithelial flap.^{47 48} One study showed a significant effect of ReGeneraTing Agents on pain levels and the number of oral analgesics taken the first few days after epi-off CXL.⁴⁹ Another study showed significant pain reduction with corneal cooling using a cold (4°C) riboflavin solution.⁵⁰ Further studies must be done to validate these experimental therapies.

Pain management strategies

Patients experience relatively high-intensity pain post-CXL, particularly in the (accelerated) epi-off technique (table 2). Many strategies have been studied to determine the most effective method in alleviating postoperative pain, with varying degrees of success. Typical pharmacological management consists of local anaesthetic eye-drops during the procedure followed postoperatively by a topical steroid to quell inflammation and antibiotic eye-drops. A variety of oral painkillers have been used as rescue medication, such as paracetamol, non-steroidal anti-inflammatory oral drugs (NSAIDs), gabapentins, and oxycontin, but the best doses and medications have not been systematically evaluated in the literature (online supplemental table). Highly gas-permeable bandage contact lenses combined with frequent instillation of preservative-free lubricants increases the level of available oxygen to the corneal

surface and promotes epithelialisation. However, the use of bandage contact lenses does not significantly alter pain scores when compared with other postoperative regimens, including occlusive patching or ointment.⁶

Gabapentin and NSAIDs are used following different (corneal refractive) surgery procedures and are potential therapeutics for CXL-related pain.¹⁰ The NSAID ketorolac reduces inflammation, whereas gabapentin works as an inhibitory neurotransmitter analogue. Gabapentin and ketorolac have comparable efficacy in post-CXL pain management for both epi-off and epi-on techniques. However, the extent of pain relief offered by these medications was not assessed, as this study did not include a natural history group without oral analgesics.

Pain management is most needed and could provide the most benefit not when the perioperative local anaesthesia wears off, but during the middle of the first postoperative night. Extended release of low-dose local anaesthesia to the injured cornea overnight, perhaps in the form of a bandage contact lens drug delivery system,⁵¹ may be a practical solution.

Typically, CXL is performed under topical anaesthetics only (online supplemental table, online supplemental material), but general anaesthetics are occasionally used in parallel with uncooperative patients.^{36 40–42} Though beyond the scope of this paper, the use of general anaesthetics is worth future study considering that CXL is increasingly common for paediatric and developmentally delayed populations.

CONCLUSIONS

Acute postsurgical pain is significant and predictable in the days following CXL and fortunately does not appear to transition into chronic pain. The trauma inflicted on the corneal afferents produces nerve damage that is detectable for months but with no apparent impact on pain or dry-eye symptoms beyond the initial insult. Accordingly, pain management strategies have focused specifically on the perioperative and immediate postoperative recovery. Conventional epi-off procedures produce more acute pain than epi-on, but pain diminishes several days after surgery in either approach. Despite the time saved by accelerated CXL, it generally results in greater pain with both epi-on and epi-off approaches.

Currently, no method of pain control following CXL is universally accepted, and there are no evidence-based guidelines for post-CXL care. More research with a translational approach should be conducted to obtain practical recommendations for CXL pain management. First of all, prospective comparative studies with standardised measurements of pain must be conducted to further study postoperative pain control in CXL. Future research should investigate promising therapies and new strategies for acute pain management in CXL, including cool CXL.⁵⁰ These findings may also apply to other surgeries that impact the cornea or shed light on chronic pain. Investigations into why acute postsurgical pain does not become chronic in CXL may aid in the

development of preventative and therapeutic strategies for chronic pain disorders. Future studies should directly compare the various epithelium removal techniques and their relationship to acute and chronic pain.

The primary goal of CXL is to manage keratoconus. In this review, we have highlighted mechanisms underlying pain in CXL as well as clinical care possibilities to improve management of CXL-related pain. Although current reports do not indicate chronic pain following CXL, managing the relatively acute postoperative pain is important, especially considering the growing number of children undergoing CXL. The absence of evidence of pain chronification does not prove its absence; given the extent of acute pain and corneal restructuring, physicians who manage chronic pain patients should consider CXL as a possible, though unproven, factor. We hope this review encourages clinicians and researchers to fine-tune treatment and postoperative care to provide the best CXL pain management.

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