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[Intervention Review]

# Corneal collagen cross-linking for treating keratoconus

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## ABSTRACT

### Background

Keratoconus is a condition of the eye that affects approximately 1 in 2000 people. The disease leads to a gradual increase in corneal curvature and decrease in visual acuity with consequent impact on quality of life. Collagen cross-linking (CXL) with ultraviolet A (UVA) light and riboflavin (vitamin B<sub>2</sub>) is a relatively new treatment that has been reported to slow or halt the progression of the disease in its early stages.

### Objectives

The objective of this review was to assess whether there is evidence that CXL is an effective and safe treatment for halting the progression of keratoconus compared to no treatment.

### Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2014, Issue 7), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to August 2014), EMBASE (January 1980 to August 2014), Latin American and Caribbean Health Sciences Literature Database (LILACS) (1982 to August 2014), Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1982 to August 2014), OpenGrey (System for Information on Grey Literature in Europe) ([www.opengrey.eu/](http://www.opengrey.eu/)), the metaRegister of Controlled Trials (mRCT) ([www.controlled-trials.com](http://www.controlled-trials.com)), ClinicalTrials.gov ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)) and the World Health Organisation International Clinical Trials Registry Platform (ICTRP) ([www.who.int/ictrp/search/en](http://www.who.int/ictrp/search/en)). We used no date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 28 August 2014.

### Selection criteria

We included randomised controlled trials (RCTs) where CXL with UVA light and riboflavin was used to treat people with keratoconus and was compared to no treatment.

## Data collection and analysis

Two review authors independently screened the search results, assessed trial quality, and extracted data using standard methodological procedures expected by Cochrane. Our primary outcomes were two indicators of progression at 12 months: increase in maximum keratometry of 1.5 dioptres (D) or more and deterioration in uncorrected visual acuity of more than 0.2 logMAR.

## Main results

We included three RCTs conducted in Australia, the United Kingdom, and the United States that enrolled a total of 225 eyes and analysed 219 eyes. The total number of people enrolled was not clear in two of the studies. Only adults were enrolled into these studies. Out of the eyes analysed, 119 had CXL (all using the epithelium-off technique) and 100 served as controls. One of these studies only reported comparative data on review outcomes. All three studies were at high risk for performance bias (lack of masking), detection bias (only one trial attempted to mask outcome assessment), and attrition bias (incomplete follow-up). It was not possible to pool data due to differences in measuring and reporting outcomes. We identified a further three unpublished trials that potentially had enrolled a total of 195 participants.

There was limited evidence on the risk of progression. Analysis of the first few participants followed up to one year in one study suggested that eyes given CXL were less likely to have an increase in maximum keratometry of 1.5 D or more at 12 months compared to eyes given no treatment, but the confidence intervals (CI) were wide and compatible with no effect or more progression in the CXL group (risk ratio (RR) 0.12, 95% CI 0.01 to 2.00, 19 eyes). The same study reported the number of eyes with an increase of 2 D or more at 36 months in the whole cohort with a RR of 0.03 favouring CXL (95% CI 0.00 to 0.43, 94 eyes). Another study reported "progression" at 18 months using a different definition; people receiving CXL were less likely to progress, but again the effect was uncertain (RR 0.14, 95% CI 0.01 to 2.61, 44 eyes). We judged this to be very low-quality evidence due to the risk of bias of included studies, imprecision, indirectness and publication bias but noted that the size of the potential effect was large.

On average, treated eyes had a less steep cornea (approximately 2 D less steep) (mean difference (MD) -1.92, 95% CI -2.54 to -1.30, 94 eyes, 1 RCT, very low-quality evidence) and better uncorrected visual acuity (approximately 2 lines or 10 letters better) (MD -0.20, 95% CI -0.31 to -0.09, 94 eyes, 1 RCT, very low-quality evidence) at 12 months. None of the studies reported loss of 0.2 logMAR acuity. The data on corneal thickness were inconsistent. There were no data available on quality of life or costs. Adverse effects were not uncommon but mostly transient and of low clinical significance. In one trial, 3 out of 12 participants treated with CXL had an adverse effect including corneal oedema, anterior chamber inflammation, and recurrent corneal erosions. In one trial at 3 years 3 out of 50 participants experienced adverse events including mild diffuse corneal oedema and paracentral infiltrate, peripheral corneal vascularisation, and subepithelial infiltrates and anterior chamber inflammation. No adverse effects were reported in the control groups.

## Authors' conclusions

The evidence for the use of CXL in the management of keratoconus is limited due the lack of properly conducted RCTs.

## PLAIN LANGUAGE SUMMARY

### Corneal collagen cross-linking for thinning of the transparent front part of the eye ('keratoconus')

#### Review question

Is corneal collagen cross-linking (CXL) a good treatment for slowing down the progression of keratoconus?

#### Background

Keratoconus is a condition where the transparent front of the eye (cornea) gets thinner and begins to bulge. This leads to vision problems, usually short-sightedness (distant objects appear blurred). The condition is more common in children and young adults and can deteriorate over time. Initially glasses and contact lenses can help. If the disease progresses, the only option may be a corneal transplant.

CXL is a new treatment for keratoconus. The eye doctor removes the outer layer of the cornea, puts in vitamin B<sub>2</sub> eye drops, and then treats the eye with ultraviolet A light radiation. This can be done in outpatients and takes about an hour.

#### Study characteristics

The searches are current to August 2014. We found three randomised controlled trials, which were done in the United States, the United Kingdom, and Australia. A total of 219 eyes were randomly allocated to treatment with CXL or no treatment. In all three studies the surgery was done in the same way. None of the studies included children.

### **Key results**

Eyes treated with CXL were less likely to have problems with progression of bulging compared to eyes that were not treated. However, the studies were small and there were some concerns about the way they were done. It is therefore difficult to say exactly how much the treatment helped. None of the studies reported the risk of eyesight getting worse but, on average, treated eyes had better vision (about 10 letters better) compared to untreated eyes. None of the studies reported on a change in quality of life for the participant. The main adverse effects were inflammation and swelling; this occurred in approximately one in 10 participants.

### **Quality of the evidence**

We judged the quality of the evidence to be very low because of problems in the way the studies were done and reported and the small number of eyes included.

## SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Corneal collagen cross-linking compared with no treatment for keratoconus						
<b>Patient or population:</b> people with keratoconus <b>Settings:</b> hospital <b>Intervention:</b> corneal collagen cross-linking <b>Comparison:</b> no or sham treatment						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No or sham treatment	Corneal collagen cross-linking				
<b>Progression</b> (increase in maximal keratometry of 1.5 dioptres or more) Follow-up: 12 months	400 per 1000	48 per 1000 (4 to 800)	RR 0.12 (0.01 to 2.0)	19 eyes (1)	⊕○○○ <b>very low</b> <sup>1-5</sup>	In the same study, increase of 2 dioptres or more at 36 months gave a RR of 0.03 (95% CI 0.00 to 0.43, 94 eyes). A different study reported RR of ‘ ‘ progression’ ’ at 18 months of 0.14 (95% CI 0.01 to 2.61, 44 eyes)
<b>Steepness of the cornea (maximal keratometry)</b> (measured using dioptres. A higher dioptre represents steeper cornea and worse outcome) Follow-up: 12 months	The mean maximal keratometry increased in the control group by 1.2 dioptres	The mean maximal keratometry in the intervention group was 1.92 dioptres less (better) (1.30 to 2.54 less)		94 eyes (1)	⊕○○○ <b>very low</b> <sup>2,4,6</sup>	

<p><b>Uncorrected visual acuity (UCVA)</b>          (measured using logMAR scale. A score of 0 = good vision, higher score is worse vision)          Follow-up: 12 months</p>	<p>The mean UCVA increased on average by 0.06 logMAR units in the control group</p>	<p>The mean UCVA in the intervention groups was 0.20 logMAR units less (i.e. better vision) (0.09 units less to 0.31 units less)</p>	<p>94 eyes (1)</p>	<p>⊕○○○ <b>very low</b><sup>2,4,6</sup></p>	<p>Another study reported mean UCVA at 18 months was 0.33 (Snellen decimal equivalent) in 22 treated eyes and 0.21 in 22 untreated eyes. In the treated eyes, the UCVA on average changed by +0.06 compared to -0.01 in the control group</p>
<p><b>Corneal thickness at the thinnest part of the cornea</b>          (measured in microns)          Follow-up: 12 months</p>	<p>The mean corneal thickness decreased on average by 5.4 μm</p>	<p>The mean corneal thickness in the intervention group was 8.93 μm thicker (0.60 μm thinner to 18.46 μm thicker)</p>	<p>94 eyes (1)</p>	<p>⊕○○○ <b>very low</b><sup>2,3,4,7</sup></p>	<p>We have reported the study with the largest numbers. Inconsistent results were seen in the other 2 studies included in this review. In 1 study there was a change of -31.4 μm in the treated group at 3 months compared to a change of -2.3 μm in the sham treatment group. In the other study, corneal thickness increased by 4 μm in 22 treated eyes compared to 6 μm in 22 untreated eyes (mean difference -2 μm, 95% CI -33.10 to 29.01)</p>
<p><b>Absolute spherical equivalent</b>          (measured in dioptres)          Follow-up: 12 months</p>	<p>The mean absolute spherical equivalent in the control group was -0.55 dioptres</p>	<p>The mean absolute spherical equivalent in the intervention group was 0.65 dioptres higher (-0.37 to 1.67)</p>	<p>94 eyes (1)</p>	<p>⊕○○○ <b>very low</b><sup>2,3,4</sup></p>	



<b>Quality of life</b> Follow-up: 12 months	Not reported.
<b>Adverse effects</b> Follow-up: 12 months	In 1 trial 3/12 participants treated with corneal collagen cross-linking had an adverse effect including corneal oedema, anterior chamber inflammation, and a recurrent corneal erosion. In 1 trial at 3 years, 3/50 participants experienced adverse events including mild diffuse corneal oedema and paracentral infiltrate, peripheral corneal vascularisation, and subepithelial infiltrates and anterior chamber inflammation. No adverse effects were reported for untreated controls in any of the studies

\*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence:

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

- 1 Downgraded for indirectness (-1) as the studies reported different cutpoints and definitions of progression.
- 2 Downgraded for risk of bias (-1) as the studies were at high or unclear risk of performance, detection, attrition and selective outcome reporting bias.
- 3 Downgraded for imprecision (-1) as the confidence intervals were wide and compatible with both benefit and harm.
- 4 Downgraded for publication bias (-1) as three unpublished studies (195 participants) identified.
- 5 Upgraded (+1) because the size of the effect was strong in both studies with approximate 90% relative risk reduction.
- 6 Downgraded for imprecision (-1) as results based on information from only 94 eyes.
- 7 Downgraded for inconsistency (-1) as different findings seen in the studies.

## BACKGROUND

### Description of the condition

Keratoconus means 'conical cornea'. It is a rare condition of the eye that affects approximately 1 in 2000 people (Rabinowitz 1998). The cornea is the main focusing surface of the eye. Keratoconus reduces vision by altering the shape of the cornea so that it becomes stretched and thin, making the vision short-sighted, irregular, and distorted. The condition can affect one or both eyes and can progress at varying rates.

### Presentation

Initially, the patient may present with either a spherical cornea or regular corneal astigmatism. Around the onset of puberty, or earlier in some instances, the cornea begins to thin and protrude, resulting in irregular astigmatism with what is usually a steep curvature. Usually, over a period of the next 10 to 20 years, the process continues until the progression gradually stops. The rate of progression is variable. The severity of the disorder at the time progression stops can range from very mild irregular astigmatism to severe thinning and protrusion with scarring (Krachmer 1984). Keratoconus is usually diagnosed during the second and third decades of life. The ectasia progresses at a variable rate, although it is more rapid at a younger age. Patients usually have myopic astigmatism and are often suspected of having the condition by their ophthalmologist or optometrist, or both, when a deterioration in visual acuity that is no longer correctable by spectacles occurs.

Hydrops is an acute complication of keratoconus where there is severe photophobia (sensitivity to light) and reduction in visual acuity due to sudden stromal oedema. This is caused by breaks in the Descemet's membrane (deep layer in the cornea) due to progressive ectasia.

Reported ocular associations of keratoconus include vernal keratoconjunctivitis, retinitis pigmentosa, and Leber's congenital amaurosis. Systemic putative associations include many of the connective tissue disorders (for example Ehlers-Danlos and Marfan syndromes), mitral valve prolapse, atopic dermatitis, and Down's syndrome (Rabinowitz 1998). The outcomes of the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study showed that keratoconus is not associated with increased risk of connective tissue disease (Wagner 2007).

Identified predisposing factors include atopic history, especially ocular allergies; rigid contact lens wear; and vigorous eye rubbing. In 13.5% of cases there is a family history of the disease (Zadnik 1996). The inheritance in these cases is thought to exhibit variable penetrance (Zadnik 1998). There is no sexual or racial predilection, although the incidence has been found to be higher or more severe in certain ethnic groups (Georgiou 2004).

There is a general observation that elderly patients with keratoconus are not seen as often in clinics, and some have postulated that the co-existing connective tissue disease may be contributory to a decreased life expectancy. However, a study showing that people with keratoconus do not have an increased mortality rate has disputed this (Moodaley 1992).

### Diagnosis

Keratoconus is unique among eye diseases in that it is typically diagnosed during peak education, income-earning, and childbearing years (Wagner 2007). Keratoconus is diagnosed based on clinical examination and corneal topographic/tomographic analysis. There are several clinical signs for which the presence or absence of each is determined by the severity of the condition. An acute angulation, made by the ectatic cornea, can be seen in the lower lid on downgaze (Munson's sign). Fleischer's ring is a ring of epithelial iron deposition around the base of the cone. Vertical striae (Vogt's), which are fine stress lines in the Descemet's membrane, are detectable posteriorly. With time there is progressive thinning of the corneal stroma, and the ectasia may be clinically detectable. An 'oil droplet' sign is often visible by direct ophthalmoscopy on viewing the red reflex in a dilated eye. Scissoring and distortion of the reflex can be seen on retinoscopy (Zadnik 1996). After repeated attacks of hydrops, stromal scarring may be visible.

Computer-assisted videophotokeratoscopy or Scheimpflug imaging are sensitive means for detecting subtle changes in topography on the anterior and posterior corneal surface and allow detailed qualitative and quantitative analysis of corneal shape. Corneal topography measures the steepening in terms of a dioptric power map of the cornea. Various topographic indices have been proposed for preclinical diagnosis of keratoconus (forme fruste) or the diagnosis of keratoconus and grading of the severity of the disease. Classification of keratoconus can be based on morphology, disease evolution, ocular signs, and index-based systems of keratoconus. Smolek, et al. have developed the Keratoconus Severity Index using a neural network approach to data collected from corneal topography (Smolek 1997). Another method used to classify the disease is the Amsler-Krumeich classification of keratoconus, which depends on mean keratometry readings on the anterior curvature sagittal map, thickness at the thinnest location, and the refractive error of the patient. This classification is useful in choosing the best approach for treating keratoconus. The keratoconus percentage index, which combines many of the earlier indices, has been shown to have a high sensitivity in the videokeratoscopic identification of keratoconus (Li 2009). Keratoconus has three characteristics seen by videokeratoscopy that are not present in normals: an increased area of corneal power surrounded by concentric areas of decreasing power, inferior-superior power asymmetry, and skewing of the steepest radial axes above and below the horizontal meridian (Rabinowitz 1998). Keratoconus Severity Score is another simple tool that was developed using common clinical mark-

ers in addition to two corneal topographic indices: average corneal power and higher-order first corneal surface wavefront root mean square error, resulting in severity score (0 to 5) (McMahon 2006). Belin/Ambrósio Enhanced Ectasia Display is an integrated application in Pentacam system (Oculus Optikgeräte GmbH, Wetzlar, Germany) that combines data from maximal keratometry, tomographic thickness distribution, and enhanced elevation to facilitate the detection of keratoconus (Ambrósio 2003; Belin 2007). Additional metrics, such as epithelial thickness mapping with very high frequency ultrasound or high-resolution optical coherence tomography, can detect early keratoconus (Li 2012; Reinstein 2009; Reinstein 2010). Newer techniques include analysing biomechanical properties of the cornea using the Ocular Response Analyzer (Reichert, Depew, NY), which so far is limited in its ability to screen for keratoconus (Fontes 2010).

To date, the best and safest method of screening/diagnosing keratoconus is to use as many data as possible in combination with established clinical parameters.

The differential diagnosis of keratoconus includes keratoglobus, pellucid marginal degeneration, and posterior keratoconus.

## Aetiology and pathogenesis

Keratoconus has been reported in various clinical settings. It is most commonly an isolated sporadic disorder, or it may be associated with other rare genetic disorders, Down's syndrome, Leber's congenital amaurosis, connective tissue disorders, atopy, hard contact lens wear, eye rubbing, and a positive family history of the disorder. Several theories have been postulated regarding the aetiology of keratoconus.

The biomechanical characteristics of the normal cornea result from the collagen scaffold and collagen compound and their bonding with the collagen fibrils. The three-dimensional configuration of the collagen lamella fundamentally codetermines the cornea's resistance. Biochemical and immunohistochemical studies of the matrix's proteoglycans show differences between normal and keratoconic corneas (Meek 2005; Raiskup-Wolf 2008).

Despite intensive biochemical investigation into the pathogenesis of keratoconus, the underlying biochemical process and its aetiological basis remain poorly understood. Corneal thinning appears to result from loss of structural components in the cornea; the reason this occurs is not clear. Theoretically, the cornea can thin because it has fewer collagen lamellae than normal, fewer collagen fibrils per lamellae, closer packing of collagen fibrils, or various combinations of these factors. These conditions may result from defective formation of extracellular constituents of corneal tissue, a destruction of previously formed components, an increased distensibility of corneal tissue with sliding collagen fibres or collagen lamellae, or a combination of these mechanisms (Akhtar 2008; Hayes 2008). However, some biochemical studies have demonstrated that collagen composition in corneas with keratoconus was unaltered. Biochemical assays and immunohistological studies of

corneas with keratoconus suggest that the loss of corneal stroma after digestion by proteolytic enzymes could be caused by increased levels of proteases and other catabolic enzymes (Rabinowitz 1998). Knowing the natural course of keratoconus is important in order to understand the rate and severity of visual change. However, it is difficult to fully appreciate the natural course of the disorder, as usually the corneal changes have begun before the patient is first seen and, after that, treatment may modify the natural course (Krachmer 1984). CLEK study findings revealed that age appears to be a factor in severity-related outcomes in keratoconus (Wagner 2007).

## Disease progression

There is a general trend for the disease to progress, leading to a gradual increase in corneal curvature and decrease in visual acuity with consequent impact on quality of life (dependency, driving, mental health, near activities, and role difficulties) (Wagner 2007). There are no definitive criteria for progression, but parameters to consider are change in refraction (both sphere and cylinder), uncorrected and best-corrected visual acuity, and corneal topographical changes. The increase of the maximum keratometry reading by 1 dioptre or more ( $\geq 1$  D) remains the most frequently reported index of disease progression (Caporossi 2010; Hersh 2011; Raiskup-Wolf 2008; Wittig-Silva 2008).

## Treatment

It is possible in the early stages to use spectacles to improve vision, but as the disease progresses, rigid gas permeable contact lenses often offer the best vision. Various contact lens designs and fittings have been developed to adapt to the challenging needs of this disease, which typically progresses. The presence of corneal scarring, significant thinning, and intolerance to contact lens wear are indications for corneal transplantation (keratoplasty). In high-income countries, keratoconus is often the most common indication for keratoplasty in young adults.

Several new therapeutic options have emerged, including refractive, optical, and tectonic interventions, which slow the progression of disease and/or delay more invasive treatment.

There are several methods for corneal transplantation. Penetrating keratoplasty (replacement of the full thickness of the cornea) and, more recently, deep anterior lamellar keratoplasty (replacement of the front layers of the cornea only) are the most commonly performed surgical interventions (Shimmura 2006).

Intrastromal rings (Intacs, Ferrara, Kerarings) are small devices that can be implanted into the cornea in an attempt to flatten the corneal profile to achieve a better uncorrected visual acuity and to enhance contact lens tolerance (Rabinowitz 2007). However, this procedure has its own limitations. Firstly, it does not affect the underlying biochemical properties of the cornea. Secondly, there

is a limit to how much corneal flattening can be achieved. Most complications of intrastromal ring implantation can be reversed by removing the segment, but serious complications can occur, such as intraoperative corneal perforation, infectious keratitis (corneal infection), damage to the central visual axis, or corneal melt (Boxer Wachler 2003; Miranda 2003). Conductive keratoplasty has been used in an attempt to reduce the severity of astigmatism (Naoumidi 2005). 'Biotics' is a sequential method of treating large and complex refractive errors by several methods often involving intraocular lens implants. It has been used in keratoconus with treatment algorithms that involve various combinations of intracorneal rings, phacoemulsification, in-bag implants, iris clipped phakic lenses, and posterior chamber phakic lenses (Leccisotti 2006). It is likely that bioengineered corneas will be available in the future for transplantation and may offer superior optical results to currently available treatments (Carlsson 2003).

Collagen cross-linking (CXL) with ultraviolet A (UVA) light and riboflavin (vitamin B<sub>2</sub>) is a relatively new treatment that has been reported to slow the progression of the disease in its early stages (Spoerl 1998; Wollensak 2003; Wollensak 2006). The improvement in vision when combined with intracorneal ring segments has been found to be greater than when using the segments alone (Chan 2007).

## Description of the intervention

CXL with UVA and topical riboflavin is carried out in sterile conditions. There are two main established methods of performing the procedure: corneal epithelium off or corneal epithelium on, but different methods are currently being developed.

### Corneal epithelium off

In this method (Wollensak 2003; Baiocchi 2009; Hayes 2008), the epithelium of the central 7 mm of cornea is removed after installing topical anaesthesia (for example proxymetacaine 0.5%). The surface is then treated by the application of riboflavin 0.1% solution (10 mg riboflavin-5-phosphate in 10 ml dextran 20% solution which is iso-osmolar 0.1% riboflavin solution) for 30 minutes beginning 5 minutes before the start of irradiation. UVA radiation of 370 nm wavelength and an irradiance of 3 mW/cm<sup>2</sup> at distance of 1 cm from the cornea is applied for a period of 30 minutes, delivering a dose of 5.4 J/cm<sup>2</sup> (Wollensak 2006). Antibiotic drops are instilled as prophylaxis and a bandage contact lens is inserted, which is then removed at the follow-up visit once epithelial healing is complete.

Variations of this protocol include the use of pilocarpine 1% pre-operatively, a treatment area of 9 mm (Vinciguerra 2009), and the selective use of steroids in the postoperative regimen to prevent corneal haze (Vinciguerra 2012). Additionally, in eyes with a corneal thickness less than 400 microns after epithelial removal, there is a risk of corneal endothelial, lenticular, or intraocular UVA

damage (Kymionis 2012). To counter this, prior to application of UVA a hypo-osmolar (hypotonic) solution of riboflavin is used to swell the corneal stroma and hence increase the corneal thickness through a denuded epithelium. This technique was tried on corneal thickness (after epithelial removal) between 320 to 400 microns (Hafezi 2009)

### Corneal epithelium on

In this method, the corneal epithelium is kept on (Chan 2007; Pinelli 2007). In 2003, Boxer Wachler, et al. proposed a slight modification of the treatment using pre-operative anaesthetic eye-drops containing benzalkonium chloride to loosen the tight junctions of the corneal epithelial cells (Boxer Wachler 2003). The use of benzalkonium chloride may allow transepithelial cross-linking treatment without removal of the epithelium. This technique was designed to reduce postoperative pain and improve patient comfort. This modification is known as C3-R (Baiocchi 2009; Vicente 2010). In this technique, 30 minutes before the UVA treatment, 1 drop of pilocarpine 2% is installed and riboflavin solution is started (1 drop every 2 minutes with minimum 16 drops over 30 minutes). Topical anaesthetic drop is started 20 minutes before the treatment (1 drop every 4 minutes, repeated 4 times). Treatment with UVA irradiation lasts for a total of 30 minutes, adding 1 drop riboflavin every 5 minutes.

In both techniques, a bandage contact lens is inserted at the end of the procedure and removed after five days. A number of modified riboflavin formulations have been introduced to facilitate diffusion through the corneal epithelium (Caporossi 2013; Koppen 2011).

### Different techniques

A hybrid technique currently used in some centres is to perform epithelial disruption in the 9 mm zone using a special disrupter to create pockmarks in the corneal epithelium (Rechichi 2013). The primary goal is to maintain as much live epithelium as possible but also promote riboflavin penetration. The secondary goal is to reduce eye inflammation and to get the contact lens out of the patient within 48 hours. Riboflavin eye drops are instilled after disruption and every 2 to 5 minutes for at least 30 minutes before UVA radiation treatment.

Recent studies aiming to reduce the procedure time to 9 minutes have used higher power (up to 30 mW/cm<sup>2</sup> compared to 3 mW/cm<sup>2</sup> in the standard procedure). The goal is to achieve a rapid treatment protocol by using higher intensity UVA and shorter irradiation time. This technique (known as flash-linking or rapid cross-linking) aims to keep an equivalent energy dose to the standard irradiation of 3 mW/cm<sup>2</sup> whilst reducing the treatment time from 30 minutes to 9 minutes (Schumacher 2011).

Another technique currently being investigated is iontophoresis transcorneal delivery technique, which is a method of facilitating the penetration of riboflavin through the cornea through the use

of a low-intensity electrical current. Compared to the classic technique, iontophoresis shortens the time needed for riboflavin penetration and the duration of exposure to UVA radiation and does not require epithelium removal (Arboleda 2014; Mastropasqua 2014).

### How the intervention might work

CXL employs the photosensitiser riboflavin (vitamin B<sub>2</sub>), which when exposed to longer wavelength ultraviolet light (370 nm UVA), will induce chemical reactions (free radical production) in the corneal stroma and ultimately result in the formation of covalent bonds between the collagen molecules, fibres, and microfibrils. This increase in collagen bonding is thought to prevent further thinning and ectasia and as such slow or halt the progression of keratoconus. Some pre-clinical investigations, including biochemical and biophysical measurements, have demonstrated enhanced corneal rigidity and greater biomechanical stability of the cornea following this treatment (Raiskup-Wolf 2008; Wollensak 2003). Wollensak, et al. have further demonstrated a significant increase in collagen fibre diameter as the underlying histopathologic correlate after CXL. Increased resistance to pepsin digestion after cross-linking has been found, which might be important for keratoconus, as a significantly elevated activity of collagenases has previously been noted (Wollensak 2004).

### Why it is important to do this review

As mentioned above, CXL is the only treatment that claims to slow down the progression of keratoconus. CXL is carried out largely unregulated with very few standardised criteria available for identification of the ideal patient to benefit from the treatment. Keratoconus is very asymmetrical and at times a very slowly progressive disease; in particular, it is well known that the rate of progression slows with age (Hovakimyan 2012; Krachmer 1984). Short-term data from trials are available, but robust evidence on the long-term efficacy and safety of CXL is not and is needed. Keratometric indices are at present the main indicators of treatment effect. Changes in corneal biomechanics, which this treatment purports to induce, have not been studied in vivo (Ashwin 2009). This review examined evidence from the current literature (and will examine future trial results as and when they become available) to provide clinicians with answers about what they can expect of this relatively new treatment. This review also provided an evidence-based reference point for people with keratoconus who seek validated information regarding the efficiency of the specific treatment.

## OBJECTIVES

The objective of this review was to assess whether there is evidence that CXL is an effective and safe treatment for halting the progression of keratoconus compared to no treatment.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We included randomised controlled trials (RCTs).

#### Types of participants

We included all studies in which participants had been diagnosed with keratoconus. We have excluded no participants according to age. We had planned to exclude studies where participants had previous treatment, but in the event we did not identify any such studies.

#### Types of interventions

We included trials that compared collagen cross-linking (CXL) (with riboflavin and ultraviolet A (UVA)) to no treatment. We excluded trials that compared different ways of doing CXL and did not have a control (no treatment) group. We excluded trials examining the use of this treatment for conditions other than keratoconus.

#### Types of outcome measures

##### Primary outcomes

Two indicators were used to measure disease progression at 12 months after treatment:

- Increase in maximal keratometry (Kmax) of more than 1.5 D
- Worsening in uncorrected visual acuity of more than 0.2 logMAR

##### Secondary outcomes

Other indicators of disease progression:

- Mean maximal keratometry in dioptres at 12 months after treatment
- Mean uncorrected visual acuity at 12 months after treatment
- Mean average corneal power in dioptres at 12 months after treatment
- Mean corneal thickness at the thinnest part of the cornea 12 months after treatment

- Mean absolute spherical equivalent at 12 months after treatment
- Contact lens intolerance developed within 12 months of treatment

Safety measures: We looked at all adverse outcomes related to CXL reported in the included studies including the following:

- Infectious keratitis
- Corneal haze and scarring
- Glare and halo
- Reduction in uncorrected or best-corrected visual acuity
- Corneal epithelial defect
- Anisometropia
- Diplopia
- Induced astigmatism
- Reduction in contrast sensitivity
- Fluctuating vision (during the day or from day to day)
- Increased or decreased light sensitivity
- Endothelial cell damage as indicated by fall in endothelial cell density

#### Quality-of-life outcomes

One aim of this review was to summarise any validated quality-of-life measures used.

#### Economic data

One aim of this review was to summarise any data on cost or economics reported in the included studies.

### Search methods for identification of studies

#### Electronic searches

We searched the Cochrane Central Register of Controlled Trials (which contains the Cochrane Eyes and Vision Group Register) (CENTRAL; 2014, Issue 7), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to August 2014), EMBASE (January 1980 to August 2014), Latin American and Caribbean Health Sciences Literature Database (LILACS) (1982 to August 2014), Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1982 to August 2014), OpenGrey (System for Information on Grey Literature in Europe) ([www.opengrey.eu/](http://www.opengrey.eu/)), the *meta*Register of Controlled Trials (*m*RCT) ([www.controlled-trials.com](http://www.controlled-trials.com)), ClinicalTrials.gov ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)) and the World Health Organisation International Clinical Trials Registry Platform (ICTRP) ([www.who.int/ictcp/search/en](http://www.who.int/ictcp/search/en)). We used no date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 28 August 2014.

See: Appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), EMBASE (Appendix 3), LILACS (Appendix 4), CINAHL (Appendix 5), OpenGrey (Appendix 6), *m*RCT (Appendix 7), ClinicalTrials.gov (Appendix 8) and the ICTRP (Appendix 9).

#### Searching other resources

We searched other resources by handsearching book chapters, contacting clinical experts, and searching the reference lists of all included studies. We emailed all contact authors from the included studies asking for further information on their methodology and results.

### Data collection and analysis

#### Selection of studies

Two review authors (ES, RK) independently assessed all retrieved citations regarding eligibility for inclusion. The same two review authors obtained full-text copies of definitely or potentially relevant studies and assessed them carefully. We had non-English trial reports translated to determine whether they met the inclusion criteria. We also recorded the reasons for excluding studies. In cases where there were disagreements between the two review authors, a third review author was involved.

#### Data extraction and management

Two review authors (ES, JE) independently extracted data. We recorded on a form information about the methods used in the trial along with the following:

1. Details of participants (age, gender, setting, number in each group, grade of keratoconus, and comparability at baseline).
2. Details of intervention(s).
3. Outcomes (including adverse effects). For dichotomous data, the number of participants assigned to each intervention was collected and the number of participants who experienced the event. For continuous data, the mean and standard deviations were collected or calculated, or the median and interquartile range if the data were skewed, for each study.
4. Percentage of participants for whom no outcome data could be obtained.

Disagreements were resolved by discussion.

#### Assessment of risk of bias in included studies

Two review authors (ES, RK) independently assessed for risk of bias based on the following parameters and using Cochrane's tool for assessing risk of bias as specified in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).



1. Method of randomisation: We considered the method used to generate the random sequence within the trials at low risk of bias if it involved a computer random number generator, random number tables, shuffled cards, or envelopes.

2. Allocation concealment: Low risk would be central allocation or numbered, sealed, opaque envelopes.

3. Masking of participants, personnel, and outcome assessment.

4. Participant attrition: Were rates of follow-up similar in comparison groups? Was the analysis based on an intention-to-treat?

5. Selective reporting in terms of outcomes, time points, subgroups, or analyses.

We assessed and graded each parameter as follows: low risk of bias, high risk of bias, and unclear risk of bias.

We emailed all first authors of included trials twice for clarification where we judged risk of bias to be unclear, but received no response.

### Measures of treatment effect

The primary outcome variables (increase in maximum keratometry of 1.5 D or more and loss of 0.2 logMAR visual acuity or more) were dichotomous, and we used the risk ratio (RR) as the measure of treatment effect. Secondary outcomes were continuous; for these, we used the mean difference as a measure of treatment effect. We planned to report medians in the event that data were skewed, but where data were reported, means were available.

### Unit of analysis issues

We included both within-person and parallel group studies. We did not do any meta-analysis. For within-person studies, we calculated confidence intervals for the measures of effect without taking into account the pairing (due to lack of appropriately reported data). This is a conservative assumption. We requested raw data from the authors via email but the authors did not supply.

In future editions of this review that may include meta-analyses, we will analyse within-person and parallel group studies separately and then combine estimates using the generic inverse variance method. If data are not adequately analysed in the published reports, we will ask for raw data from the authors. If paired studies have been used, we will assess whether or not eyes were symmetric at baseline to see whether or not a paired approach seemed plausible. We will also examine whether or not effect estimates from paired studies seem consistent with those from unpaired studies.

### Dealing with missing data

We contacted authors regarding missing data. We did an available case analysis and judged the extent to which attrition bias might be a problem in the 'Risk of bias' table. We did not look at the potential impact of missing data in a sensitivity analysis (as planned in our protocol (Hamada 2013)) due to the sparsity of data and lack of meta-analysis.

### Assessment of heterogeneity

We planned to assess heterogeneity by looking at the clinical and methodological diversity of the studies and by examining the forest plots and  $I^2$  statistic as described in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). However, this was not required as we did not do any meta-analysis.

### Assessment of reporting biases

To assess publication bias, we performed a search of clinical trials registers to identify studies that have been completed but may not have been published. We addressed selective outcome reporting as part of the 'Risk of bias' assessment ([Assessment of risk of bias in included studies](#)).

### Data synthesis

We did not conduct any meta-analysis because we found only three eligible studies, and these studies did not report the required outcomes in the correct format to enable the data to be pooled. In future updates of this review, we will meta-analyse studies provided it is sensible to do so, for example, we find no evidence of substantial heterogeneity ( $I^2$  less than 50%), or the effect estimates are in the same direction. We will use a fixed-effect model if there are three or fewer studies and a random-effects model if more studies are available.

### Subgroup analysis and investigation of heterogeneity

If sufficient data are available in future updates of this review, we will perform a subgroup analysis to assess whether severity of keratoconus has an effect on response to treatment. We will use keratometry-based classification of disease severity (mild less than 45 D, moderate 45 D to 52 D, severe greater than 52 D) (Zadnik 1996).

### Sensitivity analysis

In future updates, providing sufficient data are available, we will do two sensitivity analyses: first, excluding studies at high risk of bias in one or more domains and second, excluding studies where missing data were imputed.

### Summary of findings table

We prepared a summary of findings table presenting relative and absolute risks. One author (JE) graded the overall quality of the evidence for each outcome using the GRADE classification ([www.gradeworkinggroup.org/](http://www.gradeworkinggroup.org/)) and the other authors checked this grading. We included the following outcomes in the summary of findings table.

- Progression
- Steepness of the cornea
- Uncorrected visual acuity

- Corneal thickness
- Absolute spherical equivalent
- Quality of life
- Adverse effects

These outcomes were not selected a priori as the summary of findings tables was not planned at the protocol stage.

## RESULTS

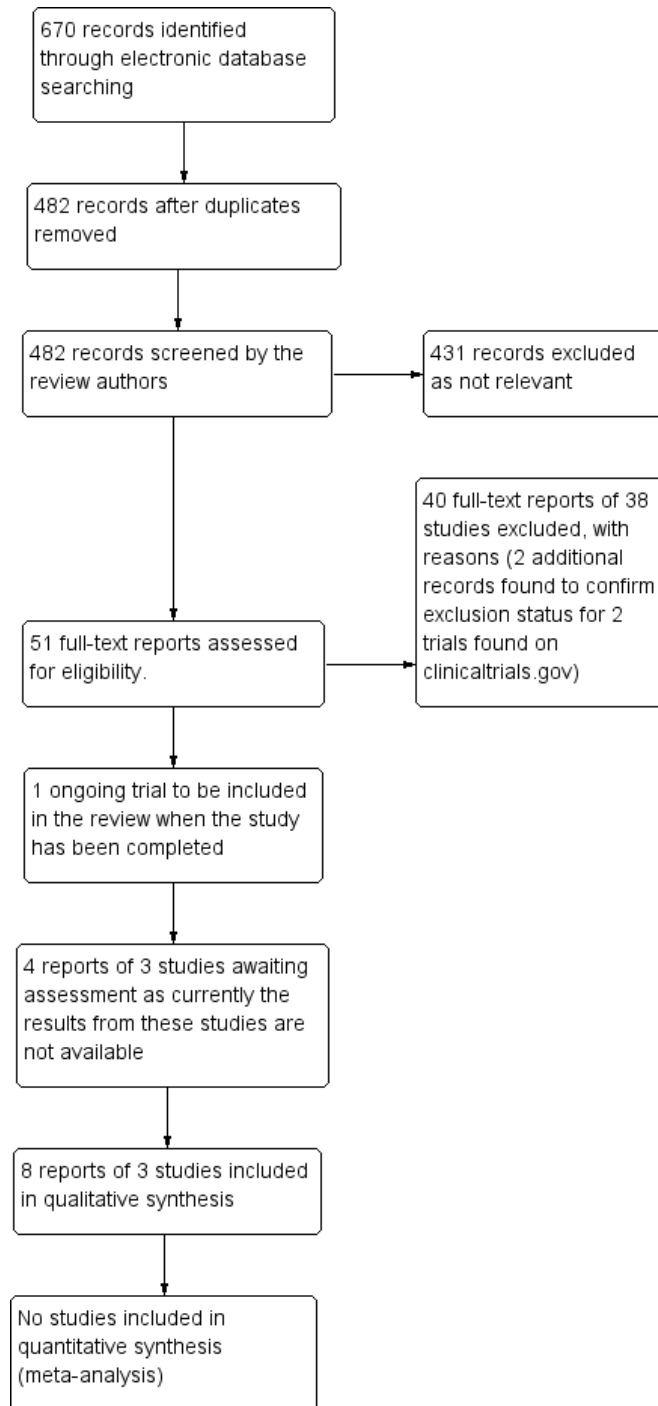
### Description of studies

#### Results of the search

The electronic searches yielded a total of 670 references ([Figure 1](#)). After removing duplicates, we reviewed 482 references and discarded 431 as not relevant to the scope of the review. We obtained 51 full-text reports to assess for potential inclusion in the review and included eight reports of three studies (see [Characteristics of included studies](#)) and excluded 40 reports of 38 studies (see [Characteristics of excluded studies](#)). We sought two additional reports of studies originally found on [clinicaltrials.gov](#) to help ascertain if these studies should be excluded. We also identified one ongoing trial (see [Characteristics of ongoing studies](#)) and aim to include this study in the review when completed, if appropriate. There were also four reports of three potentially relevant studies for which results were not currently available. If we are able to access the results for these studies, we could include them in further updates of this review (see [Characteristics of studies awaiting classification](#)).



**Figure 1. Results from searching for studies for inclusion in the review**



## Included studies

### Study populations

We included three RCTs that enrolled a total of 225 eyes and analysed 219 eyes. Out of these eyes, 119 had CXL with the epithelium off technique and 100 served as controls. The three trials were conducted in Australia (Wittig-Silva 2008), the United Kingdom (O'Brart 2011), and the United States (Hersh 2011). The number of eyes in each study was 100, 48, and 71, respectively. It was not clear how many participants were involved in Wittig-Silva 2008 or Hersh 2011; 24 people were included in O'Brart 2011.

All three trials randomly allocated eyes to treatment. O'Brart 2011 was a within-person study, but for the other two trials it was not clear how eyes within person were allocated. In Hersh 2011, apart from keratoconics, participants with iatrogenic corneal ectasia were studied, but the reports from the two groups were reported separately, and also of note is the fact that the control group was only half the size of the intervention group, and all controls were treated at three months.

All three trials included participants where there was topographic or refractive evidence of progression of keratoconus, but while O'Brart 2011 and Wittig-Silva 2008 excluded eyes where corneal pachymetry was less than 400µm, Hersh 2011 used as exclusion criterion corneal pachymetry of less than 300µm.

### Interventions and comparators

All three trials used the same technique for CXL with minimal variations. Epithelium was removed under topical anaesthesia, topical isotonic riboflavin solution of 0.1% was applied, and then the cornea was treated with UVA radiation (370 nm at 3 mW/cm<sup>2</sup>) for 30 minutes. In the trials by Wittig-Silva 2008 and O'Brart 2011,

there was no sham treatment for controls, while in Hersh 2011, the following sham treatment was used for controls: riboflavin was applied without epithelial debridement, followed by sham treatment in which the UVA light was not turned on.

### Outcomes and follow-up

Wittig-Silva 2008 reported 12-months results for a subset of the whole cohort and subsequently published 12-months and 36-months results for a larger group of participants. Hersh 2011 reported findings at 12 months, and O'Brart 2011 at 18 months follow-up.

### Funding sources

Hersh 2011 was supported in part by Peschke Meditrade GmbH, Zurich, Switzerland, and an unrestricted grant to the Department of Ophthalmology, University of Medicine and Dentistry of New Jersey-New Jersey Medical School from Research to Prevent Blindness, Inc., New York, New York, USA.

O'Brart 2011 was funded by Guy's and St. Thomas' NHS Foundation Trust, own account, NHS R&D Support Funding.

Wittig-Silva 2008 was funded by the Royal Victorian Eye and Ear Hospital Research Fund, Eye Research Australia Foundation, Scholarship for Postgraduate Studies (Faculty of Medicine and University of Melbourne), and Contact Lens Society of Australia

### Excluded studies

We excluded 38 studies. See [Characteristics of excluded studies](#).

### Risk of bias in included studies

See [Figure 2](#); [Figure 3](#).

**Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.**

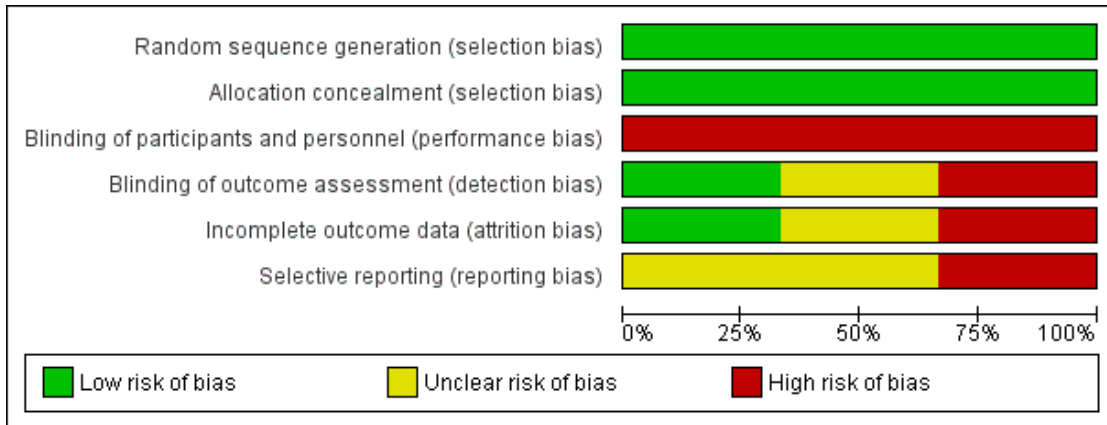


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Hersh 2011						
O'Brart 2011						
Wittig-Silva 2008						

## Allocation

Overall the trials were judged to be at low risk of selection bias. O'Brart 2011 and Wittig-Silva 2008 described computer-generated allocation schedules, and O'Brart 2011 used shuffled envelopes.

All three trials described methods to conceal the allocation. Hersh 2011 and O'Brart 2011 used sealed envelopes; Wittig-Silva 2008 described how the schedule was kept secure and managed by staff not involved in the trial.

## Blinding

All three trials were judged to be at high risk of performance bias. In two trials (O'Brart 2011; Wittig-Silva 2008), no attempt was made to mask participants or caregivers to the treatment (and indeed this would have been difficult due to the invasive nature of the treatment). Hersh 2011 had a sham treatment arm but reported that participants were aware of their randomly assigned group, so the significance of the sham treatment was unclear.

O'Brart 2011 was judged to be at low risk for detection bias as the visual acuity measurements were done by a masked observer who was not otherwise involved in the trial. For Hersh 2011, it was unclear the extent to which the outcome assessments were masked, as they did have a sham treatment group. We judged Wittig-Silva 2008 to be at high risk of detection bias, as they described the trial as "unmasked", and the treatment groups were quite different (treated/not treated).

## Incomplete outcome data

O'Brart 2011 was judged to be at low risk of attrition bias because it was a within-person study and therefore follow-up was equal between the two treatment groups.

Overall Wittig-Silva 2008 was judged to be at high risk of attrition bias due to differential follow-up: At one year 46 (92%) treated and 41 (82%) control eyes were followed up. Using last observation carried forward, data for 46 treated and 48 control eyes were reported. Over 3 years, 21 eyes in the control group left the trial, of which 12 were treated with CXL, 5 had corneal transplants, and 4 withdrew for personal reasons. In the treatment group, five people (eyes) withdrew for personal reasons. This unequal loss to follow-up meant that the control group was followed up, on average, for less time than the treatment group.

For Hersh 2011 it was unclear.

## Selective reporting

We did not have access to study protocols and in general felt we could not accurately judge the extent of selective reporting.

## Effects of interventions

See: [Summary of findings for the main comparison](#)

## Primary outcomes

See [Analysis 1.1](#)

### Increase in maximal keratometry of more than 1.5 D at 12 months after treatment

Wittig-Silva 2008 reported an interim analysis after 19 eyes (out of a total of 100 eyes) had been followed up to 1 year. Zero out of 9 eyes treated with CXL experienced an increase in maximal keratometry of 1.5 D or more at 12 months compared to 4 out of 10 eyes in the control group (risk ratio (RR) 0.12, 95% confidence interval (CI) 0.01 to 2.00).

Wittig-Silva 2008 did not report 12-months data for this outcome for the whole cohort, but at 36 months no treated eyes had increased by 2 D or more (out of 46 treated eyes), compared to 19 out of 48 eyes in the control group (RR 0.03, 95% CI 0.00 to 0.43). It must be noted that in Wittig-Silva 2008, 26 eyes were not followed up for the full 36 months, and last observation carried forward was used. The loss to follow-up was different between the two groups: 21 eyes in the control group left the trial, of which 12 were treated with CXL, 5 had corneal transplants, and 4 withdrew for personal reasons. In the treatment group, five people (eyes) withdrew for personal reasons. This unequal loss to follow-up meant that the control group was followed up, on average, for less time than the treatment group. The effect of this bias will probably be in favour of the control group (as keratoconus is a progressive disease, and the control group did not have so much time to progress). This means that the measure of effect is likely to be an underestimate of the size of the effect.

O'Brart 2011 did not report this outcome but did report "progression" at 18 months. Progression was defined as "an increase in both simulated keratometry (Orbscan II) and cone apex power by >0.75 D and consistent worsening of other measurements". According to this definition, 0 out of 22 treated eyes compared to 3 out of 22 untreated eyes progressed over the time period (RR 0.14, 95% CI 0.01 to 2.61).

Hersh 2011 did not report this outcome.

### Deterioration in uncorrected visual acuity of more than 0.2 logMAR at 12 months after treatment

None of the studies reported this outcome.

## Secondary outcomes

See [Analysis 1.2](#).

### Mean maximal keratometry in dioptres at 12 months after treatment

[Wittig-Silva 2008](#) reported that maximal keratometry in treated eyes decreased on average by 0.72 D (standard deviation (SD) 1.0) over 12 months in contrast to control eyes, where maximal keratometry increased on average by 1.2 D (SD 1.94), (mean difference (MD) -1.92 D, 95% CI -2.54 D to -1.30 D).

[O'Brart 2011](#) did not report this outcome.

[Hersh 2011](#) reported "no significant differences" between treated and control eyes at three months but did not report the data.

### Mean uncorrected visual acuity at 12 months after treatment

[Wittig-Silva 2008](#) reported that uncorrected visual acuity (UCVA) logMAR score in treated eyes decreased on average by 0.14 (SD 0.3) over 12 months in contrast to control eyes, where UCVA logMAR increased on average by 0.06 (SD 0.21) (MD -0.20, 95% CI -0.31 to -0.09).

[O'Brart 2011](#) reported that mean UCVA at 18 months was 0.33 (Snellen decimal equivalent) in 22 treated eyes and 0.21 in 22 untreated eyes. In the treated eyes, the UCVA on average changed by +0.06 compared to -0.01 in the control group. This gives a MD of 0.07 Snellen decimal equivalent (95% CI -0.04 to 0.18, estimated from P value of 0.2)

[Hersh 2011](#) reported "no significant differences" between treated and control eyes at three months but did not report the data.

### Mean average corneal power in dioptres at 12 months after treatment

[Wittig-Silva 2008](#) reported preliminary data on a subset of the trial followed up to one year. Average corneal power in treated eyes decreased on average by 1.2 D (estimate from graph, SD not reported, 9 eyes) over 12 months in contrast to control eyes, where corneal power increased on average by 1.10 D (SD not reported, 11 eyes). If we assume a SD of 1 D in both groups (based on other data in the paper), then this gives a MD of -2.30, 95% CI -3.18 to -1.42. This outcome was not reported for the whole cohort at one year.

[O'Brart 2011](#) reported that average corneal power decreased in the treated eyes over 18 months, but there was a discrepancy in the paper such that it was not clear whether the decrease was 0.62 D or 0.66 D. There was an increase of 0.14 D in the control group. As a P value was provided for the comparison between -0.66 D and 0.14 D (less than 0.001), we have estimated the CIs

for the difference between -0.66 D and 0.14 D. This gives a mean difference of -0.8 D (95% CI -0.36 to -1.24).

[Hersh 2011](#) reported "no significant differences" between treated and control eyes at three months but did not report the data.

### Mean corneal thickness at the thinnest part of the cornea 12 months after treatment

[Wittig-Silva 2008](#) reported that corneal thickness at the thinnest part of the cornea in treated eyes increased on average by 3.53  $\mu\text{m}$  (SD 23.7, 46 eyes) over 12 months in contrast to control eyes, where corneal thickness decreased on average by 5.4  $\mu\text{m}$  (SD 23.4, 48 eyes) (MD 8.93, 95% CI -0.60 to 18.46).

In [Hersh 2011](#) there was a change in pachymetry (thinnest part of the cornea) of -31.4  $\mu\text{m}$  (SD not reported) in the treated group at three months compared to a change of -2.3  $\mu\text{m}$  (no SD reported) in the control group.

In [O'Brart 2011](#) ultrasonic central corneal pachymetry increased by 4  $\mu\text{m}$  in 22 treated eyes compared to 6  $\mu\text{m}$  in 22 untreated eyes. (MD -2  $\mu\text{m}$ , 95% CI -33.01 to 29.01 (CI estimated from p-value of 0.9)).

### Mean absolute spherical equivalent at 12 months

[Wittig-Silva 2008](#) reported change in absolute spherical equivalent in treated eyes of 0.1 D (SD 2.6, 46 eyes) over 12 months compared to control eyes, where absolute spherical equivalent changed by -0.55 D (SD 2.42, 48 eyes). This gives a MD of 0.65 D, 95% CI -0.37 to 1.67.

### Contact lens intolerance developed within 12 months of treatment

Only one study mentioned contact lens intolerance ([O'Brart 2011](#)). Three out of 22 participants were contact lens intolerant pre-operatively. Two of these three participants ended up having intrastromal corneal ring segment insertion.

### Adverse outcomes

Only [O'Brart 2011](#) and [Wittig-Silva 2008](#) described adverse effects in their papers. In [O'Brart 2011](#), overall three participants were noted to have an adverse effect, including corneal oedema, anterior chamber inflammation, and a recurrent corneal erosion. In [Wittig-Silva 2008](#), 36-month results document 3 participants with adverse events: 1 case with mild diffuse corneal oedema and a paracentral infiltrate, 1 case with peripheral corneal vascularisation, and 1 case with subepithelial infiltrates and anterior chamber inflammation. No adverse effects were reported for any controls in any of the studies.

### Quality-of-life outcomes

Hersh 2011 reported this for the cohort of treated participants but did not provide a comparison between treated and untreated participants. The other studies did not report quality of life.

### Economic data

The included studies did not report economic data.

## DISCUSSION

### Summary of main results

We found three eligible trials that compared CXL versus no treatment, but one of these trials reported very little useable data. It was not possible to pool data due to differences in measuring and reporting outcomes. All three trials were at high risk of bias. We identified a further three unpublished trials.

There was indirect information on the risk of progression (which we defined as increase of 1.5 D or more in maximum keratometry). The available data suggest that there may be in the order of an 80% to 90% relative risk reduction in progression over 12 months, but we are very uncertain as to the size of the effect ([Summary of findings for the main comparison](#)).

Other data reported suggested that on average treated eyes had a less steep cornea (approximately 2 D less steep) and better uncorrected visual acuity (approximately 2 lines or 10 letters better), but again we judged the quality of the evidence to be very low, as it was largely derived from one trial at high risk of bias and there was the possibility of publication bias. The data on corneal thickness were inconsistent.

There were no data available on quality of life.

Adverse effects were not uncommon. In 1 trial, 3 out of 12 participants treated with CXL had an adverse effect, including corneal oedema, anterior chamber inflammation, and a recurrent corneal erosion. In 1 trial at 3 years, 3 out of 50 participants had experienced adverse events, including mild diffuse corneal oedema and a paracentral infiltrate, peripheral corneal vascularisation, and subepithelial infiltrates and anterior chamber inflammation.

### Overall completeness and applicability of evidence

Overall the evidence is incomplete, with only three trials reported with small sample sizes and at high risk of bias. Important outcomes, such as risk of visual acuity loss and quality-of-life measures, have not been reported. Only one trial followed up participants for longer than one year. As keratoconus is a slowly progressing disease, longer follow-up may be important.

With respect to applicability, the participants included in these studies were reasonably representative of patients likely to be interested in this treatment. We did not find any studies in children, which is an important omission in the evidence. The surgical techniques used are similar to those used in clinical practice.

### Quality of the evidence

The overall quality of the evidence was judged to be very low ([Summary of findings for the main comparison](#)). The main reasons for downgrading the evidence included risk of bias in the included studies, imprecision, indirectness and publication bias.

### Potential biases in the review process

We used standard methods expected by Cochrane. Search screening and data extraction were done independently by two review authors. We have clarified and amended the protocol for this review a little--in particular clarifying the comparison group and refining the outcomes. We do not believe that this will have introduced any bias into the review but note that the outcomes selected for presentation in the summary of findings table were not planned a priori but were selected while the review was in progress. We have documented all changes in [Differences between protocol and review](#).

### Agreements and disagreements with other studies or reviews

Although there are not many RCTs available, we did find a few systematic reviews and meta-analyses in the literature. The major one is performed by NICE ([NICE 2013](#); [Craig 2014](#)), which includes RCTs and prospective studies. This review concluded that there is evidence for the effectiveness of CXL in halting the progression of keratoconus. Performing meta-analysis by comparing qualitatively different maximal keratometry (Kmax) ([NICE 2013](#); [Gore 2013](#)) is clinically questionable, as different topography instruments have been used in different studies. Although most studies have used increase in Kmax of more than or equal to 1 D to report progression, we have chosen 1.5 D, as repeatability variations and limitations in measurement accuracy of most topographers is a well-known factor ([Szalai 2012](#)). In fact, in their meta-analysis, [Gore 2013](#), by using 1 D difference in Kmax to measure progression and regression, found that 10% of controls were found to have regression, something that does not normally happen in keratoconic corneas, confirming that 1.5 D is more appropriate clinically. Another meta-analysis, by [Chunyu 2014](#), concluded that further research from randomised trials is necessary to confirm whether CXL is an effective treatment. The difficulty in performing meta-analysis of RCTs is once more highlighted as we can see that the way studies are reported can be misleading for review authors. For

example, the study by [Henriquez 2011](#) identified by NICE as an RCT does not fit the strict criteria to be included in our review, as controls were recruited separately and their methodology did not include random allocation of treatment. Additionally, [Chunyu 2014](#) did not identify the fact that [Hersh 2011](#) was published in multiple publications which may have introduced bias.

## AUTHORS' CONCLUSIONS

### Implications for practice

Despite the numerous prospective and retrospective studies available in the literature and the fact that CXL seems to be accepted worldwide as a breakthrough treatment in the management of keratoconus, evidence is limited due to the lack of properly conducted RCTs. If strict criteria are used and only data from RCTs accepted, then there is a lack of evidence that CXL is indeed an effective treatment in halting the progression of keratoconus.

### Implications for research

Higher-quality studies are needed before an appropriate meta-analysis can be conducted to confirm the importance of this treatment. However, things look promising, as there seem to be multiple ongoing registered studies looking into the effectiveness of CXL, as well as studies looking into modifications of the treatment protocols.

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Vinciguerra P, Albe E, Trazza S, Seiler T, Epstein D. Intraoperative and postoperative effects of corneal collagen cross-linking on progressive keratoconus. *Archives of Ophthalmology* 2009;**127**(10):1258–65.

**Vinciguerra 2012**

Vinciguerra P, Albé E, Frueh BE, Trazza S. Two-year corneal cross-linking results in patients younger than 18 years with documented progressive keratoconus. *American Journal of Ophthalmology* 2012;**154**(3):520–6.

**Wagner 2007**

Wagner H, Barr JT, Zadnik K. Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study: methods and findings to date. *Contact Lens and Anterior Eye* 2007;**30**(4): 223–32.

**Wollensak 2003**

Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. *American Journal of Ophthalmology* 2003;**135**(5):620–7.

**Wollensak 2004**

Wollensak G, Wilsch M, Spoerl E, Seiler T. Collagen fiber diameter in the rabbit cornea after collagen crosslinking by riboflavin/UVA. *Cornea* 2004;**23**(5):503–7.

**Wollensak 2006**

Wollensak G. Crosslinking treatment of progressive keratoconus: new hope. *Current Opinion in Ophthalmology* 2006;**17**(4):356–60.

**Zadnik 1996**

Zadnik K, Barr J, Gordon M, Edrington T. Biomicroscopic signs and disease severity in keratoconus. Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study Group. *Cornea* 1996;**15**(2):139–46.

**Zadnik 1998**

Zadnik K, Barr JT, Edrington TB, Everett DF, Jameson M, McMahon TT, et al. Baseline findings in the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study. *Investigative Ophthalmology and Visual Science* 1998;**39**(13): 2537–46.

**References to other published versions of this review****Hamada 2013**

Hamada S, Patwary S, Amissah-Arthur KN, Bunce C, McDonnell PJ. Corneal collagen cross-linking for treating keratoconus. *Cochrane Database of Systematic Reviews* 2013, Issue 6. [DOI: 10.1002/14651858.CD010621]

\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies [ordered by study ID]

#### Hersh 2011

Methods	<p>Parallel group RCT</p> <p>Results reported by eye, but more eyes enrolled than people and unclear whether there was also within-person randomisation</p> <p>Study recruited participants with ectasia due to keratoconus and iatrogenic (after surgery for myopia). Only the keratoconus participants were included in this review</p>
Participants	<p>Country: USA</p> <p>Number of people randomised: not reported, (77 eyes)</p> <p>Average age: Not reported</p> <p>% women: Not reported</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> <li>• 14 years of age or older</li> <li>• axial topography pattern consistent with keratoconus</li> <li>• an inferior-superior ratio greater than 1.5 on topography mapping</li> <li>• corrected distance visual acuity worse than 20/20</li> <li>• diagnosis of progressive keratoconus, which was defined as 1 or more of the following changes over a period of 24 months: an increase of 1.00 D or more in the steepest keratometry measurement, an increase of 1.00 D or more in manifest cylinder, an increase of 0.50 D or more in MRSE.</li> </ul> <p>Exclusion criteria:</p> <ul style="list-style-type: none"> <li>• history of corneal surgery</li> <li>• corneal pachymetry less than 300 mm</li> <li>• history of chemical injury or delayed epithelial healing, pregnancy or lactation during the course of the study</li> </ul>
Interventions	<ul style="list-style-type: none"> <li>• CXL, following epithelial removal, with riboflavin 0.1% and UVA (370 nm at 3 mW/cm<sup>2</sup>) (n = 49 eyes)</li> <li>• Sham treatment (n = 28 eyes)</li> </ul> <p><i>“The sham control group received riboflavin 0.1% ophthalmic solution alone. In this group, the epithelium was not removed. Riboflavin was administered topically every 2 minutes for 30 minutes. Next, the cornea was exposed to a sham treatment in which the UVA light was not turned on, during which time riboflavin was administered topically every 2 minutes for an additional 30 minutes. The sham control patients were followed for 3 months postoperatively, at which point the study eye crossed over to the treatment group and received full CXL treatment.”</i> Hersh 2011 page 150</p>
Outcomes	<p>From clinical trials registry entry:</p> <p>Primary outcome:</p> <ul style="list-style-type: none"> <li>• Change in keratometry at 3 and 12 months</li> </ul> <p>No secondary outcomes listed.</p> <p>The following outcomes were reported in various publications:</p> <ul style="list-style-type: none"> <li>• Change in maximum keratometry values (Hersh 2011)</li> <li>• Change in average keratometry values (Hersh 2011)</li> <li>• Change in BSCVA (Hersh 2011)</li> </ul>

	<ul style="list-style-type: none"> <li>• Refractive sphere, astigmatism, MRSE (Hersh 2011, reported not statistically significant only, no data)</li> <li>• Adverse effects (Hersh 2011)</li> <li>• Patient questionnaire on visual functioning including driving, reading, double vision, glare, halos, dryness, pain, foreign body sensation (Brooks 2012, intervention group only)</li> <li>• Corneal thickness (Greenstein 2011)</li> <li>• Higher-order aberrations (Greenstein 2011, intervention group only)</li> <li>• Biomechanical changes (Greenstein 2011a)</li> </ul> <p>Follow-up: 1, 3, 6, and 12 months          Note: As the sham control group was treated at 3 months, comparisons are valid up to 3 months only</p>	
Notes	<p>Date study conducted: December 2007 to April 2011 (from trials register), but main publication accepted for publication in 2010</p> <p>Funding: <i>“Supported in part by Peschke Meditrade GmbH, Zurich, Switzerland, and an unrestricted grant to the Department of Ophthalmology, UMDNJ-New Jersey Medical School from Research to Prevent Blindness, Inc., New York, New York, USA”</i></p> <p>Conflict of interest: <i>“No author has a financial or proprietary interest in any material or method mentioned.”</i></p> <p><i>“Dr. Hersh is a paid medical consultant to Avedro, Inc.”</i></p> <p>Trial registration: NCT00647699</p>	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	<i>“Randomization was computer generated...”</i> Hersh 2011 page 150
Allocation concealment (selection bias)	Low risk	<i>“... on the procedure day, a sealed envelope was opened revealing whether the eye would be in the sham or treatment group”</i> Hersh 2011 page 150
Blinding of participants and personnel (performance bias) All outcomes	High risk	<i>“Patients were aware of their randomly assigned group.”</i> Hersh 2011 page 150 but the control group was given a sham procedure, it is not clear why if participants were told which group they were in
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Control group was given a sham procedure, but participants were aware of their status (see above)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Follow-up not reported.

**Hersh 2011** (Continued)

Selective reporting (reporting bias)	Unclear risk	We did not have access to the study protocol and could not accurately judge the extent of selective reporting
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**O’Brart 2011**

Methods	Within-person RCT Eyes randomly allocated to treatment, treated and untreated groups compared using unpaired t tests
Participants	Country: UK Number of people randomised: 24 (48 eyes) Average age: 30 years (range 21 to 42) % women: 21 Inclusion criteria: <ul style="list-style-type: none"> <li>early to moderate keratoconus (grade I to III according to the Amsler-Krumeich classification) with documented evidence or reported progression with reduced uncorrected visual acuity or BSCVA by more than 1 line and/or worsening of refractive or corneal astigmatism, keratometry, or cone apex power by 0.75 D over the previous 18 months.</li> </ul> Exclusion criteria: <ul style="list-style-type: none"> <li>advanced keratoconus where corneal irregularity/scarring prevented acquisition of accurate refractive and topographic data</li> <li>central corneal thickness &lt; 400 mm</li> <li>age &lt; 18 years</li> <li>pregnancy</li> <li>other active ocular pathology</li> <li>previous anterior segment surgery</li> <li>diabetes</li> <li>inability to remove rigid contact lenses for 3 weeks prior to examinations</li> </ul>
Interventions	<ul style="list-style-type: none"> <li>CXL, following epithelial removal, with riboflavin 0.1% and UVA (370 nm at 3 mW/cm<sup>2</sup>) (n = 24 eyes)</li> <li>Observation (n = 24 eyes)</li> </ul>
Outcomes	<ul style="list-style-type: none"> <li>Best corrected visual acuity</li> <li>Uncorrected visual acuity</li> <li>Spherical equivalent refractive error</li> <li>Refractive astigmatism</li> <li>Orbscan-simulated keratometry</li> <li>Adverse events</li> </ul> Follow-up: 1 week; 3, 6, 12, 18 months (outcomes reported at 18 months)
Notes	Date study conducted: June 2006 to December 2007 (anticipated recruitment dates as reported on trials register entry) Funding: Guy’s and St. Thomas’ NHS Foundation Trust, own account, NHS R&D Support Funding Conflict of interest: reported “none”



Trial registration: ISRCTN08013636		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<i>"Eyes were randomised to receive treatment using a shuffled closed envelope system by a member of staff not involved in the study. There were 36 envelopes (18 for right and 18 left). Sixteen right eyes and eight left eyes were randomly selected for treatment."</i> Page 1520
Allocation concealment (selection bias)	Low risk	<i>"Eyes were randomised to receive treatment using a shuffled closed envelope system by a member of staff not involved in the study. There were 36 envelopes (18 for right and 18 left). Sixteen right eyes and eight left eyes were randomly selected for treatment."</i> Page 1520
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel were not masked due to the nature of the intervention. Subjective measurements (visual-acuity assessment and refraction) in participants were undertaken by a masked observer (PP) not involved with either the randomisation process or the surgical procedure
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<i>"Subjective measurements (visual-acuity assessment and refraction) were undertaken by a masked observer (PP), not involved with either the randomisation process or the surgical procedure."</i> Page 1520
Incomplete outcome data (attrition bias) All outcomes	Low risk	Within-person study, so follow-up equal between treatment groups
Selective reporting (reporting bias)	Unclear risk	We did not have access to the study protocol and could not accurately judge the extent of selective reporting

Methods	<p>Parallel group RCT</p> <p>If both eyes of a participant were eligible, each eye was randomised independently</p>
Participants	<p>Country: Australia</p> <p>Number of people randomised: Not stated. 100 eyes</p> <p>Average age: 26 years</p> <p>% women: 43</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> <li>• age 16 to 50 years</li> <li>• unequivocal clinical and videokeratographic diagnosis of keratoconus</li> <li>• clinically significant progression of the ectasia over the preceding 6 to 12 months.</li> </ul> <p>Progression was considered to be confirmed if at least 1 or more of the following criteria were met: an increase of at least 1.00 D in the steepest simulated Kmax derived from computerized videokeratography or in the steepest meridian measured by manual keratometry; an increase in astigmatism as determined by manifest subjective refraction of at least 1.00 D; an increase of 0.50 D in MRSE; or a 0.1 mm or more decrease in back optic zone radius of the best-fitting contact lens.</p> <p>Exclusion criteria:</p> <ul style="list-style-type: none"> <li>• minimum corneal thickness 400 <math>\mu\text{m}</math></li> <li>• axial corneal scarring</li> <li>• previous refractive surgery or other corneal surgery</li> <li>• history of chemical burns, severe infections, or other corneal or ocular surface disease</li> <li>• pregnant or breastfeeding at the time of the treatment</li> </ul>
Interventions	<ul style="list-style-type: none"> <li>• CXL, following epithelial removal, with riboflavin 0.1% and UVA (370 nm at 3 mW/cm<sup>2</sup>) (n = 47 eyes)</li> <li>• Observation (n = 49 eyes)</li> </ul> <p>Eyes randomised to control were offered compassionate CXL (no earlier than 6 months after randomisation) during the course of study if continuing and significant progression was noted</p>
Outcomes	<p>As reported on clinical trials register entry:</p> <p>Primary outcome:</p> <ul style="list-style-type: none"> <li>• Maximum simulated keratometry value measured using computerised videokeratography (Orbscan II; Bausch and Lomb Surgical, Utah). Participants recruited after November 2007 were also imaged with Scheimpflug imaging (Pentacam HR, Oculus, Germany).</li> </ul> <p>Secondary outcomes:</p> <ul style="list-style-type: none"> <li>• Uncorrected visual acuity expressed as logMAR</li> <li>• BSCVA expressed as logMAR</li> <li>• Subjective refraction (sphere and cylinder) performed by trained orthoptists</li> <li>• Minimum simulated keratometry value measured using computerised videokeratography (Orbscan II; Bausch and Lomb Surgical, Utah). Participants recruited after November 2007 were also imaged with Scheimpflug imaging (Pentacam HR, Oculus, Germany).</li> <li>• Corneal thickness at the thinnest point using ultrasound pachymetry (Pachymeter SP-3000; Tomey, Nagoya, Japan), computerised videokeratography (Orbscan II; Bausch and Lomb Surgical, Utah) and Scheimpflug imaging (Pentacam HR, Oculus,</li> </ul>

	<p>Germany)</p> <ul style="list-style-type: none"> <li>• Endothelial cell density using the SP-2000 Specular Microscope (Topcon Corp, Tokyo, Japan)</li> <li>• Intraocular pressure using the Tono-Pen XL (Medtronic, Jacksonville, Florida) and Goldmann applanation tonometer (Haag-Streit, Koeniz, Switzerland)</li> </ul> <p>Follow-up: 5 years (on clinical trial register).          Outcomes reported to date: BSCVA and maximum and average keratometry values at 3, 6, 12, 24, and 36 months. At 12 months, results from 46 treated and 48 control eyes reported using LOCF</p>
Notes	<p>Date study conducted: June 2006 to June 2009 (as reported on trials register entry)          Funding: Royal Victorian Eye and Ear Hospital Research Fund, Eye Research Australia Foundation, Scholarship for Postgraduate Studies (Faculty of Medicine and University of Melbourne), and Contact Lens Society of Australia          Conflict of interest: reported <i>“The authors have no financial interest in the materials presented herein.”</i>          Trial registration: ACTRN12613000143729          Paper was published in 2011. <a href="https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=363630">https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=363630</a></p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<i>“Enrolled eyes were randomized separately to either the treatment or control groups using a computer generated randomization plan with blocks of 10. If both eyes of 1 patient qualified for participation in the study, each eye was randomized independently”</i> Page 813, Wittig-Silva 2014
Allocation concealment (selection bias)	Low risk	<i>“The randomisation plan was maintained in a secure location by a staff member in another hospital department not involved with the recruitment or conduct of the study”</i> Page 813, Wittig-Silva 2014
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study was described as open label (masking not used) on clinical trials registry entry
Blinding of outcome assessment (detection bias) All outcomes	High risk	The study was described as open label (masking not used) on clinical trials registry entry. <i>“All images were acquired and analyzed in an unmasked manner”</i> . Page 813, Wittig-Silva 2014

Incomplete outcome data (attrition bias) All outcomes	High risk	Differential follow-up: At one year 46 (92%) treated and 41 (82%) control eyes followed up to 12 months. Using LOCF, data for 46 treated and 48 control eyes were reported. Over 3 years, 21 eyes in the control group left the trial, of which 12 were treated with CXL, 5 had corneal transplants, and 4 withdrew for personal reasons. In the treatment group, five people (eyes) withdrew for personal reasons. This unequal loss to follow-up meant that the control group was followed up, on average, for less time than the treatment group
Selective reporting (reporting bias)	High risk	Different cut-points used at different time periods: 1.5D or more reported at one year and 2D or more reported at 36 months

BSCVA: best spectacle-corrected visual acuity  
 CXL: Collagen cross-linkage  
 D: dioptre  
 Kmax: maximal keratometry  
 LOCF: last observation carried forward  
 logMAR: logarithm of the minimum angle of resolution  
 MRSE: manifest refraction spherical equivalent  
 RCT: randomised controlled trial  
 UVA: ultraviolet A

**Characteristics of excluded studies [ordered by study ID]**

Study	Reason for exclusion
Alessio 2013	Not an RCT
Caporossi 2010	Not an RCT
Caporossi 2013	Not an RCT
Coskunseven 2009	Not an RCT
Doors 2009	Not an RCT
Gkika 2012	Not an RCT
Goldich 2010	Not an RCT

(Continued)

Greenstein 2013	Not an RCT
Grewal 2009	Not an RCT
Hallahan 2014	Not an RCT
Henriquez 2011	Not an RCT
Holopainen 2011	Not an RCT
ISRCTN04451470	RCT comparing epithelium on or off
ISRCTN29378493	RCT comparing use of contact lenses before surgery or not
Jordan 2014	Not an RCT
Kilic 2012	Not an RCT
Koller 2009	Not an RCT
Kránitz 2014	Not an RCT
Mastropasqua 2013	RCT comparing two different cross-linking methods
Mazzotta 2007	Not an RCT
NCT01143389	RCT comparing two different riboflavin regimens
NCT01152541	RCT comparing two different riboflavin regimens
NCT01181219	RCT comparing epithelium on or off
NCT01325298	RCT comparing two different UVA dosing regimens
NCT01344187	RCT comparing riboflavin versus placebo
NCT01459679	RCT comparing three different treatment regimens
NCT01464268	RCT comparing two different riboflavin regimens
NCT01643226	RCT comparing riboflavin versus placebo
NCT01708538	RCT comparing epithelium on or off
NCT01868620	RCT comparing iontophoretic CXL with standard CXL
NCT01972854	RCT comparing riboflavin versus placebo

(Continued)

NCT02009709	RCT comparing two different irradiance levels
Poli 2013	Not an RCT
Razmjoo 2014	RCT comparing total and partial removal of the epithelium
Rechichi 2013	Not an RCT
Salman 2013	Not an RCT
Viswanathan 2013	Not an RCT
Wisse 2014	Not an RCT

RCT: randomised controlled trial

### Characteristics of studies awaiting assessment [ordered by study ID]

#### NCT00626717

Methods	RCT
Participants	30
Interventions	CXL with riboflavin and UVA light versus sham treatment
Outcomes	Keratoconus progression and endothelial cell loss
Notes	Primary completion date: December 2012 Principal investigator confirmed publication under review March 2015

#### NCT00841386

Methods	RCT
Participants	Target:150
Interventions	CXL with riboflavin and UVA irradiation versus sham treatment
Outcomes	<ul style="list-style-type: none"><li>• Best corrected visual acuity</li><li>• Spherical equivalent power of the cornea (best spectacle refraction)</li><li>• Kmax: the maximum corneal curvature</li><li>• Average corneal power of the cornea in the central 4 mm</li></ul>

**NCT00841386** (Continued)

Notes	Primary completion date: December 2011 Email sent to principal investigator October 2014 and March 2015 with no response
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**Serapicos 2009**

Methods	RCT
Participants	Target: 15
Interventions	CXL with riboflavin and UVA light versus control
Outcomes	Stop progression of keratoconus in cornea imaging exams
Notes	Primary completion date: August 2009 Abstract reporting first two cases published 2009 Email sent to principal investigator October 2014 and February 2015 with no response

CXL: Collagen cross-linkage

RCT: randomised controlled trial

UVA: ultraviolet A

**Characteristics of ongoing studies** [author-defined order]**NCT01604135**

Trial name or title	Collagen crosslinking for keratoconus--a randomized controlled clinical trial (CXL-RCT)
Methods	RCT
Participants	Target: 200
Interventions	CXL with riboflavin and UVX
Outcomes	Kmax (non-progression)
Starting date	May 2012
Contact information	Madeleine Zetterberg, 00463431000, madeleine.zetterberg@anatcell.gu.se
Notes	NCT01604135

BSCVA: best spectacle-corrected visual acuity

CXL: Collagen cross-linkage

Kmax: maximal keratometry

RCT: randomised controlled trial  
UVA: ultraviolet A



## DATA AND ANALYSES

### Comparison 1. Corneal collagen cross-linking versus sham or no treatment

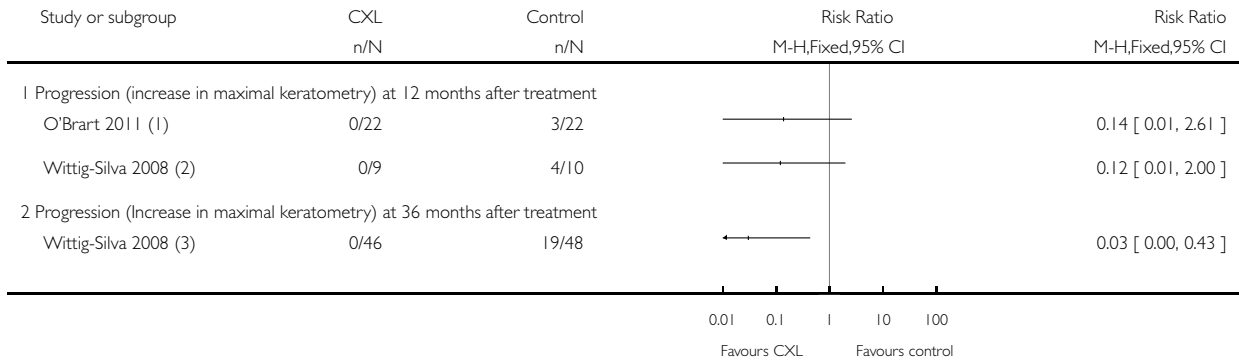
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary outcomes	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Progression (increase in maximal keratometry) at 12 months after treatment	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Progression (Increase in maximal keratometry) at 36 months after treatment	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Secondary outcomes	2		Mean Difference (Fixed, 95% CI)	Totals not selected
2.1 Mean maximal keratometry in dioptres at 12 months after treatment	1		Mean Difference (Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Mean uncorrected visual acuity at 12 months after treatment	1		Mean Difference (Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Change in mean corneal thickness ( $\mu\text{m}$ ) at the thinnest part of the cornea 12 months after treatment	2		Mean Difference (Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 Mean average corneal power in dioptres at 12 months after treatment	2		Mean Difference (Fixed, 95% CI)	0.0 [0.0, 0.0]
2.5 Mean absolute spherical equivalent at 12 months after treatment	1		Mean Difference (Fixed, 95% CI)	0.0 [0.0, 0.0]

**Analysis 1.1. Comparison 1 Corneal collagen cross-linking versus sham or no treatment, Outcome 1 Primary outcomes.**

Review: Corneal collagen cross-linking for treating keratoconus

Comparison: 1 Corneal collagen cross-linking versus sham or no treatment

Outcome: 1 Primary outcomes



(1) At 18 months: progression was "an increase in both simulated keratometry (Orbscan II) and cone apex power by >0.75 D and consistent worsening of other measurements"

(2) Increase of 1.5D or more

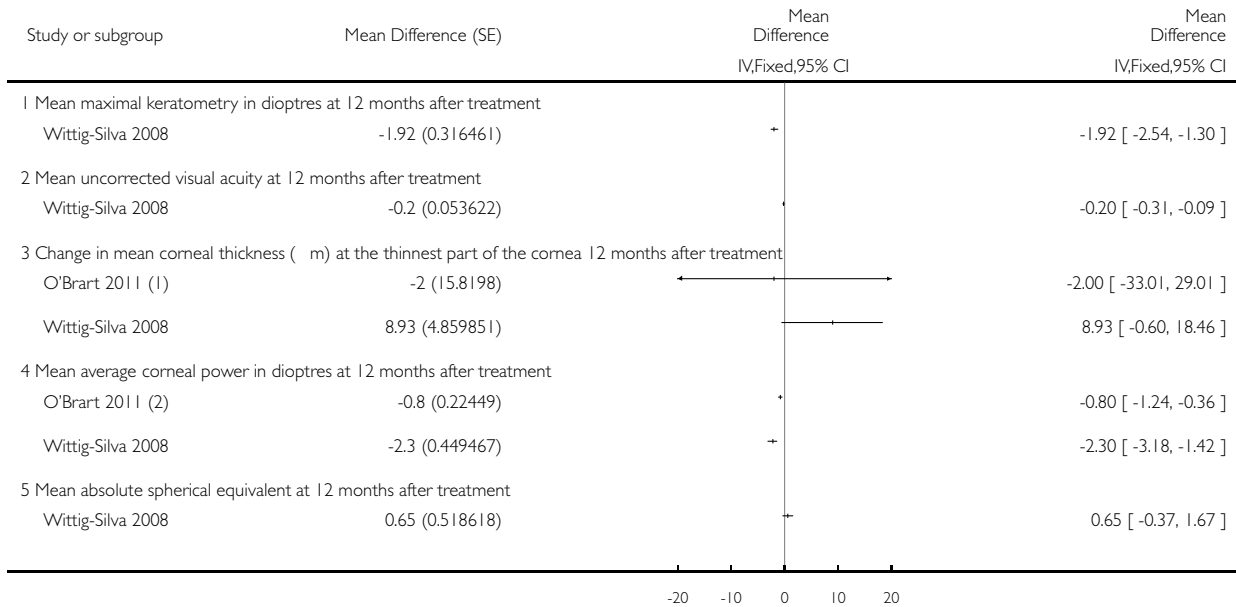
(3) Increase of 2D or more

## Analysis 1.2. Comparison 1 Corneal collagen cross-linking versus sham or no treatment, Outcome 2 Secondary outcomes.

Review: Corneal collagen cross-linking for treating keratoconus

Comparison: 1 Corneal collagen cross-linking versus sham or no treatment

Outcome: 2 Secondary outcomes



(1) 18 months follow-up

(2) 18 months follow-up

## APPENDICES

### Appendix 1. CENTRAL search strategy

- #1 MeSH descriptor Keratoconus
- #2 keratoconus
- #3 ectasia
- #4 (#1 OR #2 OR #3)
- #5 MeSH descriptor Collagen
- #6 collagen cross near/2 link\*
- #7 collagen crosslink\*
- #8 CCL
- #9 CXL
- #10 C3R

#11 (#5 OR #6 OR #7 OR #8 OR #9 OR #10)

#12 (#4 AND #11)

## Appendix 2. MEDLINE (OvidSP) search strategy

1. randomized controlled trial.pt.
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. exp keratoconus/
14. keratoconus.tw.
15. ectasia.tw.
16. or/13-15
17. exp collagen/
18. (collagen cross adj2 link\$.)tw.
19. collagen crosslink\$.tw.
20. CCL.tw.
21. CXL.tw.
22. C3R.tw.
23. or/17-22
24. 16 and 23
25. 12 and 24

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville ([Glanville 2006](#)).

## Appendix 3. EMBASE (OvidSP) search strategy

1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random\$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
13. (clin\$ adj3 trial\$.)tw.
14. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$)).tw.
15. exp placebo/
16. placebo\$.tw.
17. random\$.tw.
18. exp experimental design/

19. exp crossover procedure/
20. exp control group/
21. exp latin square design/
22. or/12-21
23. 22 not 10
24. 23 not 11
25. exp comparative study/
26. exp evaluation/
27. exp prospective study/
28. (control\$ or prospectiv\$ or volunteer\$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. exp keratoconus/
34. keratoconus.tw.
35. ectasia.tw.
36. or/33-35
37. exp collagen/
38. (collagen cross adj2 link\$).tw.
39. collagen crosslink\$.tw.
40. CCL.tw.
41. CXL.tw.
42. C3R.tw.
43. or/37-42
44. 36 and 43
45. 32 and 44

#### **Appendix 4. LILACS search strategy**

keratoconus or ectasia and collagen cross link\$ or collagen crosslink or CCL or CXL

#### **Appendix 5. CINAHL (EBSCO) search strategy**

- S24 S12 and S23
- S23 S15 and S22
- S22 S16 or S17 or S18 or S19 or S20 or S21
- S21 C3R
- S20 CXL
- S19 CCL
- S18 collagen crosslink\*
- S17 collagen cross link\*
- S16 (MH "Collagen")
- S15 S13 or S14
- S14 ectasia
- S13 keratoconus
- S12 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11
- S11 TX allocat\* random\*
- S10 (MM "Quantitative Studies")
- S9 (MM "Placebos")
- S8 TX placebo\*
- S7 TX random\* allocat\*

S6 (MM "Random Assignment")

S5 TX randomi\* control\* trial\*

S4 TX ((singl\* n1 blind\*) or (singl\* n1 mask\*)) or TX ((doubl\* n1blind\*) or (doubl\* n1 mask\*)) or TX ((tripl\* n1 blind\*) or (tripl\* n1mask\*)) or TX ((trebl\* n1 blind\*) or (trebl\* n1 mask\*))

S3 TX clinic\* n1 trial\*

S2 PT Clinical trial

S1 (MH "Clinical Trials+")

The search filter for trials at the beginning of the CINAHL strategy was developed by the Scottish Intercollegiate Guidelines Network ([SIGN 2010](#)).

## Appendix 6. OpenGrey search strategy

keratoconus AND collagen cross

## Appendix 7. metaRegister of Controlled Trials search strategy

(keratoconus or ectasia) and (collagen cross or CCL or CXL)

## Appendix 8. ClinicalTrials.gov search strategy

(keratoconus OR ectasia) AND (collagen cross OR CCL OR CXL)

## Appendix 9. ICTRP search strategy

keratoconus OR ectasia = Condition AND collagen cross OR CCL OR CXL = Intervention

## CONTRIBUTIONS OF AUTHORS

Conceiving the review: Cochrane Eyes and Vision Group

### Protocol:

Designing the review protocol: SH, PJM, SP, KAA

Providing general advice on the protocol: PJM

Writing the protocol: SH, SP, KAA, CB

### Review:

Co-ordinating the review: ES, SH

Statistical advice: CB

Screening included and excluded studies: ES, RK

Screening ongoing studies: ES, KAA, SP

Downloading of full text articles: RK, ES

Assessment of risk of bias: RK, ES, JE

Data extraction: ES, RK, JE

Analysis: RK, ES, JE

Critical review of the manuscript: PJM

Writing up the manuscript: ES, JE, RK, SH

## DECLARATIONS OF INTEREST

ES: None known

RK: None known

JE: None known

CB is a co-applicant of an National Institute for Health Research (NIHR) Efficacy and Mechanism Evaluation (EME) application to assess the efficacy and safety of cross-linking in children with keratoconus.

KAA: None known

SP: None known

PJM: None known

SH: None known

## SOURCES OF SUPPORT

### Internal sources

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### External sources

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- National Institute for Health Research (NIHR), UK.
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- The NIHR also funds the CEVG Editorial Base in London.

The views expressed in this publication are those of the authors and not necessarily those of the NIHR, NHS, or the Department of Health.

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol for this review was not explicit about how modifications of the CXL technique were to be handled. We decided to include only trials of treatment versus control in this review. There are a large number of ongoing studies that compare modifications of the technique and they will be included in future separate Cochrane reviews.

In this review's original protocol we defined mainly dichotomous secondary outcome measures using various cutpoints. However, these cutpoints were not reported. Trials in this field generally report these outcomes as continuous measures. Given the sparsity of the data, we felt that we would lose potentially relevant information, so we amended the secondary outcome measures to allow collection of continuous data.

The protocol did not specify the methods to be used when compiling the summary of findings table. We have prepared a summary of findings table but note the outcomes for presenting were selected at the same time as the review was being prepared.

## **INDEX TERMS**

### **Medical Subject Headings (MeSH)**

Collagen [\*chemistry]; Confidence Intervals; Cross-Linking Reagents [\*therapeutic use]; Disease Progression; Keratoconus [\*therapy]; Photosensitizing Agents [radiation effects; therapeutic use]; Randomized Controlled Trials as Topic; Riboflavin [radiation effects; therapeutic use]; Ultraviolet Therapy

### **MeSH check words**

Adult; Humans