

Photochemical corneal collagen cross-linkage using riboflavin and ultraviolet A for keratoconus and keratectasia

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1 Recommendations

This document replaces previous guidance on photochemical corneal collagen cross-linkage using riboflavin and ultraviolet A for keratoconus (interventional procedure guidance 320).

Most of the published evidence on photochemical corneal collagen cross-linkage (CXL) using riboflavin and ultraviolet A (UVA) for keratoconus and keratectasia relates to the technique known as 'epithelium-off' CXL. 'Epithelium-on (transepithelial) CXL' is a more recent technique and less evidence is available on its safety and efficacy. Either procedure (epithelium-off or epithelium-on CXL) can be combined with other interventions, and the evidence base for these combination procedures (known as 'CXL-plus') is also limited. Therefore, different recommendations apply to the variants of this procedure, as follows.

- 1.1 Current evidence on the safety and efficacy of epithelium-off CXL for keratoconus and keratectasia is adequate in quality and quantity. Therefore, this procedure can be used provided that normal arrangements are in place for clinical governance, consent and audit.
- 1.2 Current evidence on the safety and efficacy of epithelium-on (transepithelial) CXL, and the combination (CXL-plus) procedures for keratoconus and keratectasia is inadequate in quantity and quality. Therefore, these procedures should only be used with special arrangements for clinical governance, consent and audit or research.
- 1.3 Clinicians wishing to undertake epithelium-on (transepithelial) CXL, or the combination (CXL-plus) procedures should take the following actions:
 - Inform the clinical governance leads in their NHS trusts.
 - Ensure that patients and their parents or carers understand the uncertainty about the efficacy and safety of the procedures in the long term and provide them with clear information. In addition, the use of NICE's [information for the public](#) is recommended.
 - [Audit](#) and review clinical outcomes of all patients having these procedures for keratoconus and keratectasia.

- 1.4 Patient selection for these procedures should include assessment of corneal thickness and consideration of the likelihood of disease progression.
- 1.5 The procedures should only be carried out by ophthalmologists with expertise in managing corneal disease and specific training in the use of ultraviolet light or by appropriately trained staff under their supervision.
- 1.6 NICE encourages further research into CXL using riboflavin and UVA for keratoconus and keratectasia, especially epithelium-on (transepithelial) CXL and the combination (CXL-plus) procedures. Details of the techniques used should be clearly described. Reported outcomes should include visual acuity, corneal topography and quality of life. Data on long-term outcomes for all types of CXL using riboflavin and UVA for keratoconus and keratectasia would be useful – specifically data about prevention of progression to corneal transplantation and about repeat procedures and their efficacy.

2 Indications and current treatments

- 2.1 Keratoconus is a degeneration of the structure of the cornea in which the corneal surface thins and begins to bulge into a cone shape. This causes refractive error, which is usually a myopic shift and is often associated with astigmatism, leading to visual impairment. It commonly affects children and young adults and may be progressive. Iatrogenic keratoconus (for example, as a result of laser-assisted in situ keratomileusis [LASIK] surgery) is called keratectasia.
- 2.2 In mild to moderate keratoconus, visual acuity can be corrected using spectacles, contact lenses and in some cases intracorneal ring segment (ICRS) implantation. Keratectasia can be managed by using contact lenses or ICRS implantation. In advanced disease corneal surgery, including deep lamellar keratoplasty or penetrating keratoplasty, may be needed.

3 The procedures

- 3.1 The CXL procedures are normally done as outpatient procedures using topical anaesthesia, and typically take 60–90 minutes.

- 3.2 In epithelium-off CXL, the epithelium is first abraded with a blunt spatula to allow penetration of riboflavin into the corneal tissue. Riboflavin eye drops are applied to the corneal surface before the procedure and intermittently during the procedure. The corneal surface is exposed to UVA radiation: precise timings and treatment protocols vary. Postoperatively, topical antibiotics and anti-inflammatory drops are normally prescribed, with topical steroids if necessary. In some cases, a bandage contact lens may also be used for a few days. The procedure is done on 1 eye at a time and may also be repeated if needed.
- 3.3 In epithelium-on (transepithelial) CXL, the corneal epithelial surface is left intact (or may be partially disrupted) and a longer riboflavin loading time is needed.
- 3.4 Sometimes the procedure is used in combination with other interventions such as ICRS implantation, photorefractive keratectomy (PRK) or phakic intraocular lens (PIOL) implantation to improve visual acuity. These combination procedures are referred to as 'CXL-plus'.
- 3.5 The mechanism of action of the CXL procedures is not fully understood: they may increase the number of 'anchors' that bond collagen fibres together and strengthen the cornea. This is expected to stop the progression of the disease but the duration of benefit is uncertain.

4 Efficacy

This section describes efficacy outcomes from the published literature that the Committee considered as part of the evidence about these procedures. For more detailed information on the evidence, see the [systematic review](#) and the addendum to the systematic review.

- 4.1 A systematic review of the published evidence on these procedures was commissioned by NICE.

Epithelium-off CXL

- 4.2 In the studies included in the systematic review for epithelium-off CXL, meta-analysis of the change between preoperative and postoperative data for topography reported significant improvements in maximum keratometric values (max K) at 6, 12 and 24 months (-0.8 dioptres [D] at 6 months and -1.0 D at 12 and 24 months), and mean and minimum keratometric values (mean K and min K) at 12 months only (-1.0 D and -0.7 D for mean K and min K respectively).
- 4.3 Meta-analysis results for visual acuity reported significant improvement in corrected visual acuity (CVA) (-0.20 LogMAR) but not uncorrected visual acuity (UCVA) between intervention and control eyes on the LogMAR scale at 12 months follow-up. Meta-analysis of the change between preoperative and postoperative data showed significant improvements in UCVA postoperatively at 6, 12 and 24 months. Improvements on the LogMAR scale were in the order of -0.15 for UCVA and -0.10 for CVA at various time points.
- 4.4 Meta-analysis results for astigmatism reported no significant differences between the treatment and control groups at 12 months (-1.42 D). Differences between preoperative and postoperative data showed significant improvements at 6, 12 and 24 months (-0.4 D at 6 months, -0.7 D at 12 months and -0.5 D at 24 months). Change in spherical equivalence (SE) was only significant at 12 months (there was a reduction of between 0.3 and 0.5 D).
- 4.5 Meta-analysis of the change between preoperative and postoperative data showed a significant decrease (-14.4 micrometres) in central corneal thickness and no significant difference in intraocular pressure at 12 months follow-up.

Epithelium-off CXL in combination with other interventions (CXL-plus)

- 4.6 A randomised controlled trial in 48 eyes with progressive keratoconus (43 patients) compared 2 sequences of combined CXL and intracorneal ring segment (ICRS) implantation with a mean interval between treatments of

7 months. Group 1 had epithelium-off CXL followed by ICRS implantation and group 2 were treated by ICRS implantation followed by epithelium-off CXL. The mean UCVA and corrected distance visual acuity (CDVA) had improved significantly in both groups 6 months after the procedures (each group gained 1 Snellen line in UCVA, and group 1 gained 1 line in CDVA but group 2 gained only half a line). The same study reported statistically significant improvements in the mean SE, cylinder and mean K values in both groups but there was more improvement in CDVA, SE (2.76 D versus 0.93 D), and mean K (3.3 D versus 1.1 D) in group 2 than in group 1.

- 4.7 A randomised comparative case series of 42 eyes (21 patients) with bilateral keratoconus and 50 micrometres of epithelium removed by photorefractive keratectomy (PRK) compared 2 levels of exposure to UVA (both eyes were treated with CXL). In both groups mean uncorrected distance visual acuity improved, from 20/60 to 20/38 and from 20/62 to 20/40 Snellen lines respectively; CVA improved from 20/30 to 20/25 Snellen lines; mean SE was reduced by 2.5 D and 2.1 D; mean refractive cylinder was reduced by 2.9 D and 2.5 D; max K was reduced by 3.4 D and 2.9 D at 24 months.
- 4.8 A case series of 11 eyes (11 patients with progressive keratoconus) treated with CXL 6 months before phakic intraocular lens (PIOL) implantation and followed up 6 months after the PIOL implantation reported statistically significant improvement in mean UCVA (by 0.24 LogMAR 6 months after CXL, and by 1.24 LogMAR 6 months after PIOL) and CVA (by 0.02 LogMAR and 0.1 LogMAR at the 2 time points), reduction in mean K values (by 1.26 D and 2.14 D at the 2 time points), SE (by 0.45 D and 5.43 D at the 2 time points) and cylinder values (by 0.16 D and 0.55 D at the 2 time points).

Epithelium-on (transepithelial) CXL with or without additional interventions (CXL-plus)

- 4.9 A comparative case series of 51 eyes (51 patients with progressive keratoconus) treated with epithelium-on (transepithelial) CXL reported improvements in mean CDVA (by 0.036 LogMAR for CXL versus 0.039 LogMAR for control, $p < 0.05$), and reduction in mean K values (by 0.51 D

after CXL versus 1.61 D for control, $p>0.05$) and SE (0.35 D after CXL versus 0.83 D for control, $p<0.05$) at 12 months follow-up.

- 4.10 A case series of 14 eyes (10 patients with mild to moderate keratoconus) treated with epithelium-on (transepithelial) CXL and combined same-day corneal implants reported improvements in mean best corrected visual acuity (BCVA) (from 0.24 LogMAR to 0.16 LogMAR, $p=0.34$), and mean K values (45.83 D to 44.03 D, $p=0.0023$) at 3 years follow-up.
- 4.11 A case series of 21 eyes (13 patients) treated with ICRS implantation followed by CXL after a mean of 4 months reported improvements in mean UCVA and BCVA 6 months after CXL (UCVA from 0.05 to 0.23 LogMAR, $p=0.951$; BCVA from 0.18 to 0.41 LogMAR, $p=0.08$). The study also reported reductions in SE and cylindrical and mean keratometric values after ICRS implantation (2.8 D, $p<0.05$; 2.1 D, $p<0.05$; and 2.5 D, $p<0.05$ respectively) which were maintained 6 months after CXL.
- 4.12 The specialist advisers listed efficacy outcomes as arrest of progression of keratoconus and stabilisation of the corneal shape measured by topography, refraction and keratometry, refractive astigmatism, change in corneal thickness, cone apex power, quality of life and contact lens independence.

5 Safety

This section describes safety outcomes from the published literature that the Committee considered as part of the evidence about these procedures. This safety evidence is not subdivided by procedure variant because similar adverse events were reported for each. For more detailed information on the evidence, see the [systematic review](#) and the addendum to the systematic review.

- 5.1 Infections were reported in 8 single case reports. In 4 of these patients there was no major long-term adverse impact, visual acuity was reduced in 1 patient and no further details were reported in 3 patients.
- 5.2 Sterile keratitis associated with scarring or loss of vision or needing keratoplasty was reported in 3% (4/117) of patients in a case series of

117 patients. This was treated with high-dose topical or subconjunctival corticosteroids and 2 patients had a persistent decrease in BCVA. Deep stromal infiltrates with scarring at 2 months despite treatment with antibiotics was reported in a single case report.

- 5.3 Stromal scar developed in 4 patients (3 cases in 1 study); in 3 patients, the UCVA increased significantly despite scars, and in the other patient visual acuity was corrected with a lens.
- 5.4 Corneal oedema within 24 hours after CXL and inflammation for 2–3 weeks, iris atrophy and pigment dispersion were reported in a case series of 10 patients. These resolved in 1 patient and improved in 4 patients after treatment. Corneal oedema that developed in a single case report resolved after 6 months' treatment but scarring and poor visual acuity remained.
- 5.5 Corneal melting was reported in 1 single case report. This patient was initially treated with tissue glue and bandage contact lens application but needed penetrating keratoplasty on day 12. Perforation due to corneal melting was reported in 2 single case reports. These patients were treated by penetrating keratoplasty and antibiotics with no long-term adverse impact.
- 5.6 Corneal burn and ulcer were reported in 3 single case reports; 1 patient was treated by phototherapeutic keratectomy (CVA improved from 20/69 to 20/20 at 28 months) and treatment details were not reported for the other 2 patients.
- 5.7 Corneal haze with diffuse subepithelial opacification and paracentral corneal thinning associated with scarring was reported in a single case report. This disappeared only gradually despite intensive therapy.
- 5.8 Stromal haze was reported in all eyes in a randomised controlled trial of 10 patients comparing same-day ICRS and CXL with ICRS and CXL 6 months later. This resolved eventually in both groups (the time period was not reported). Mild posterior linear stromal haze at 1 month after CXL with PRK was reported in 46% of eyes (13/28) in a case series of 28 eyes (23 patients). At 12 months follow-up, this had decreased in density but had not completely disappeared.

- 5.9 The specialist advisers listed anecdotal adverse events as delayed epithelial healing, bilateral corneal infection and transient recurrent erosion syndrome. In addition, a specialist provided information about a single occurrence of corneal perforation after the procedure.

6 Committee comments

- 6.1 The Committee noted that these procedures may be useful for some disabled people who have keratoconus or keratectasia and who would need to wear contact lenses, but are unable to do so.
- 6.2 The Committee noted that the primary aim of the procedures is to stabilise vision by halting progression of keratoconus or keratectasia but that many of the studies reported improvement of vision as a secondary outcome.
- 6.3 The Committee noted that CXL techniques and precise treatment regimens are continuing to develop and evolve.
- 6.4 The Committee noted commentary from a patient group describing the serious impact that keratoconus or keratectasia can have on employment and quality of life. The Committee recognised the potential benefits that these procedures might offer, if further evidence supports their efficacy.

7 Further information

- 7.1 This guidance requires that clinicians undertaking the epithelium-on (transepithelial) CXL and combination (CXL-plus) procedures make special arrangements for audit. NICE has identified relevant audit criteria and has developed an [audit tool](#) (which is for use at local discretion).

Information for patients

NICE has produced information on these procedures for patients and carers ([Information for the public](#)). It explains the nature of the procedures and the guidance issued by NICE, and has been written with patient consent in mind.

About this guidance

NICE interventional procedures guidance makes recommendations on the safety and efficacy of the procedure. It does not cover whether or not the NHS should fund a procedure. Funding decisions are taken by local NHS bodies after considering the clinical effectiveness of the procedure and whether it represents value for money for the NHS. It is for healthcare professionals and people using the NHS in England, Wales, Scotland and Northern Ireland, and is endorsed by Healthcare Improvement Scotland for implementation by NHSScotland.

This guidance was developed using the NICE interventional procedures guidance process.

It updates and replaces NICE interventional procedure guidance 320.

We have produced a [summary of this guidance for patients and carers](#). Tools to help you put the guidance into practice and information about the evidence it is based on are also [available](#).

Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the available evidence. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. This guidance does not, however, override the individual responsibility of healthcare professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

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