Epithelium-off corneal cross-linking surgery compared with standard care in 10- to 16-year-olds with progressive keratoconus: the KERALINK RCT

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Scientific summary

The KERALINK RCT

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Scientific summary

Background

Keratoconus is a disease of the cornea affecting vision that is usually diagnosed in the second and third decades. The abnormality of corneal shape and thickness tends to progress from the age at onset until around the end of the third decade and then stabilise spontaneously. The KERALINK trial was designed to compare the efficacy and safety of corneal cross-linking in stabilising the progression of keratoconus with standard care by spectacle or contact lens correction in children and young patients. Keratoconus is characterised by thinning and distortion of the cornea that results in visual loss from complex refractive error and corneal opacification. The prevalence in Europe has been reported as 1 in 1163 (Nielsen K, Hjortdal J, Aagaard Nohr E, Ehlers N. Incidence and prevalence of keratoconus in Denmark. *Acta Ophthalmol* Scand 2007;**85**:890–2) and 1 in 375 (Godefrooij DA, de Wit GA, Uiterwaal CS, Imhof SM, Wisse RP. Age-specific incidence and prevalence of keratoconus: a nationwide registration study. *Am J Ophthalmol* 2017;**175**:169–72). Initial referral to hospital clinics typically occurs during the second or third decade (the mean age at diagnosis is 28 years), with progression until the early 30s in most affected eyes.

In its early stages keratoconus causes worsening of vision on account of increasing myopia and irregular astigmatism. Spectacle correction provides good visual acuity in early disease only; later, increasing irregular astigmatism requires correction with rigid contact lenses to achieve best vision. Patients with more advanced keratoconus lose contact lens-corrected visual acuity on account of corneal opacification, and corneal transplant surgery is eventually required in > 20% of patients. Keratoconus first diagnosed in children is often more advanced than that first diagnosed in adults, with faster subsequent disease progression.

The most important parameters used in the assessment of keratoconus are the curvature of the cornea [presented as dioptre power (D)], the apical corneal thickness in µm, refraction and best corrected visual acuity. Early disease can be detected by corneal topography, which demonstrates thinning and irregularity of corneal curvature. Quantification of steepness of the corneal curvature in horizontal, vertical and multiple oblique meridians identifies the mean power in the meridian of maximum corneal steepness (K2) and the point of maximum steepness (K_{max}).

Although current routine clinical care involves treatment of the consequences of keratoconus on refraction or replacement of the diseased cornea by a transplant, the concept of stabilising keratoconus and arresting its progression at a stage when there is still good uncorrected or spectacle-corrected vision is relatively recent. Corneal cross-linking increases the stiffness of the cornea, which can arrest the progression of early keratoconus. It is currently the only intervention for this purpose. In the epithelium-off corneal cross-linking procedure, the corneal epithelium is removed, riboflavin eye drops are administered and the cornea is exposed to ultraviolet light for ≥ 8 minutes. Corneal cross-linking has been reported to be effective in arresting keratoconus progression in the majority of treated adult eyes in a number of non-randomised studies (including Henriquez *et al.* 2011 and Hersh *et al.* 2011) and randomised controlled trials [O'Brart DP, Chan E, Samaras K, Patel P, Shah SP. A randomised, prospective study to investigate the efficacy of riboflavin/ultraviolet A (370 nm) corneal collagen cross-linkage to halt the progression of keratoconus. *Br J Ophthalmol* 2011;**95**:1519–24, and Wittig-Silva C, Chan E, Islam FM, Wu T, Whiting M, Snibson GR. A randomized, controlled trial of corneal collagen cross-linking in progressive keratoconus: three-year results. *Ophthalmology* 2014;**121**:812–21]. In the larger study by Wittig-Silva *et al.* in patients aged 16–50 years a significant difference in progression of corneal power in the steepest axis (termed 'K_{max}' by these authors but in later publications widely designated 'K2') between corneal cross-linking-treated and control eyes was reported: an improvement

in corneal cross-linking-treated eyes with flattening of K_{max} by −1.03 ± 0.19 D compared with an increase in the K_{max} of control eyes of +1.75 ± 0.38 D at 36 months (Wittig-Silva C, Chan E, Islam FM, Wu T, Whiting M, Snibson GR. A randomized, controlled trial of corneal collagen cross-linking in progressive keratoconus: three-year results. *Ophthalmology* 2014;**121**:812–21). Adverse effects were not uncommon but mostly transient, including corneal oedema, superficial opacification and recurrent corneal erosions. Despite increasing information in relation to the efficacy of corneal cross-linking, a Cochrane Review conducted in 2015 concluded that evidence for the use of corneal cross-linking in the management of keratoconus is limited because of the lack of properly conducted randomised controlled trials (Sykakis E, Karim R, Evans JR, Bunce C, Amissah-Arthur KN, Patwary S, *et al.* Corneal collagen cross-linking for treating keratoconus. *Cochrane Database Syst Rev* 2015;**3**:CD010621).

A number of observational studies of corneal cross-linking in keratoconus in younger subjects (aged < 19 years) have been published, each with limitations but each reporting effectiveness. Inclusion criteria included several parameters that are well recognised to be characterised by inter-test variability. Findings included improved visual acuity, reduced K_{max}, reduced myopic spherical equivalent on refraction testing and flattening on keratometry readings compared with pre-corneal cross-linking. Godefrooij *et al.* reported progression in 22% within 5 years of corneal cross-linking (Godefrooij DA, Soeters N, Imhof SM, Wisse RP. Corneal cross-linking for pediatric keratoconus: long-term results. *Cornea* 2016;**35**:954–8). Although the findings from these studies suggested that there was a beneficial effect of corneal cross-linking, more robust evidence is required to inform practice. Of note, no randomised trial has been undertaken in young patients.

The KERALINK trial was designed to investigate the efficacy and safety of the established technique of corneal cross-linking in progressive keratoconus in the paediatric age group, in which there is high potential for keratoconus progression on account of early disease onset. KERALINK was a multicentre randomised controlled trial in this patient group evaluating epithelium-off corneal cross-linking, the technique of corneal cross-linking that has been demonstrated to be effective in adults. Although we intend to follow up the trial participants for several years to ascertain the duration of keratoconus stability, it is clear that arrested progression in a paediatric patient is likely to (1) obviate the need for contact lens correction and for later corneal transplant surgery and (2) have correspondingly greater health and cost benefits than if corneal cross-linking was undertaken in adults.

Trial design

An observer-masked, randomised controlled, parallel-group superiority trial in patients aged 10–16 years with progressive keratoconus receiving corneal cross-linking and standard care or standard care only.

Methods

Participants and interventions

Patients aged 10–16 years were recruited following confirmation of progressive keratoconus in one or both eyes on the basis of increase in K_{max} or K2 of at least 1.5 D over a minimum of 3 months. Participants were randomised to receive corneal cross-linking or standard care alone. The corneal cross-linking procedure comprised the removal of the corneal epithelium, administration of riboflavin eye drops (VibeX Rapid™; Avedro, Inc., a Glaukos company, Glaukos Corporation, San Clemente, CA, USA) and application of ultraviolet light using standardised parameters. Participants in the standard-care group received spectacles or contact lenses as necessary to correct vision.

Outcome measures

The primary outcome measure was K2, measured using Pentacam (Pentacam HR, Oculus GmbH, Wetzlar, Germany) corneal topography, at 18 months post randomisation. Secondary outcomes were keratoconus

progression (defined as increase of > 1.5 D in K2), time to progression, uncorrected and corrected visual acuity, refraction, corneal thickness at the keratoconus apex and vision-related quality of life assessed by Child Health Utility 9D and Cardiff Visual Ability Questionnaire for Children. Safety was analysed in all participants. Patients in both groups were followed up at 3, 6, 9, 12, 15 and 18 months post randomisation. Quality-of-life questionnaires were completed at 6, 12 and 18 months post randomisation. At each trial visit an observer, masked to the randomised allocation, obtained triplicate K2 and K_{max} measurements, the mean value of which was used in analyses.

Sample size

Using our definition of progression as an increase in K2 of > 1.5 D, a sample size of 46 patients was estimated to be required to detect a difference between groups at the 5% significance level with 90% power, assuming a standard deviation of 1.5 D. The total sample size was increased to 60 patients (30 in each group) to allow for up to 24% loss to follow-up. These estimates were based on 12- and 24-month data reported by Wittig-Silva *et al.*, from which we estimated a pooled standard deviation of the changes of 1.476 D. Following adjustment of the sample size to take account of 10% loss to follow-up, and assuming that 20% of the standard-care group would cross over to corneal cross-linking or proceed to corneal transplantation, our planned total sample size of 60 patients would still provide at least 80% power to detect the clinically important difference.

Randomisation

Patients were randomised in a 1 : 1 ratio to receive either corneal cross-linking or standard care using an independent online randomisation service. This computer-generated system was custom designed to trial requirements and used a minimisation algorithm incorporating a random element, stratifying by treatment centre and whether progression was confirmed in one eye or both eyes at randomisation.

Statistical analysis

Analysis of the primary outcome was conducted following the intention-to-treat principle, with all randomised patients analysed in their allocated group whether or not they received their randomised treatment. A multilevel repeated measures linear regression model was used to estimate the difference between the treatment groups in K2 values at 18 months, adjusting for baseline values. A sensitivity analysis was conducted on the primary outcome to assess the robustness of results to treatment crossover or failure to receive any treatment following randomisation.

Each continuous secondary outcome measure on the study eye was analysed using a multilevel repeated-measures linear regression model: uncorrected and best corrected visual acuity [measured as logMAR (logarithm of the minimum angle of resolution) using Early Treatment of Diabetic Retinopathy Study vision testing chart], apical corneal thickness measurement (measured using ultrasound) and spherical equivalent refraction.

For categorical secondary outcomes, logistic regression models were fitted to examine the effect of treatment on keratoconus progression (yes/no), defined as increase in K2 of > 1.5 D from randomisation to 18 months or requirement for change from spectacles to rigid contact lenses for correction of vision and refractive astigmatism (absolute value of cylinder power > 0.75 D). Subgroup analysis was undertaken to investigate whether the effect of treatment differed according to ethnicity or history of atopy. We carried out exploratory analyses using both K2 and K_{max} values to establish which is a more sensitive measure of clinically/visually significant progression of keratoconus.

Results

Of the 60 recruited patients, all in the corneal cross-linking group and 28 patients in the standard-care group were analysed (intention to treat). Five patients crossed over from standard care to corneal cross-linking after 9 months and one patient in the corneal cross-linking group did not undergo the allocated procedure.

Primary outcome

The mean K2 in the study eye 18 months following randomisation was 49.7 D (standard deviation 3.8 D) in the corneal cross-linking group and 53.4 D (standard deviation 5.8 D) in the standard-care group. The adjusted difference in K2 in the study eye was −3.0 D (95% confidence interval −4.93 to −1.08 D; $p = 0.002$), meaning that K2 was 3 D lower at 18 months post randomisation in eyes receiving corneal cross-linking than in those receiving standard care.

Secondary outcomes

- Keratoconus progression in the study eye within 18 months occurred in only two patients (7%) randomised to corneal cross-linking, compared with 12 patients (43%) randomised to standard care. Cox proportional hazards regression analysis found that patients in the corneal cross-linking group had an 87% lower hazard of progression than those receiving standard care alone.
- Mean uncorrected and corrected visual acuity in the two groups diverged with time since randomisation. On average, the study eye of patients in the corneal cross-linking group had significantly better uncorrected and best corrected visual acuity at 18 months than the study eye of patients receiving standard care alone ($p = 0.002$ and $p = 0.002$, respectively).
- We found no significant differences between the corneal cross-linking group and the standard-care group in refraction, measured as spherical equivalent, or in apical corneal thickness at 18 months.
- Patients' quality of life improved from baseline in the corneal cross-linking group at 18 months as measured using Cardiff Visual Ability Questionnaire for Children and Child Health Utility 9D, but there was no significant difference between groups at 18 months ($p = 0.22$ and 0.14, respectively).
- There were no treatment-related adverse events in either group.

Conclusions

Main findings

The primary trial outcome finding was that corneal power in the steepest meridian (K2) in the study eye was 3 D lower in patients receiving corneal cross-linking than in those receiving standard care, and this difference was statistically significant. The finding of significant differences in uncorrected and best corrected visual acuity between the trial groups indicates that patients randomised to corneal cross-linking had significantly better vision at 18 months without and with spectacle correction, indicating that the difference between the groups was also clinically significant.

An important secondary outcome demonstrating efficacy of corneal cross-linking in halting keratoconus progression in this trial age group was that progression in the study eye by 18 months occurred in only 2 patients (7%) randomised to corneal cross-linking compared with 12 (43%) randomised to standard care. Time-to-event analysis indicated an 87% lower hazard of progression on the corneal cross-linking group ($p = 0.008$). These primary and secondary trial outcomes provide clear evidence of efficacy of corneal cross-linking in stabilising keratoconus progression in 10- to 16-year-olds with progressive keratoconus. There were no treatment related adverse events in either group.

Our findings in context of previously published reports

With respect to the important findings on keratoconus progression and visual acuity, our results are in agreement with those from randomised controlled trials in adult patients comparing corneal cross-linking with standard care for keratoconus. Our findings reduce the uncertainty on efficacy of corneal cross-linking and provide clear evidence in the paediatric age group.

The finding of significant progression in only 43% of patients receiving standard care, as defined by K2 change > 1.5 D after 18 months, is of particular note in the context of previously published reports. Earlier publications from uncontrolled studies reporting the effectiveness of corneal cross-linking in halting keratoconus progression in young patients could now be re-evaluated in the light of our observation.

It is possible that, in these uncontrolled studies, keratoconus that reportedly did not progress in some patients who were treated with corneal cross-linking might have spontaneously stabilised without intervention.

Strengths of the trial

Evidence is provided on progressive keratoconus up to the age of 16 years, a population in which there is currently no published randomised evidence. As the prognosis for long-term vision when keratoconus onset occurs at a young age is known to be poor, the greatest need is to identify the efficacy of corneal cross-linking in paediatric patients.

Precision in measurement of corneal power

Our trial used methods that directly address the key problem of measurement variability in corneal topography and used a definition of progression that required a greater change in K2, itself a more representative measure of corneal power than K_{max}, which has been more widely used in earlier studies.

Future work

The most important questions to be answered are whether or not (1) the arrest of keratoconus progression induced by corneal cross-linking is maintained in the long term and (2) the proportion of those receiving standard care who show significant progression increases with time.

Trial registration

This trial is registered as ISRCTN17303768 and EudraCT 2016-001460-11.

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