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A randomised, prospective study to investigate the efficacy of riboflavin/ultraviolet A (370 nm) corneal collagen cross-linkage to halt the progression of keratoconus

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ABSTRACT

Aims A blind, randomised, prospective, bilateral study to investigate the efficacy of riboflavin/ultraviolet A corneal collagen cross-linkage to halt the progression of keratoconus.

Methods 24 patients with early/moderate bilateral keratoconus with recent progression were recruited. One eye was randomly assigned to undergo collagen cross-linkage following epithelial removal with riboflavin 0.1% and ultraviolet A (370 nm at 3 mW/cm^2). The other remained untreated as a control. The follow-up was 18 months in 22 patients.

Results At 18 months, Orbscan II 3 mm, 5 mm keratometry and simulated astigmatism and cone apex power and wave-front measurements (Keraton Scout), including root mean square, coma and pentafoil showed significant reductions from baseline in treated compared with untreated eyes ($p=0.04$). In treated eyes at 18 months, the best spectacle-corrected acuity improved ($p=0.01$), and Orbscan II-simulated keratometry ($p<0.001$), 3 mm keratometry ($p=0.008$), simulated astigmatism ($p=0.007$), cone apex power ($p=0.002$), root mean square, coma, spherical aberration, secondary astigmatism and pentafoil ($p=0.05$) decreased from baseline. One treated eye experienced transient recurrent corneal erosions; otherwise there were no complications attributable to the treatment.

Conclusions Corneal collagen cross-linkage appears to be an effective and safe modality to halt the progression of keratoconus. Improvements in visual and topographic parameters are seen in some eyes.

INTRODUCTION

Keratoconus is a degenerative, non-inflammatory disorder, characterised by stromal thinning and secondary conical ectasia, resulting in irregular astigmatism and visual loss.[1] It is the commonest corneal dystrophy affecting one in 2000. Its pathophysiology is undetermined, thought to include biochemical, physical and genetic factors, and probably the final common pathway for several different disorders. Mild cases may be corrected with spectacles and soft contact lenses, while rigid contact lenses provide visual rehabilitation in the majority. Progressive disease can result in contact-lens intolerance and corneal scarring. Surgical intervention, typically corneal transplantation, is necessary in 10–25%.[2–5]

Riboflavin/ultraviolet A (UVA) corneal collagen cross-linkage is the first treatment which may stabilise keratoconus.[6] In laboratory studies, it increases stress–strain measurements of stromal tissue and its resistance to enzymatic digestion and thermal damage, and reduces its hydration rate.[7–11] It is thought to induce physical cross-linking of collagen via the lysyl oxidase pathway.[12]

Clinical studies have demonstrated its efficacy. In two initial uncontrolled studies, there was stabilisation of keratoconus with no alteration in corneal transparency and a reduction in keratometry.[12 13] Long-term follow-up has demonstrated stabilisation in 98% with continued reduction in keratometry and improvements in best spectacle-corrected visual acuity (BSCVA).[14] Other studies have demonstrated similar outcomes with reductions in corneal power and improvements in BSCVA and uncorrected visual acuity (UCVA).[15 16]

There is a paucity of randomised prospective clinical studies in the literature. The only published study to date presents interim results with limited follow-up.[17] We therefore designed this randomised, bilateral, observer-masked, prospective study (ISRCTN08013636). Twenty-four subjects with early to moderate bilateral keratoconus with reported progression were recruited. One eye of each was randomly assigned to undergo cross-linkage, with the other eye remaining untreated as a control over the 18-month follow-up period.

METHODS

Subjects

Following ethics committee and Medical Health Research Authority approval, 24 subjects were recruited from the corneal clinics at our hospital. The mean age was 29.6 years (range 21–42, median 30). Nineteen patients were male, and five were female.

Inclusion criteria included early to moderate keratoconus (grade I to III according to the Amsler-Krumeich classification) with documented evidence or reported progression with reduced UCVA or BSCVA by more than one line and/or worsening of refractive or corneal astigmatism, keratometry or cone apex power by 0.75 dioptre (D) over the previous 18 months.

Exclusion criteria included advanced keratoconus where corneal irregularity/scarring prevented acquisition of accurate refractive and topographic data, central corneal thickness <400 μm, age

<18 years, pregnancy, other active ocular pathology, previous anterior segment surgery, diabetes and inability to remove rigid contact lenses for 3 weeks prior to examinations.

Subjects were counselled as to the study aims and randomisation procedure. Written background information was given. An ophthalmic and medical history was taken, including refractive history, contact lens history, ophthalmic problems past and current, and family history.

Objective and subjective refraction, Snellen decimal equivalent UCVA and BSCVA, scanning-slit based topography (Orbscan II, Bausch & Lomb, Munich, Germany), Placido-disc based videokeratography with corneal wavefront analysis (Keraton Scout Corneal Analyzer, Optikon 2000, Rome, Italy), ultrasonic central corneal pachymetry (Pachmate DGH55, DGH Technology, Exton, Pennsylvania), slit-lamp biomicroscopy, tonometry and mydriatic funduscopy were performed. 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. For Orbscan II examinations, two scans for each eye were taken, and the average of values calculated. For Keraton Scout examinations, four scans for each eye were taken, and the highest-quality scan closest to the average keratometry values was selected for wavefront analysis and cone apex power measurement. The cone apex power was determined using the Cone Location and Magnitude Index.[18] The Cone Location and Magnitude Index software locates the cone centre and magnitude, by finding the steepest curvature with a 2.00 mm circle within the central 8.00 mm zone. The area-corrected average of all points outside the circle is subtracted from the area-corrected average of the points within the 2.00 mm circle. The area-corrected average of the points within the 2.00 mm circle is compared with a 2.00 mm circle 180° away. Results are used to determine if the steep area represents a cone.[18] From these examinations, 21 measure variables were analysed as outcome measures (see tables 1–5).

Prior to surgery, nine patients were wearing and tolerating well rigid contact lenses, four were wearing soft toric lenses, and 11 were managing with spectacles, three of whom had tried lenses and were intolerant of them. Patients were asked to refrain from rigid lens wear for 3 weeks and soft lens wear for 1 week prior to examinations.

We aimed to recruit 36 patients based. Owing to difficulties in recruitment from our single centre of patients who fitted the selection criteria, agreed to randomisation where the less affected eye may be treated and were willing to adhere to the rigorous follow-up protocol, only 24 subjects were recruited.

Table 1 Pre- and 18-month postoperative results in treated eyes (n=22)

Parameter	Preoperative	18 months	Difference	p Value
Spherical equivalent refractive error (D)	−2.34	−1.52	+0.82	0.06
Refractive astigmatism (DC)	−3.8	−4.3	−0.5	0.1
Uncorrected visual acuity (Snellen decimal equivalent)	0.27	0.33	+0.06	0.2
Best spectacle-corrected visual acuity (Snellen decimal equivalent)	0.82	0.94	+0.12	0.01
Pachymetry (μm)	483	487	+4	0.5
Orbscan-simulated keratometry (D)	47.14	46.52	−0.62	<0.001
Orbscan-simulated astigmatism (D)	4.1	3.6	−0.5	0.007
Orbscan 3 mm keratometry (D)	46.45	46.04	−0.41	0.008
Orbscan 5 mm keratometry (D)	45.08	44.7	−0.38	0.1
Keraton-simulated keratometry (D)	47.16	46.86	−0.3	0.1
Keraton-simulated astigmatism (D)	3.7	3.47	−0.23	0.1
2.00 mm cone apex power (D)	53.9	53.0	−0.9	0.002

D, dioptres; DC, diopters of cylinder.

Table 2 Pre- and 18-month postoperative results in untreated eyes (n=22)

Parameter	Preoperative	18 months	Difference	p Value
Spherical equivalent refractive error (D)	−2.66	−2.55	+0.11	0.7
Refractive astigmatism (DC)	−3.92	−4.56	−0.64	0.002
Uncorrected visual acuity (Snellen decimal equivalent)	0.22	0.21	−0.01	0.5
Best spectacle-corrected visual acuity (Snellen decimal equivalent)	0.78	0.91	+0.13	0.02
Pachymetry (μm)	482	488	+6	0.1
Orbscan-simulated keratometry (D)	47.08	47.22	+0.14	0.3
Orbscan-simulated astigmatism (D)	3.71	3.75	+0.04	<0.8
Orbscan 3 mm keratometry (D)	46.42	46.58	+0.16	0.3
Orbscan 5 mm keratometry (D)	44.75	44.88	+0.13	0.2
Keraton-simulated keratometry (D)	47.14	47.26	+0.12	0.6
Keraton-simulated astigmatism (D)	3.36	3.56	+0.2	0.1
2.00 mm cone apex power (D)	52.8	52.7	−0.1	0.6

D, dioptres; DC, diopters of cylinder.

Surgical procedure

Fully informed consent was obtained. 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.

Prior to surgery, three drops of tetracaine 1% and one of chloramphenicol 0.5% were instilled over 5 min. The patient was positioned beneath an operating microscope, the eyelid skin cleaned with chlorhexidine gluconate 2% and a lid speculum inserted. A 9.00 mm area of central epithelium was removed using a disposable corneal epithelial spatula (Malosa Medical, Elland, UK). Five drops of riboflavin 0.1% (manufactured in house based on the recipe developed by the original investigators[12]) were instilled. A period of 5 min elapsed before UVA exposure. UVA exposure was for 30 min and was identical in all 24 eyes utilising 370 nm UVA radiation, calibrated prior to surgery with a UV light meter at 3 mW/cm^2 with a beam diameter of 8.00 mm. Two UVA lamps were used, with the first 10 patients being treated with a device manufactured in-house

Table 3 Comparison of the difference between baseline and 18 months between treated and untreated eyes for refractive, visual and topographic measurements

Parameter	Treated eyes	Untreated eyes	Difference	p Value
Spherical equivalent refractive error (D)	+0.82	+0.11	+0.71	0.2
Refractive astigmatism (DC)	−0.5	−0.64	−0.14	0.9
Uncorrected visual acuity (Snellen decimal equivalent)	+0.06	−0.01	+0.07	0.2
Best spectacle-corrected visual acuity (Snellen decimal equivalent)	+0.12	+0.13	−0.1	0.98
Pachymetry (μm)	+4	+6	+2	0.9
Orbscan-simulated keratometry (D)	−0.66	+0.14	−0.8	<0.001
Orbscan-simulated astigmatism (D)	−0.5	+0.04	−0.54	0.04
Orbscan 3 mm keratometry (D)	−0.41	+0.16	−0.57	0.007
Orbscan 5 mm keratometry (D)	−0.38	+0.13	−0.51	0.04
Keraton-simulated keratometry (D)	−0.3	+0.12	−0.42	0.2
Keraton-simulated astigmatism (D)	−0.23	+0.2	−0.43	0.03
2.00 mm cone apex power (D)	−0.9	−0.1	−0.8	0.04

D, dioptres; DC, diopters of cylinder.

Table 4 Pre- and 18-month postoperative results (±1 SD) in treated eyes (n=22) corneal wave-front higher-order aberrations

Parameter	Preoperative (μm)	18 months (μm)	Difference (μm)	p Value
Root mean square	3.15±1.72	2.97±1.55	−0.18	0.01
Coma	2.78±1.76	2.63±1.59	−0.15	0.03
Trefoil	0.89±0.41	0.81±0.28	−0.08	0.2
Spherical aberration	0.11±0.54	0.03±0.62	−0.08	0.03
Secondary astigmatism	0.63±0.32	0.54±0.27	−0.09	0.004
Quatrefoil	0.27±0.2	0.23±0.15	−0.04	0.06
Secondary coma	0.31±0.21	0.27±0.19	−0.04	0.07
Secondary trefoil	0.19±0.16	0.16±0.13	−0.03	0.2
Pentafoil	0.10±0.08	0.08±0.07	−0.02	0.05

based on those used in the initial clinical studies[12 13] and utilising 370 nm emitting diodes (Roithner Lasertechnik, Vienna, Austria). In the next 14, the CMB Vega X-linker (CSO, Florence, Italy) was used. During UVA exposure, riboflavin 0.1% eye drops were administered every 3–5 min and tetracaine 1% drops administered if the patient reported discomfort.

Postoperative treatment and assessment

Following surgery, ofloxacin 0.3% and chloramphenicol 1% were administered, and the eye padded. Oral analgesics, ibuprofen 400 mg PRN three times a day and codeine phosphate 30–60 mg PRN four times a day, were prescribed. Three phials of benoxinate 0.4% were given, with instructions to be administered if the postoperative pain was severe and with a maximum dosage of 1 drop only every 2 h for a maximum of 48 h. Ofloxacin 0.3% eye drops were administered four times a day for 1 week and chloramphenicol 1% ointment at night for 2 weeks.

Postoperative examinations were at 1 week and at 1, 3, 6, 12 and 18 months. The patient was questioned concerning ophthalmic symptoms, and an examination was performed, including UCVA, BSCVA, objective and subjective refraction, Placido-disc and scanning-slit topography, corneal pachymetry, slit-lamp biomicroscopy, tonometry and mydriatic funduscopy.

Vector analysis

To investigate vector astigmatic change in the manifest refraction, a vector analysis was performed according to the system described by Retzlaff *et al.*[19]

Statistical methods

Paired Student t tests were used to compare preoperative and postoperative outcomes within the treated and untreated groups, and unpaired t tests were used to compare variables between the treated and untreated groups. Results with two-sided $p<0.05$ were considered statistically significant.

Table 5 Pre- and 18-month postoperative results (±1 SD) in untreated eyes (n=22) corneal wave-front higher-order aberrations

Parameter	Preoperative (μm)	18 months (μm)	Difference (μm)	p Value
Root mean square	3.08±1.39	3.10±1.48	+0.02	0.7
Coma	2.74±1.44	2.82±1.52	+0.08	0.1
Trefoil	0.85±0.43	0.81±0.39	−0.04	0.3
Spherical aberration	0.03±0.47	−0.03±0.48	−0.06	0.2
Secondary astigmatism	0.60±0.32	0.55±0.29	−0.05	0.4
Quatrefoil	0.21±0.11	0.17±0.08	−0.04	0.003
Secondary coma	0.32±0.24	0.31±0.22	−0.01	0.8
Secondary trefoil	0.15±0.09	0.13±0.08	−0.02	0.3
Pentafoil	0.06±0.03	0.08±0.06	+0.02	0.2

RESULTS

Preoperative data

Preoperatively, there were no differences between treated and untreated eyes in terms of spherical equivalent refractive error (SEQ), cylindrical correction, UCVA, BSCVA, topographic keratometric and astigmatic measurements, cone apex power, pachymetry and higher-order aberrations up to the fifth order ($p<0.3$).

Perioperative data and early postoperative recovery

Surgery was uncomplicated. Typically, further administration of tetracaine 1% drops was required 10–15 min following epithelial debridement, owing to reported sensations of ocular discomfort.

All patients reported ocular pain during the first 48 h, which typically settled over the following 48 h. At 1 week, the epithelial defect was closed in all eyes. In all but one eye, UCVA and BSCVA returned to preoperative levels by 1 month. In one eye, UCVA returned to preoperative levels at 1 month, but BSCVA was reduced until 3 months. At 1 month, an anterior stromal haze developed in all eyes within the treated area. This cleared in all eyes by the sixth postoperative month.

Spherical equivalent refractive error

Preoperatively, the mean SEQ in treated eyes was −2.34 D, and at 18 months, it was −1.52 D, representing a mean +0.82 D reduction in myopic SEQ (p=0.06) (table 1).

Preoperatively, the mean SEQ in untreated eyes was −2.66 D, and at 18 months, it was unchanged at −2.55 D (p=0.7) (table 2).

Comparison of the differences between baseline and 18 months between treated and untreated eyes for SEQ did not reach statistical significance (p=0.2) (table 3).

Refractive cylindrical correction

Preoperatively, the mean cylindrical error in treated eyes was −3.8 diopters of cylinder (DC) at 82°, and at 18 months, it was not significantly different at −4.3 DC at 82° (p=0.1) (table 1). Vector analysis demonstrated a mean 1.97 D change.[19]

Preoperatively, the mean cylindrical error in untreated eyes was −3.9 DC at 99°, and at 18 months, it had increased to −4.56 D at 95° (p=0.002) (table 2). Vector analysis demonstrated a mean 2.32 D change.[19]

Comparison of the differences between baseline and 18 months between treated and untreated eyes for cylindrical refractive error did not reach statistical significance (p=0.8) (table 3).

VISUAL PERFORMANCE

Uncorrected visual acuity

Preoperatively, the mean UCVA in treated eyes was 0.27, and at 18 months, it was unchanged at 0.33 (p=0.2) (table 1).

Preoperatively, the mean UCVA in untreated eyes was 0.22, and at 18 months, it was unchanged at 0.21 (p=0.5) (table 2).

Comparison of the differences between baseline and 18 months between treated and untreated eyes for UCVA did not reach statistical significance (p=0.2) (table 3).

Best spectacle corrected visual acuity

Preoperatively, the mean BSCVA in treated eyes was 0.8, and at 18 months, it had significantly increased to 0.94 (p=0.01) (table 1).

Preoperatively, the mean BSCVA in untreated eyes was 0.78, and at 18 months, it had significantly increased to 0.91 (range 0.25–1.2) (p=0.02) (table 2).

Comparison of the differences between baseline and 18 months between treated and untreated eyes for BSCVA did not reach statistical significance (p=0.98) (table 3).

Corneal pachymetry

Preoperatively, the mean pachymetric measurement in treated eyes was 483.4 μm, and at 18 months, it was unchanged at 486.8 μm (p=0.5) (table 1).

Preoperatively, the mean pachymetric measurement in untreated eyes was 481.6 μm, and at 18 months, it was unchanged at 487.7 μm (p=0.1) (table 2).

Comparison of the differences between baseline and 18 months between treated and untreated eyes for pachymetric measurements did not reach statistical significance (p=0.9) (table 3).

CORNEAL TOPOGRAPHY

Orbscan II measurements

Preoperatively, the mean simulated keratometry in treated eyes was 47.1 D, and at 18 months, it had decreased significantly to 46.5 D (p<0.001) (range −0.6 to +1.85 D). Statistically significant differences from preoperative values were also present at 6 and 12 months (figure 1). There were no differences in values at 6, 12 and 18 months (figure 1).

Preoperatively, the mean 3.00 mm keratometry in treated eyes was 46.45 D, and at 18 months, it had decreased significantly to 46.04 D (p=0.008). Preoperatively, the mean 5.00 mm keratometry in treated eyes was 45.08 D. At 18 months, it was unchanged at 44.7 D (p=0.1). Preoperatively, the mean simulated astigmatism (difference in maximum and minimum simulated keratometry) in treated eyes was 4.1 D, and at 18 months, it was significantly reduced at 3.6 D (p=0.007) (table 1).

Preoperatively, the mean simulated keratometry in untreated eyes was 47.1 D, and at 18 months, it was unchanged at 47.2 D (p=0.3). Preoperatively, the mean 3.00 mm keratometry in untreated eyes was 46.42 D, and at 18 months, it was unchanged at 46.58 D (p=0.3). Preoperatively, the mean 5 mm keratometry in untreated eyes was 44.75 D, and at 18 months, it was unchanged at 44.88 D (p=0.1). Preoperatively, the mean simulated astigmatism in untreated eyes was 3.7 D. At 18 months, it was unchanged at 3.75 D (p=0.8) (table 2).

Comparison of the differences between baseline and 18 months between treated and untreated eyes reached statistical significant for simulated keratometry (p<0.001), simulated astigmatism (p=0.04), 3 mm keratometry (p=0.007) (range −0.5 to +2.6 D) and 5 mm keratometry (p=0.04) (range −0.75 to +4.9 D), with treated eyes showing mean reductions in values and untreated eyes increasing (table 3).

Keraton Scout Corneal Analyzer

Preoperatively, the mean simulated keratometry in treated eyes was 47.2 D, and at 18 months, it was unchanged at 46.9 D (p=0.2). Preoperatively, the mean simulated astigmatism (difference in maximum and minimum simulated keratometry) in treated eyes was 3.7 D, and at 18 months, it was unchanged at 3.47 D (p=0.1) (table 1).

Preoperatively, the mean cone apex power in treated eyes was 53.9 D, and at 18 months, it was significantly reduced at 53.0 D (p=0.002) (range −1.35 to +3.69 D) (table 1). Statistically significant differences from preoperative values were also present at 12 months (figure 2) but not at 6 months, although there was a significant reduction in apex power from 6 to 18 months (p=0.01) (figure 2).

Preoperatively, the mean simulated keratometry in untreated eyes was 47.14 D, and at 18 months, it was unchanged at 47.26 D (p=0.6). Preoperatively, the mean simulated astigmatism in treated eyes was 3.36 D, and at 18 months, it was unchanged at 3.56 D (p=0.1). Preoperatively, the mean cone apex power in untreated eyes was 52.8 D, and at 18 months, it was unchanged at 52.7 D (p=0.6) (table 2).

Comparison of the differences between baseline and 18 months between treated and untreated eyes for simulated keratometry did not reach statistical significance (p=0.2), but for simulated astigmatism (p=0.03), which decreased in treated eyes and increased in untreated eyes, and cone apex power (p=0.04), significant differences were found (table 3).

Corneal wave-front measurements

Analyses of higher-order aberrations of the anterior corneal surface for a 6.0 mm pupil diameter preoperatively and at 18 months for treated and untreated eyes are shown in tables 4, 5.

In treated eyes, root mean square (RMS) values (p=0.01), coma (p=0.03), spherical aberration (p=0.03), secondary astigmatism (p=0.004) and pentafoil (p=0.05) were all significantly reduced at 18 months compared with preoperative levels (table 4).

In untreated eyes, quatrefoil values (p=0.003) were reduced at 18 months; all other values were unchanged (table 5).

Comparison of the differences between baseline and 18 months between treated and untreated eyes reached statistical significance for RMS (p=0.02), coma (p=0.008) and pentafoil (p=0.03), with mean values in treated eyes decreasing and those in untreated eyes increasing (table 6).

Improvement/progression of ectasia

Five treated eyes (23%) showed evidence of reduction of ectasia at 18 months, identified on the basis of a decrease in both simulated keratometry (Orbscan II) and cone apex power by >0.75 D and improvements in other refractive, visual, topographical keratometric and astigmatic parameters as well as RMS, coma, astigmatism, trefoil, secondary coma and secondary

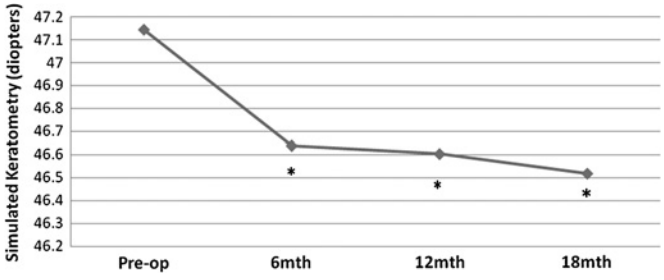

Figure 1 Mean simulated keratometry (Orbscan II) with time. *Statistically significant differences from preoperative values, p=0.002.

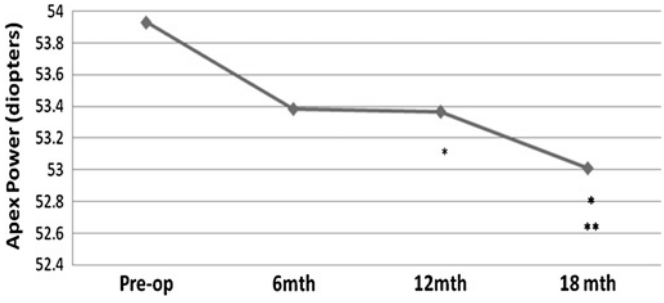

Figure 2 Mean apex power with time. *Statistically significant differences from preoperative values, p=0.05. **Statistically significant reduction in apex power at 18 months compared with values at 6 months p=0.01.

Table 6 Comparison of the difference between baseline and 18 months between treated and untreated eyes for wave-front measurements

Parameter	Treated eyes (μm)	Untreated eyes (μm)	Difference (μm)	p Value
Root mean square	−0.19	+0.02	−0.21	0.02
Coma	−0.15	+0.08	−0.23	0.008
Trefoil	−0.08	−0.04	−0.04	0.6
Spherical aberration	−0.08	−0.06	−0.02	0.7
Secondary astigmatism	−0.09	−0.05	−0.04	0.4
Quatrefoil	−0.04	−0.04	0	0.8
Secondary coma	−0.04	−0.01	−0.03	0.1
Secondary trefoil	−0.03	−0.02	−0.01	0.8
Pentafoil	−0.02	+0.02	−0.04	0.03

astigmatism. In contrast, three untreated eyes (14%) showed evidence of progression with an increase in both simulated keratometry (Orbscan II) and cone apex power by >0.75 D and consistent worsening of other measurements. No treated eyes appeared to show any evidence of progression, and no untreated eyes appeared to show any evidence of improvement, based on these criteria.

Complications

One patient experienced symptoms of recurrent corneal erosion with discomfort on waking in the treated eye during the first 9 months following surgery. Symptoms settled on topical lubricants. All patients who could tolerate contact lenses preoperatively were able to do so following surgery. Two of three patients who were contact-lens-intolerant preoperatively underwent intrastromal corneal ring segment insertion after the 18-month follow-up period.

DISCUSSION

Our study was designed as a randomised, bilateral, observer-masked prospective trial to investigate the efficacy of riboflavin/UVA corneal collagen cross-linkage. It was also designed to overcome some problems that can be encountered when undertaking a clinical study of keratoconus, including accurate assessment of outcome measures, the influence of contact lens wear and the variability in the natural history of the condition.

Keratoconus with its associated irregular astigmatism can make accurate assessment of subjective measurements (visual acuity and refraction) problematic. Even objective measurements, such as video-topography, can be limited due to epithelial irregularity and corneal scarring. We therefore only included patients with mild to moderate disease with no scarring or epithelial anomalies. We used a masked observer (an experienced hospital optometrist) to perform all subjective measurements and, in the case of topography, used two systems.

Some of our patients were reliant on rigid contact lenses. These have a potential to alter refractive and topographic measurements. We only included patients who were willing to remove hard lenses for 3 weeks prior to examinations. Although, we could not verify that this was always undertaken, as patients wore lenses in both eyes, and the study was bilateral and randomised, any potential for rigid lenses to bias our results should be minimised.

The progression of keratoconus is variable. Some cases remain stable for years or indefinitely, and others progress rapidly or experience occasional exacerbations. Typically, keratoconus progresses for 10–20 years before stabilising in middle age.[1] As the primary aim of the cross-linkage procedure is to halt progression, we enrolled patients who reported recent progression. We chose a follow-up period of 18 months in order to allow a reasonable time period to elapse during which progression might have been expected to occur.

Adverse events in our study were minimal and transient. All treated eyes exhibited some degree of anterior corneal haze in the early postoperative period which cleared by 6 months. There were no long-term complications associated with loss of corneal (or lenticular) transparency. There were no episodes of corneal infection, infiltration or scarring in our series, although these have been reported within the literature.[20–22]

The results of our study are encouraging. At 18 months, Orbscan-simulated and 3 mm keratometry and astigmatism, Keraton Scout-simulated astigmatism, cone apex power, RMS, coma and pentafoil decreased in treated eyes and increased/remained unchanged in untreated eyes, with significant differences between the means of postoperative changes from baseline (tables 3, 6). In treated eyes, there were significant improvements in 10 of 21 analysed parameters, including BSCVA, Orbscan simulated and 3 mm keratometry, simulated astigmatism and Keraton Scout calculated cone apex power, RMS, coma, secondary astigmatism, spherical aberration and pentafoil (tables 1, 4). In the case of cone apex power, there also appeared to be a continuing improvement with time (figure 2), a finding supported by the results of a recently published long-term paper.[14] In contrast, in untreated eyes there was significant worsening of refractive astigmatism. There were improvements in BSCVA in both groups, but these might be explained by our patients undergoing repeated refractive examinations every few months. No treated eyes appeared to progress during the follow-up period, with five (23%) showing consistent improvements. In contrast, three untreated eyes (14%) showed consistent deterioration in all parameters, which suggested progression. Such results are consistent with those from previous published studies[12–17] and provide further evidence that corneal collagen cross-linking using riboflavin and UVA not only appears to halt the progression of ectasia but can improve some visual and topographic parameters.

Competing interests None.

Ethics approval Ethics approval was provided by the Guy's and St Thomas' Ethic Committee.

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