Contralateral Eye Study of Corneal Collagen Cross-linking With Riboflavin and UVA Irradiation in Patients With Keratoconus

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ABSTRACT

PURPOSE: To assess the progression of keratoconus in patients treated with collagen cross-linking with riboflavin and ultraviolet A (UVA) irradiation.

METHODS: Thirty-eight eyes of 19 patients with progressive keratoconus were enrolled in a prospective comparative study. Average follow-up was 9±2 months (range: 5 to 12 months). The worse eye was treated with collagen cross-linking, and the fellow eye served as the control. Corneal epithelium was mechanically removed. Riboflavin 0.1% solution in dextran T-500 20% solution was applied every 2 to 3 minutes for 30 minutes throughout the irradiation. Ultraviolet A irradiation (370 nm) was performed using a commercially available UVA lamp for 30 minutes.

RESULTS: The group treated with collagen cross-linking demonstrated a mean decrease (less myopic) in spherical equivalent refraction and cylinder of 1.03±2.22 diopters (D) (range: −5.25 to +3.75 D) and 1.04±1.44 D (range: −2.00 to +4.00 D), respectively ($P<.01$), and an increase in uncorrected visual acuity (UCVA) and best spectacle-corrected visual acuity (BSCVA) of 0.06±0.05 (range: 0.00 to 0.20) and 0.10±0.14 (range: −0.10 to 0.34), respectively ($P<.01$). The maximal curvature decreased by 1.57±1.14 D (range: 0.00 to 3.90 D), and intraocular pressure increased by 2±2 mmHg (range: −1 to 6 mmHg), which was statistically significant. No statistical difference was noted regarding central corneal thickness ($P=.06$) and endothelial cell count ($P=.07$). The untreated group showed no statistical difference for any of the clinical parameters, apart from UCVA and BSCVA, which decreased by 0.08±0.12 (range: −0.40 to 0.10) and 0.06±0.09 (range: −0.20 to 0.10), respectively ($P<.01$).

CONCLUSIONS: Riboflavin/UVA collagen cross-linking appears to be efficacious in inhibiting the progression of keratoconus by reducing the corneal curvature, spherical equivalent refraction, and refractive cylinder in eyes with progressive keratoconus at average 9-month follow-up. [*J Refract Surg*. 2009;25:371-376.]

Keratoconus is an asymmetric, bilateral, progressive, and noninflammatory ectasia due to gradual biomechanical instability of the cornea. Its reported frequency is approximately 1 in 2000 in the general population.[1] The condition usually begins at puberty and progresses in approximately 20% of patients to such an extent that penetrating keratoplasty becomes necessary to preserve vision.[1]

Once the patient becomes contact lens intolerant, there are few surgical alternatives for correction. Expectations are limited, and consequences may be unpredictable, anatomically and functionally.[1] Only recently have advancements in corneal transplants become available, such as deep anterior lamellar keratoplasty and intra-lamellar keratoplasty, and the introduction of intracorneal rings, such as Intacs (Addition Technology Inc, Des Plaines, Ill), Ferrara rings (Ferrara Ophthalmics, Validolid, Spain), and Kerarings (Mediphacos Ophthalmic Professionals, São Paulo, Brazil) have provided additional alternatives to treat keratoconus.[2-5]

These vision-correcting methods attempt to regularize the front surface of the cornea while maintaining the biomechanical stability within the underlying stroma. In cases where the irregular astigmatism is progressive, such as keratoconus, pellucid marginal degeneration, and postoperative laser-induced iatrogenic ectasia, the corneal stroma is structurally weakened and may worsen following tissue ablation procedures.

Corneal collagen cross-linking with riboflavin and ultraviolet A (UVA) is a new technique of corneal tissue strengthening by using riboflavin as a photosensitizer and UVA to

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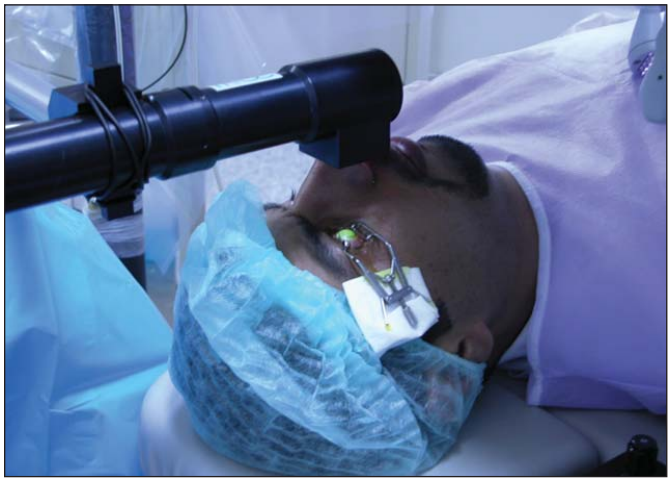

Figure 1. Treatment in progress with the cornea soaked with riboflavin and irradiated by the ultraviolet lamp.

increase the formation of intra- and inter-fibrillar covalent bonds by photosensitized oxidation.[6] This technique is similar to photo-polymerization in polymers, where biomechanical stabilization of the cornea is achieved. To correct irregular astigmatism due to a biomechanically unstable cornea, a primary intervention, such as collagen cross-linking, should be considered to potentially stabilize the cornea.

The aim of the present study was to compare the progression of keratoconus in fellow eyes when only one eye was treated with collagen cross-linking.

PATIENTS AND METHODS

Thirty-eight eyes of 19 patients (12 males and 7 females) with a mean age of 22±5 years (range: 18 to 30 years) and progressive keratoconus confirmed by an increase of maximal curvature on computerized corneal topography by at least 1.00 diopter (D) in the previous 6 months were enrolled in this prospective comparative study. The eye of each patient that showed more progression during the specified period was treated with collagen cross-linking, while the fellow eye served as the control. The average follow-up was 9±2 months (range: 5 to 12 months).

The following examinations were performed before and after surgery on all patients: uncorrected (UCVA) and best spectacle-corrected visual acuity (BSCVA) with manifest refraction in a bright environment, corneal topographic evaluation with the Pentacam (Oculus, Wetzlar, Germany), slit-lamp microscopy, indirect ophthalmoscopy, tonometry, and endothelial cell count by noncontact endothelial microscope (Noncon ROBO; Konan, Hyogo, Japan).

Because of the more advanced stage of keratoconus, the treated eyes showed worse UCVA and BSCVA, higher spherical equivalent refraction, cylinder, and maximal curvature (max K), and lower pachymetry. No statistical difference was noted regarding intraocular pressure (IOP) or endothelial cell count between the treated and untreated groups.

Patient inclusion criteria were keratoconus grade I to III according to the Amsler-Krumeich classification,[7] age ⩾18 years, contact lens intolerance, proof of evolution of the disease, and corneal thickness of at least 400 µm at the thinnest point. Exclusion criteria for this study were expectation for visual improvement; grade IV keratoconus; hydrops; corneal opacities; severe atopy; recurrent corneal erosion syndrome; herpetic keratitis; corneal dystrophies; endothelial cell count <1000 cell/mm^2; collagen vascular, autoimmune diseases, or other systemic diseases; pregnancy; and breast feeding. Paired Student *t* test was used for the statistical analysis.

All operations were performed by one surgeon (E.C.) from March 2006 to March 2007 at Dunya Eye Hospital, Istanbul, Turkey. The treatment procedure was conducted under sterile conditions in an operating theater. Topical anesthetic eye drops were applied. After abrasion of the corneal epithelium of 7 mm, 0.1% riboflavin solution in 20% dextran (PESCHKE Meditrade GmbH, Huenenberg, Switzerland) was applied on the cornea every 3 minutes for 30 minutes. The saturation of the cornea with riboflavin and its presence in the anterior chamber was monitored closely by slit-lamp inspection prior to treatment. Riboflavin saturation ensures the formation of free radicals whereas riboflavin shielding ensures the protection of deeper ocular structures, such as the corneal endothelium. Prior to treatment, ultrasound pachymetry was performed over the deepithelialized cornea at the thinnest point to ensure a minimal corneal thickness of 400 µm.

Ultraviolet A irradiation was performed using an optical system (Koehler illumination) consisting of an array of seven UVA diodes with a potentiometer in series to allow for regulation of voltage (UV-X, PESCHKE Meditrade GmbH) (Fig 1). Prior to treatment, intended 3 mW/cm^2 surface irradiance (5.4 J/cm^2 surface dose) was calibrated using a UVA meter (LaserMate-Q; LASER 2000, Wessling, Germany) at a working distance of 6 cm. Irradiance was performed for 30 minutes using 3 mW/cm^2, corresponding to a surface dose of 5.4 J/cm^2. During treatment, riboflavin solution and topical anesthetic (oxybuprocaine 0.4%) were applied every 2 to 3 minutes to saturate the cornea with riboflavin and prevent it from drying.

After treatment, ofloxacin 0.3% (Exocine; Allergan, Irvine, Calif) was applied and a bandage contact lens was fit to the corneal surface until re-epithelialization.

TABLE 1

Pre- and Postoperative Data for the Collagen Cross-linking Group

	Mean±Standard Deviation (Range)							
	SEQ (D)	Cyl (D)	UCVA	BSCVA	Max K (D)	Pachymetry (μm)	IOP (mmHg)	ECC (cells/mm²)
Preop	−5.76±4.31 (−15.50 to −1.00)	−4.26±2.04 (−9.00 to −1.50)	0.10±0.09 (0.01 to 0.30)	0.29±0.15 (0.05 to 0.60)	54.02±4.15 (46.80 to 64.00)	457±21 (420 to 498)	9±2 (5 to 11)	2624±213 (2247 to 3003)
Mean 9 mo postop	−4.73±2.90 (−12.00 to −0.88)	−3.22±1.79 (−6.25 to −0.50)	0.16 0.12 (0.05 to 0.40)	0.40±0.18 (0.10 to 0.70)	52.45±4.01 (46.30 to 62.70)	446±26 (390 to 504)	11±2 (7 to 15)	2596±234 (2159 to 3047)
P Value	<.01	<.01	<.01	<.01	<.01	.065	<.01	.051

SEQ = spherical equivalent refraction, Cyl = cylinder, UCVA = uncorrected visual acuity, BSCVA = best spectacle-corrected visual acuity, IOP = intraocular pressure, ECC = endothelial cell count

TABLE 2

Pre- and Postoperative Data for the Control Group

	Mean±Standard Deviation (Range)							
	SEQ (D)	Cyl (D)	UCVA	BSCVA	Max K (D)	Pachymetry (μm)	IOP (mmHg)	ECC (cells/mm²)
Preop	−2.48±1.67 (−5.50 to 0.75)	−2.67 1.69 (−6.25 to −0.50)	0.35±0.25 (0.05 to 0.90)	0.61±0.28 (0.10 to 1.00)	48.32±3.00 (44.10 to 54.70)	469±19 (430 to 497)	11±2 (7 to 14)	2645±157 (2331 to 2907)
Mean 9 mo postop	−2.45±1.96 (−5.87 to 0.88)	−2.66±1.88 (−6.00 to 0.00)	0.27±0.22 (0.05 to 0.80)	0.55±0.26 (0.10 to 1.00)	48.36±3.27 (42.80 to 54.40)	469±22 (428 to 500)	11±2 (6 to 14)	2624±158 (2345 to 2915)
P value	.441	.472	<.01	<.01	.446	.411	.461	.131

SEQ = spherical equivalent refraction, Cyl= cylinder, UCVA = uncorrected visual acuity, BSCVA = best spectacle-corrected visual acuity, IOP = intraocular pressure, ECC = endothelial cell count

Typically, the contact lens was removed 3 days postoperatively. Topical steroid dexamethasone phosphate 0.1% (Maxidex, Alcon-Couvreur, Belgium) was administered four times daily, with gradual decrease of dosage over the following 2 months.

RESULTS

The group treated with collagen cross-linking showed a mean decrease (less myopic) in spherical equivalent refraction and cylinder of 1.03±2.22 D (range: −5.25 to +3.75 D) and 1.04±1.44 D (range: −2.00 to +4.00 D), respectively, and an increase in UCVA and BSCVA of 0.06±0.05 (range: 0.00 to 0.20) and 0.10±0.14 (range: −0.10 to 0.34), respectively. The max K decreased by 1.57±1.14 D (range: 0.00 to 3.90 D), and IOP increased by 2±2 mmHg (range: −1 to 6 mmHg). Additionally, central corneal thickness decreased by 11±22 μm (range: 248 to 49 μm), and endothelial cell count decreased by 28±71 cells/mm² (range: −159 to 128 cells/mm²) without reaching statistical significance (Table 1).

In comparison, spherical equivalent refraction and cylinder in the untreated group decreased by 0.03±0.96 D (range: −2.88 to 12.25 D) and 0.01±0.81 D (range: −1.50 to +1.50 D), respectively, without reaching statistical significance. Maximum K increased by 0.04±1.34 D (range: −4.00 to 3.20 D). Intraocular pressure and central corneal thickness changed modestly by 0±2 mmHg (range: −6 to 4 mmHg) and 0±11 μm (range: −16 to 27 μm), respectively, whereas endothelial cell count decreased by 20±76 cells/mm² (range: −238 to 129 cells/mm²). The decrease in UCVA and BSCVA by 0.08±0.12 (range: −0.40 to 0.10, [P<.01]) and 0.06±0.09 (range: −0.20 to 0.10, [P<.01]), respectively, was statistically significant (Table 2).

All treatments were uneventful, with the contact lens being removed between 3 and 4 days postoperatively. Some patients showed a slight stromal edema with cotton-like stromal opacities at 1-month follow-up (Fig 2). These signs disappeared 3 months after treatment.

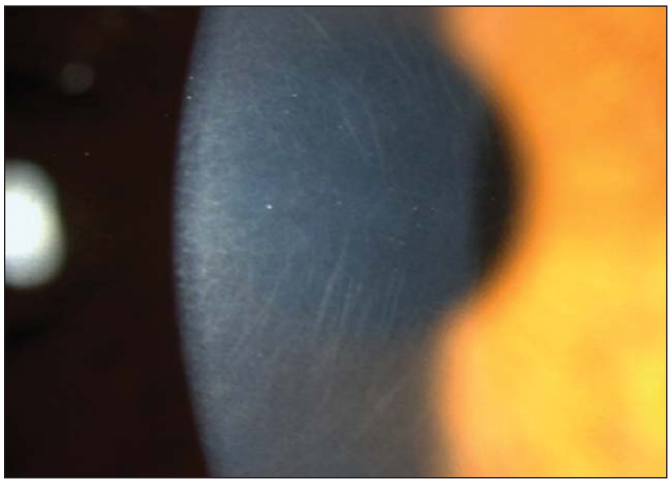

Figure 2. Slit-lamp examination 1 month after collagen cross-linking treatment shows transient stromal and epithelial edema with a mild cotton-like hazy appearance within the corneal stroma.

CASE REPORT

A 16-year-old boy presented with BSCVA 0.1 with manifest refraction −6.00 −4.25 × 115 in the right eye. Corneal thickness was 455 µm with max K of 52.20 D. In the left eye, BSCVA was 0.9 with manifest refraction −0.25 −0.75 × 62, and corneal thickness was 485 µm with max K of 42.40 D. Corneal topography showed the typical signs of keratoconus in both eyes. The right eye was affected more and was treated with collagen cross-linking. Ten months after treating the right eye, BSCVA increased to 0.5, manifest refraction reduced by >1.00 D to −5.00 −3.50 × 110. Corneal thickness was 449 µm with max K reduced by 1.00 D to 51.20 D. At the same time, BSCVA in the left eye worsened to 0.7 with manifest refraction −1.00 −1.50 × 60, corneal thickness slightly reduced to 479 µm, and max K increased to 43.70 D (Fig 3).

DISCUSSION

The key indication for the use of collagen cross-linking is to inhibit the progression of corneal ectasias, such as keratoconus and pellucid marginal degeneration.[8] Collagen cross-linking may also be effective in the treatment and prophylaxis of iatrogenic keratectasia resulting from LASIK.[9] Beyond keratectasia, the new technique can also be used in treating corneal melting conditions or infectious keratitis because cross-linking strengthens a collagenolytic cornea while UVA irradiation sterilizes the infectious agent.[10]

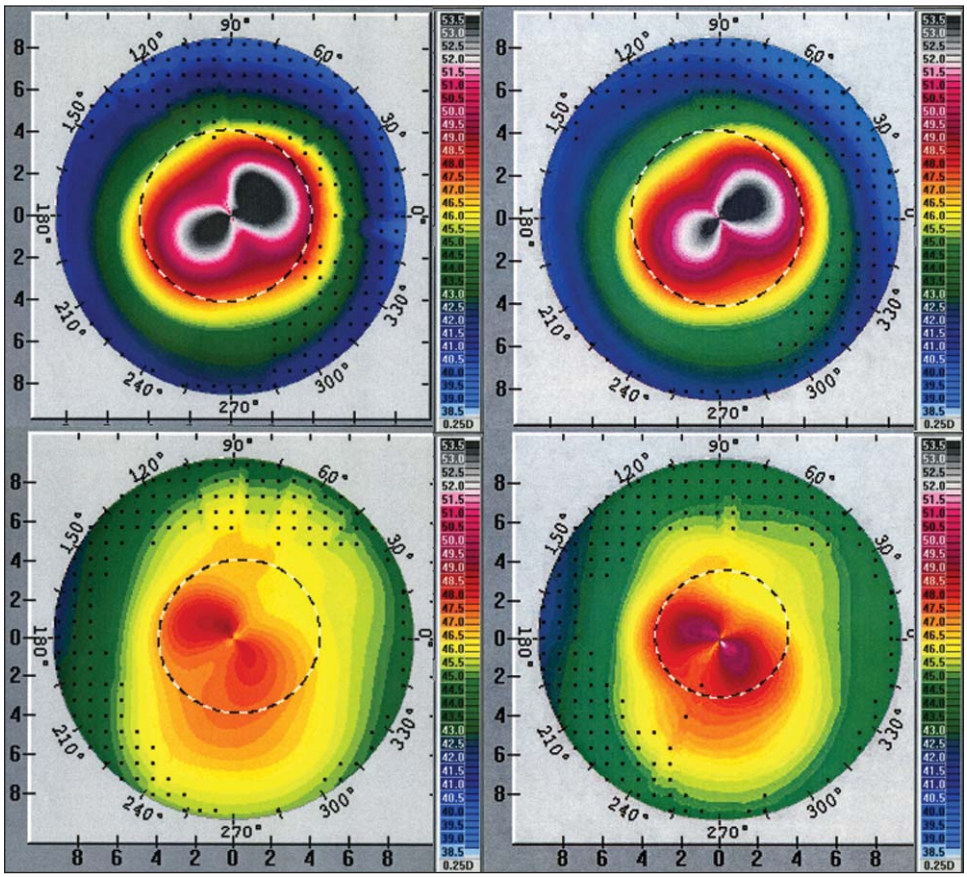

Figure 3. Tangential topographic maps illustrate improvements in corneal topography. **Upper left)** On the day of collagen cross-linking. **Upper right)** Ten months after collagen cross-linking was performed, a regression of max K of more than 1.00 D and a reduction of the area of keratoconus can be observed. **Lower left)** Control eye on the day of collagen cross-linking. **Lower right)** Ten months later, progression of the central max K of more than 1.00 D can be noted.

In vitro studies show that the UVA light arriving to an intact cornea is absorbed within its lamellae by approximately 30%, while an additional 50% of the UVA absorption occurs in the lens.[6] On the other hand, in the presence of riboflavin acting as a photosensitizer, the cornea absorbs a considerable amount of UV light. Thus, using the irradiance of 3 mW/cm^2 of UVA and 0.1% riboflavin, as much as 95% of UVA light will be absorbed within the cornea. This results in a twenty-fold reduction of the original irradiance from 3 mW/cm^2 of UVA (at the corneal surface) to 0.15 mW/cm^2 (at the endothelial level), which is below the cytotoxic threshold for endothelium of 0.36 mW/cm^2.[11-13]

For the sake of comparison, the same UVA irradiance at the corneal surface as used in this study can be measured at noon during an average sunny summer day in the tropics (23° latitude and 800 m above sea level).

Even with the expected reduction of irradiance from the corneal surface towards deeper layers of corneal stroma, as described above, the irradiation levels still exceed the threshold to a depth of approximately 300 µm. Keratocyte apoptosis in the anterior segment of the corneal stroma has therefore been described, and a demarcation line between the treated and untreated cornea has been clearly shown in in vitro studies.[11-13] Confocal microscopy studies also show that repopulation of keratocytes is visible 1 month after treatment, reaching its preoperative quantity and quality in terms of functional morphology within 6 months after treatment.[14]

The first in vivo controlled clinical study, which included 23 eyes with moderate or advanced progressive keratoconus, showed that collagen cross-linking was effective in halting the progression of keratoconus over a period of up to 4 years.[8] In this study, a mean preoperative progression of keratometry (max K) by 1.42 D in 52% of eyes over a 6-month period immediately prior to treatment was followed by a postoperative decrease in 70% of eyes. The statistics also revealed a reduction of max K by 2.01 D, whereas the postoperative spherical equivalent refraction was reduced by an average of 1.14 D. Also during this time, 22% of the untreated fellow control eyes had average postoperative progression of keratectasia of 1.48 D.

Our results confirm previous findings: the group treated with collagen cross-linking showed a similar mean decrease in spherical equivalent refraction by 1.03±2.22 D (range: −5.25 to 13.75 D) and cylinder by 1.04±1.44 D (range: −2.00 to +4.00 D), whereas max K decreased by 1.57±1.14 D (range: 0.00 to 3.90 D).

Tan et al[3] described a new approach for treating keratoconus—intra-lamellar keratoplasty, where the donor tissue is tuck-folded as a 250-µm lamella through a 3.0-mm incision into a corneal pocket previously prepared by femtosecond laser. This method produced a comparable reduction of spherical equivalent refraction, cylinder, and max K by 1.13 D, 1.82 D, and 1.14 D, respectively.

Compared to the study by Tan et al, Miranda et al[5] reported a higher reduction of spherical equivalent refraction and max K by more than 2.50 D and 6.00 D, respectively, using Ferrara rings. Their study included 26 eyes diagnosed with keratoconus grades III and IV. The Ferrara rings flattened the central and peripheral cornea, thus displacing the corneal apex to its physiological position in front of the pupil by reducing the paracentral ectasia commonly seen in keratoconic corneas.

When compared to other treatment methods for keratoconus such as penetrating keratoplasty, deep lamellar keratoplasty, or intracorneal rings, collagen cross-linking shows only a modest reduction in spherical equivalent refraction, cylinder, and max K. However, the collagen cross-linking method used in the present study stops or slows down, rather than reverts, the progression of keratoconus. The small regression that occurred may be explained as an effect of the rearrangement of corneal lamellae and the surrounding matrix.[6] Due to an increased number of cross-linking sites within the collagen molecule after collagen cross-linking, stiffer fibrils and lamellae are likely generated. This process produces a rearrangement of corneal lamellae and the consequent relocation of the surrounding matrix, which, in turn, results in the reduction of the central corneal curvature.

Although collagen cross-linking resulted in a decrease of spherical equivalent refraction, astigmatism, and max K, UCVA and BSCVA increased modestly up to one line. Other studies with alternative treatment methods showed more than two-line increase in BSCVA after implantation of Ferrara rings,[5] INTACS,[4] and deep lamellar penetrating keratoplasty.[2]

This leads us to the following hypothesis: If collagen cross-linking treatment stops or slows the progression of keratoconus, whereas other methods reshape the cornea, a logical solution would be to combine the two treatment methods to synergize their effect. Pre-treatment with an alternative method would significantly reshape the cornea by flattening and regularizing it, which would be followed by collagen cross-linking to stabilize the cornea in this newly achieved state. Alternatively, the collagen cross-linking procedure could be done first, followed by a reshaping procedure. A study of the combined treatment is under way, and the results will be a presented in a separate study.

Safety issues were considered when validating central corneal thickness, endothelial cell count, and IOP. Central corneal thickness decreased by 11±22 µm (range:

−48 to 49 µm), and endothelial cell count decreased by 28±71 cells/mm² (range: −159 to 128 cells/mm²) without reaching statistical significance. After 6 months, the treated corneas returned to their near-anatomical and physiological properties. However, the IOP increased by 2±2 mmHg (range: −1 to 6 mmHg). This finding was not a safety concern but rather demonstrated the efficacy of cross-linking: a stiffer cornea measures at a higher IOP[15] that is similar to the observed IOP measurement differences between the thicker and thinner corneas.[16]

The untreated group showed no statistical difference in terms of spherical equivalent refraction, cylinder, and max K during follow-up. As the control group started with a better visual acuity and a milder picture of keratoconus without preoperative progression, a relative stability of these parameters was expected. A slight decrease of less than one line in UCVA and BSCVA, although statistically significant, is not likely to have any significant clinical impact. It may, however, imply progression of keratoconus in the control eye.

Collagen cross-linking has also been used successfully in stopping the advancement of iatrogenic ectasia in eyes after excimer laser ablation. In a recently published study,[17] collagen cross-linking was performed in 10 patients with a formerly undiagnosed forme fruste keratoconus or pellucid marginal corneal degeneration who underwent LASIK for myopic astigmatism and subsequently developed iatrogenic keratectasia. Collagen cross-linking led to an arrest and/or partial reversal of keratectasia over a postoperative follow-up period of up to 25 months as demonstrated by pre- and postoperative corneal topography and reduction of maximal K-readings.

Riboflavin/UVA collagen cross-linking appears to be an efficacious procedure in inhibiting the progression of irregular astigmatism due to keratoconus while reducing the corneal curvature, spherical equivalent refraction, and refractive cylinder in eyes with corneal instability due to progressive keratoconus.

AUTHOR CONTRIBUTIONS

Study concept and design (E.C., M.R.J., F.H.); data collection (E.C.); data analysis and interpretation (E.C., M.R.J., F.H.); drafting of the manuscript (E.C., M.R.J.); critical revision of the manuscript (E.C., M.R.J., F.H.); statistical expertise (M.R.J., F.H.); administrative, technical or material support (E.C.)

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