Corneal collagen crosslinking in post-LASIK keratectasia

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ABSTRACT

Background/aims To evaluate the effect of corneal collagen crosslinking with riboflavin and UV-A as a treatment option for postlaser in situ keratomileusis keratectasia.

Methods Crosslinking was carried out in 22 eyes of 15 patients with iatrogenic keratectasia. Follow-up, according to a standardised protocol (uncorrected visual acuity (UCVA), best-corrected visual acuity (BCVA), slit-lamp examination, pachymetry and topography), was performed preoperatively 1, 3, 6 and 12 months after crosslinking.

Results The mean BCVA was 0.19 (SD$\pm$0.21) logMAR preoperatively, 0.25 (SD$\pm$0.17) 1 month, 0.20 (SD$\pm$0.20) 3 months, 0.18 (SD$\pm$0.21) 6 months and 0.15 (SD$\pm$0.14) 12 months postoperatively (statistically significant postop1—postop6, p=0.0335). The maximum k-readings were 44.12 (SD$\pm$3.97) preoperatively, 46.23 (SD$\pm$4.14) 1 month, 43.88 (SD$\pm$4.25) 3 months, 45.06 (SD$\pm$5.07) 6 months and 44.43 (SD$\pm$4.06) 12 months postoperatively (statistically significant preop—postop1, p=0.0281).

Conclusion Crosslinking in patients with iatrogenic keratectasia stabilised the UCVA and BCVA as well as the maximum k-readings in our cohort. It seems to be a safe and promising procedure to stabilise the refraction and the corneal topography, and thus to stop the progression of visual loss, thereby avoiding or delaying disease progression and keratoplasty.

INTRODUCTION

Since the first description of laser in situ keratomileusis (LASIK),[1] several million patients have undergone this surgery. The intra- and postoperative complications were reduced with the improvement in mechanical microkeratomes and introduction of new femtosecond laser systems. However, refractive surgery cuts and removes corneal tissue by creating a flap and removing tissue from the stromal bed. Therefore, in all excimer laser procedures, the corneal biomechanics are clearly weakened.[2 3]

Iatrogenic keratectasia is a rare but major sight-threatening complication after LASIK[4] and was first described in 1998.[5] Since then, many reports of keratectasia have been published.[6—8] Keratectasia is characterised by a progressive corneal steepening which can occur centrally or inferiorly combined with severe refractive changes, loss of visual acuity (VA) and a stromal thinning of the cornea.[9] Risk factors for its development are thin corneas, a thin residual stromal bed, deep ablations, enhancement treatments and preoperative abnormalities such as forme fruste keratoconus.[10 11] Keratectasia also

appears in eyes treated according to the current guidelines without any risk factors.[9]

It is important to diagnose this condition at an early stage in order to achieve or maintain good visual acuity and avoid severe procedures such as a keratoplasty. Various methods have been developed to address keratoconus which have also been used in post-LASIK keratectasia, such as rigid gas-permeable contact lenses, intracorneal ring segments (eg, INTACS), anterior lamellar and penetrating keratoplasty.[8 12—15] However, rigid contact lenses and intracorneal ring segments do not stop the progression of the disease.

Corneal collagen crosslinking was first described in 1997[16] and was soon utilised to treat keratoconus.[17] Crosslinking represents a photo-oxidative technique of collagen crosslinking using riboflavin as a photosensitiser for UV-A-light[18] and has the ability to increase the corneal biomechanical stability by inducing chemical covalent bonds, bridging amino groups of stromal collagen fibrils, thereby increasing their intra- and interfibrillar rigidity.[19] It has been used to arrest the progression of keratoconus since 2003.[17] The research and clinical studies have demonstrated that corneal crosslinking stabilises the weakened cornea and refraction, halting the progression of keratoconus.[18 20 21] Thus, it reduces the need for a keratoplasty in a majority of cases. Since keratectasia formation appears to be very similar to other ectatic conditions of the cornea, such as keratoconus or pellucid marginal degeneration, similar treatments have been used in order to manage post-LASIK ectasia.

The aim of this study was to evaluate the effect of corneal crosslinking in the treatment of post-LASIK keratectasia.

MATERIALS AND METHODS

In this prospective, non randomised clinical study, 22 eyes of 15 patients (six female, nine male) with a history of LASIK and the development of iatrogenic keratectasia after LASIK were included. Ectasia was diagnosed according to Pallikaris et al by the slit-lamp appearance of corneal thinning in the area of ectasia, unstable topographical steepening (more than 1.0 dioptre (D), figure 1), decreased visual acuity, and/or unstable refraction.[22] The patients were referred to our clinic after the onset of symptoms of ectasia between 2 weeks and 10 years after the LASIK procedure (mean: 38.7 months, SD$\pm$35.1). Symptoms included progressive loss of vision, blurry vision and frequently changing refraction, with increasing myopia and astigmatism.

All patients underwent a full ophthalmic evaluation before corneal crosslinking treatment. This

Clinical science

Figure 1 Example of untreated corneal ectasia evolution over 7 months.
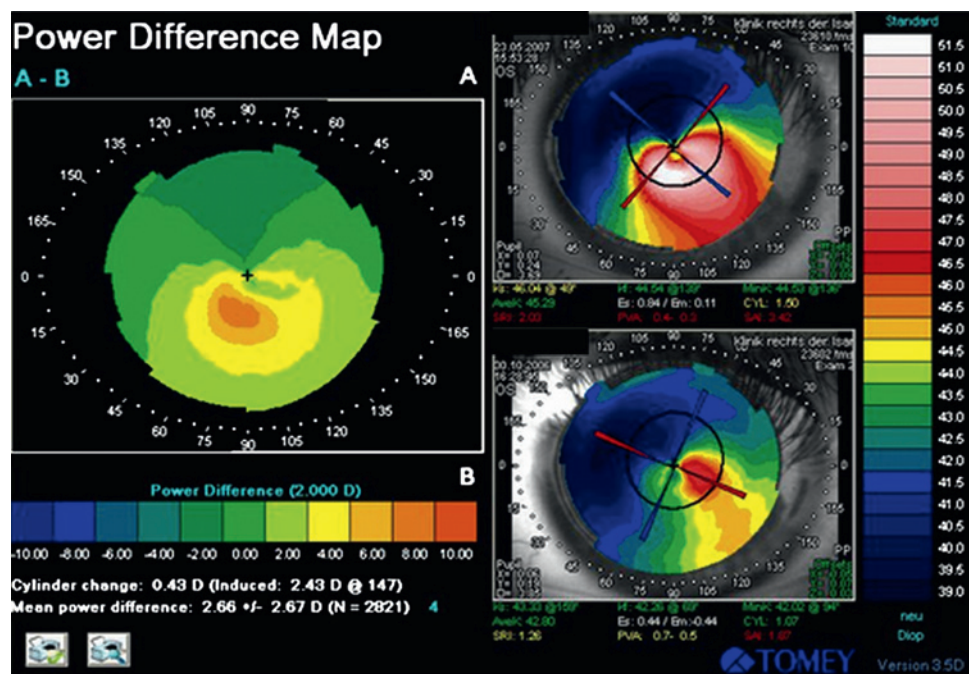
included a detailed history and a complete examination with objective (Topcon KR 8900, Topcon Deutschland GmbH, Willich Germany) and manifest refraction, uncorrected (UCVA) and best spectacle-corrected visual acuity (BSCVA), a slit-lamp examination, ultrasound pachymetry (Tomey SP-3000, Tomey, Erlangen, Germany), corneal topography (Tomey TMS 4, Tomey, Erlangen, Germany), applanation tonometry (Goldmann Applanation Tonometer, Haag-Streit, Köniz, Switzerland) and a dilated fundus examination.

The inclusion criteria for treatment were progressive keratectasia after refractive surgery (figure 1) as well as a pachymetry greater then 400 µm. Exclusion criteria included a corneal thickness less than 400 µm and central corneal scars.

The corneal crosslinking was performed in the outpatient operating room under sterile conditions. The ocular surface was anaesthetised with topical proxymetacaine hydrochloride 0.5% eye-drops (Proparacain, Ursapharm, Saarbrücken, Germany, two drops at a 30 s interval) followed by a mechanical corneal debridement of 8 mm in diameter.

To photosensitise and saturate the cornea, a topical 0.1% riboflavin isotonic solution (Medio-Haus Medizinprodukte GmbH, Neudorf, Germany) was applied every 5 min for 30 min. After this period, UV-A irradiation (370 nm) with a surface irradiance of 3 mW/cm^{2} was carried out at a distance of 10 cm for 30 min using a commercially available system (UV-X, Peschke, Nürnberg, Germany).[19] This surface irradiance was controlled and calibrated using the UV-A metre (LaserMate-Q; LASER 2000, Wessling, Germany) before the patient was exposed. During the UV-A-exposure period, riboflavin was applied every 5 min to guarantee the required concentration and keep the cornea moistened. At the end of the surgery, the corneal surface was washed thoroughly with BSS, and a bandage contact lens (Pure Vision, Bausch & Lomb, Berlin, Germany) soaked in levofloxacin 5 mg/ml (Oftaquix sine, Santen, Germering, Germany) was applied until the epithelial closure was complete.

Until the removal of the bandage contact lens, the postoperative therapy consisted of topical preservative-free antibiotics (levofloxacin 5 mg/ml) and lubrication (carbomer 2%,

Vidisic EDO Gel, Dr Mann GmbH, Berlin, Germany) six times a day. Diclofenac tablets (Diclofenac-ratiopharm 50 mg; Ratiopharm, Ulm, Germany) and Pregabalin 75 mg (Lyrica, Pfizer Pharma, Berlin, Germany) were distributed to the patient to be taken as needed.

Postoperatively, the patients were examined daily until complete reepithelialisation. Follow-up examinations, according to a standardised protocol, assessed patients' objective and manifest refraction, UCVA, BSCVA, slit-lamp biomicroscopy, ultrasound corneal pachymetry (Tomey SP-3000) and corneal topography (Tomey Topographic Modelling System, TMS-4) and were performed 1, 3, 6 and 12 months after corneal crosslinking. We also analysed the following topographic indices: the surface asymmetry index (SAI), which detects alteration of corneal asymmetry by comparing areas of the cornea 180° apart and acts as a disease progression marker; the surface regularity index (SRI), which can be used to predict the optical outcome one might expect from corneal topography values. The third index assessed was the keratoconus prediction index (KPI), a composite calculated index that gives a measure of certainty of detection of the diagnosis of keratoconus.[23]

For statistical analysis, GraphPad Instat software for Windows was used (GraphPad Software, La Jolla, California). To test for a normal distribution of the parameters, we used the method of Kolmogorov and Smirnov, and to evaluate the statistical significance, we used a two-tailed paired t test. All p values >0.05 were interpreted as not statistically significant, values between 0.01 to 0.05 were interpreted as statistically significant (*), and values between 0.001 and 0.01 were interpreted as statistically very significant (**).

RESULTS

The mean age of the patients at the time of onset of keratectasia was 38.4 years (SD±8.13, range 27—51). The surgical procedure was uneventful in all cases. Postoperatively, a trace haze was present in 10 eyes and disappeared during the first 3 months.

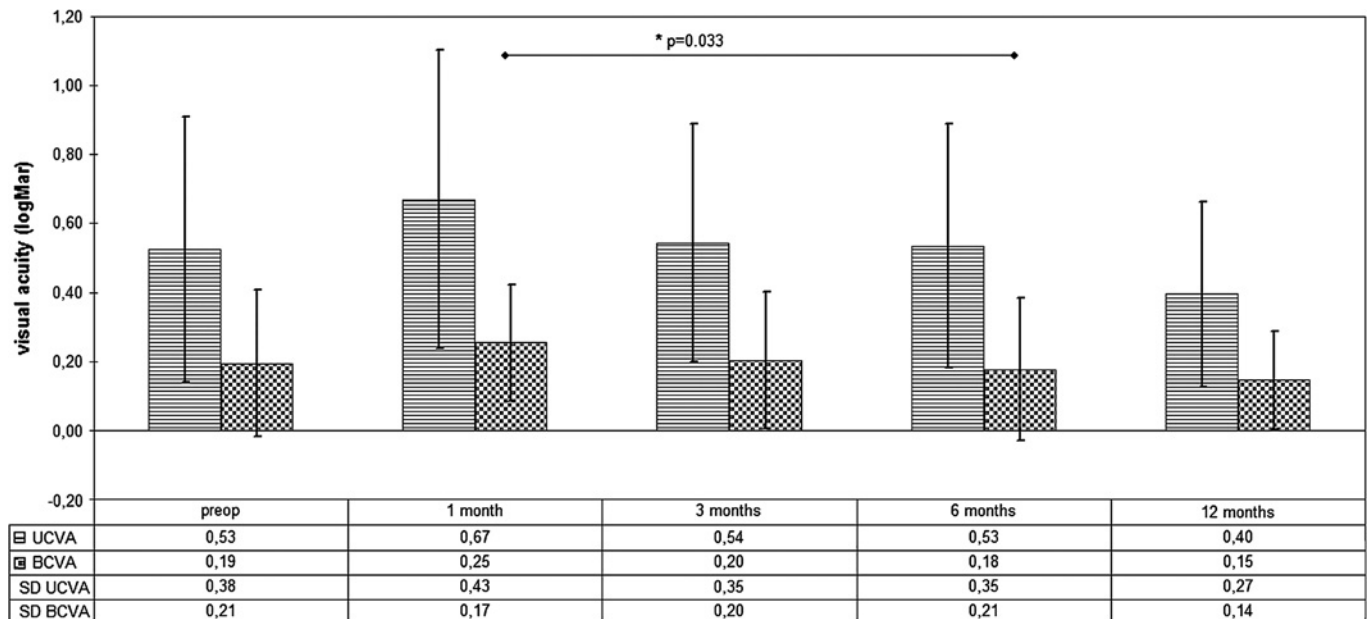The mean UCVA and BSCVA are shown in figure 2. The UCVA changed from 0.53 (SD±0.38) logMAR preoperatively to

Figure 2 Variation of uncorrected visual acuity (UCVA) and best spectacle-corrected visual acuity (BCVA) during the whole follow-up.

0.67 (SD±0.43) logMAR 1 month after corneal crosslinking. After 3 months, UCVA was 0.54 (SD±0.35) logMAR. The 6-month postoperative evaluation showed an UCVA of 0.53 (SD±0.35) logMAR, and after the first year, we had a mean UCVA of 0.40 (SD±0.27) logMAR. The changes were not statistically significant.

The preoperative BSCVA was 0.19 (SD±0.21) logMAR and changed to 0.25 (SD±0.17) logMAR after the first postoperative month. After 3 months, the BSCVA was 0.20 (SD±0.20) logMAR and was 0.18 (SD±0.21) logMAR 6 months after corneal crosslinking. The 12-month results showed a mean BSCVA of 0.15 (SD±0.14) logMAR. The change from 1 month postoperatively to 6 months postoperatively was statistically significant (p=0.0335*). All other changes were not statistically significant.

The refractive changes are shown in figure 3. The spherical equivalent changed from −2.39 D (SD±2.03) preoperatively to −3.31 D (SD±3.33) 1 month, −2.67 D (SD±2.38) 3 months,
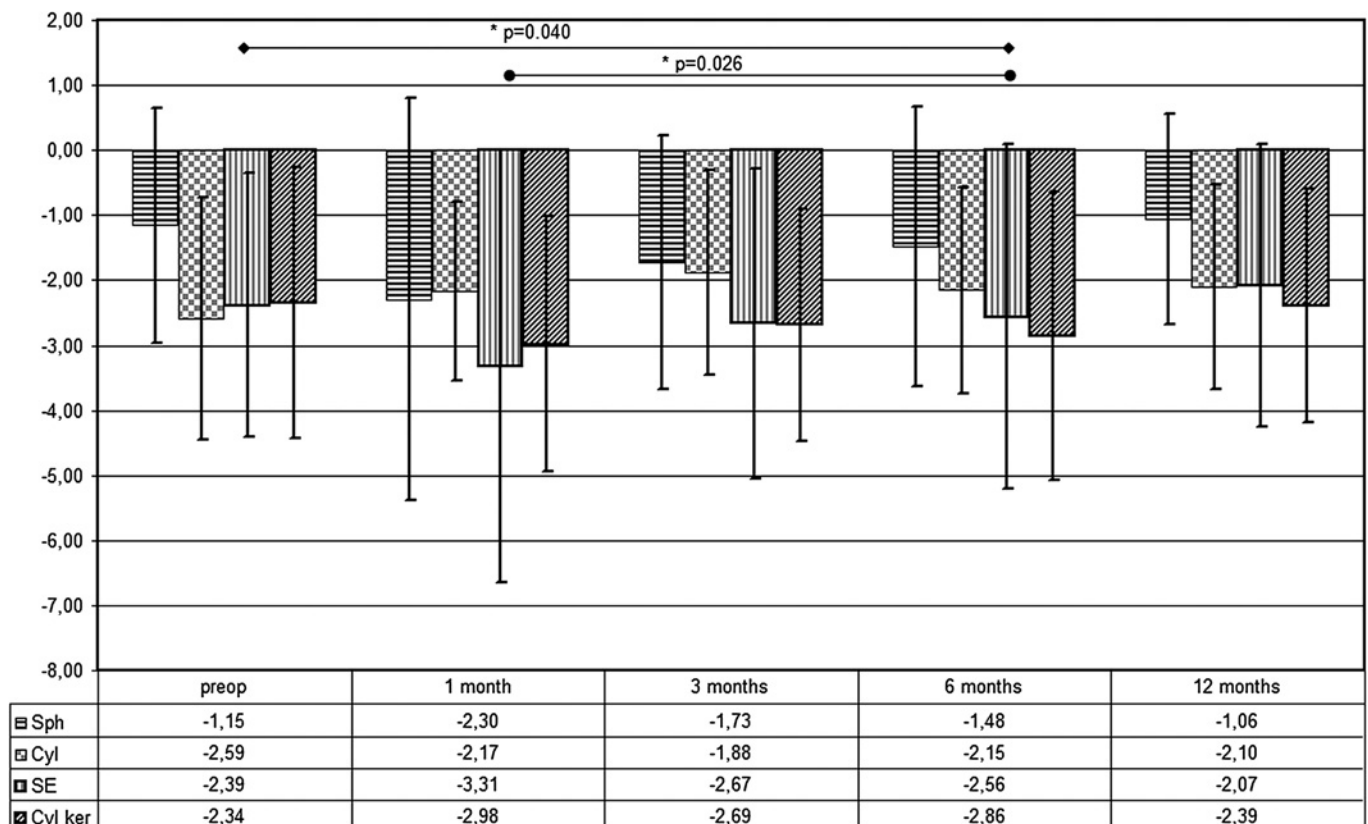

Figure 3 Changes in sphere (Sph), cylinder (Cyl) and spherical equivalent (SE). Cyl ker, keratometric cylinder.

−2.56 D (SD±2.65) 6 months and −2.07 D (SD±2.18) 12 months after corneal crosslinking. The changes from preoperatively to 6 months postoperatively (p=0.0404*) and from 1 month postoperatively to 6 months postoperatively (p=0.0269 *) were statistically significant. All other changes were not statistically significant.

The manifest cylinder (figure 3) changed from −2.59 D (SD±1.86) preoperatively to −2.17 D (SD±1.38) 1 month, −1.88 D (SD±1.57) 3 months, −2.15 D (SD±1.59) 6 months and −2.10 D (SD±1.58) 12 months after corneal crosslinking. The changes were not statistically significant.

The k-values are shown in figure 4. The maximum and minimum k-readings were, respectively, 44.12 D (SD±3.97) and 41.78 D (SD±2.69) preoperatively, 46.23 D (SD±4.14) and 43.25 D (SD±2.66) 1 month, 43.88 D (SD±4.25) and 41.20 D (SD±2.88) 3 months, 45.06 D (SD±5.07) and 42.20 D (SD±3.22) 6 months and 44.43 D (SD±4.06) and 42.04 D (SD±2.67) 12 months after corneal crosslinking. The change from preoperatively to 1 month postoperatively was statistically significant (p=0.0281*) in the maximum k-readings. All other changes in the maximum k-readings as well as all changes in the minimum k-readings were not statistically significant.

The topographic astigmatic values (figure 3) were −2.34 D (SD±2.09) preoperatively, −2.98 D (SD±1.97) 1 month, −2.69 D (SD±1.79) 3 months, −2.86 D (SD±2.22) 6 months and −2.39 D (SD±1.80) 12 months after the operation. The changes were not statistically significant.

The mean SRI preoperatively was 1.13 (SD±0.63). In the first postoperative month, the mean SRI changed to 1.42 (SD±0.57), 3 months after crosslinking it was 1.01 (SD±0.48), 6 months after surgery 1.01 (SD±0.61) and 12 months after crosslinking

0.73 (SD±0.53). The changes from preoperatively to 12 months (p=0.0077**) and from 1 month to 12 months postoperatively (p=0.0017**) were statistically very significant. All other changes were not statistically significant.

Preoperatively, the mean SAI was 1.84 (SD±134), 1 month after crosslinking, it increased to 2.62 (SD±1.45), and 3 months postoperatively, it changed to 1.83 (SD±1.43). Six months postoperatively, the SAI was 1.79 (SD±1.41), and 12 months after crosslinking 1.49 (SD±1.11). The changes were not statistically significant.

Preoperatively, the mean KPI was 0.32 (SD±0.12), 1 month after crosslinking, it increased to 0.38 (SD±0.12), and 3 months after, it decreased to 0.30 (SD±0.11). Six months after crosslinking, the KPI was 0.31 (SD±0.12), and 12 months postoperatively, it was 0.29 (SD±0.11). The change from the first postoperative month to the third postoperative month was statistically significant (p=0.0291*). All other changes were not significant.

DISCUSSION
Iatrogenic keratectasia still lacks an efficacious and predictable treatment option

Corneal crosslinking is known to work mainly in the anterior two-thirds of the cornea.[9][24] This represents a challenge using corneal crosslinking in post-LASIK ectasia, for the flap does not contribute to the mechanical stability of the cornea. Hence, we would expect it to be less effective in this situation compared with the treatment of keratoconus or PMD.

Up to now, only two papers have been published regarding corneal crosslinking exclusively in post-LASIK ectasia. Kohlhaas
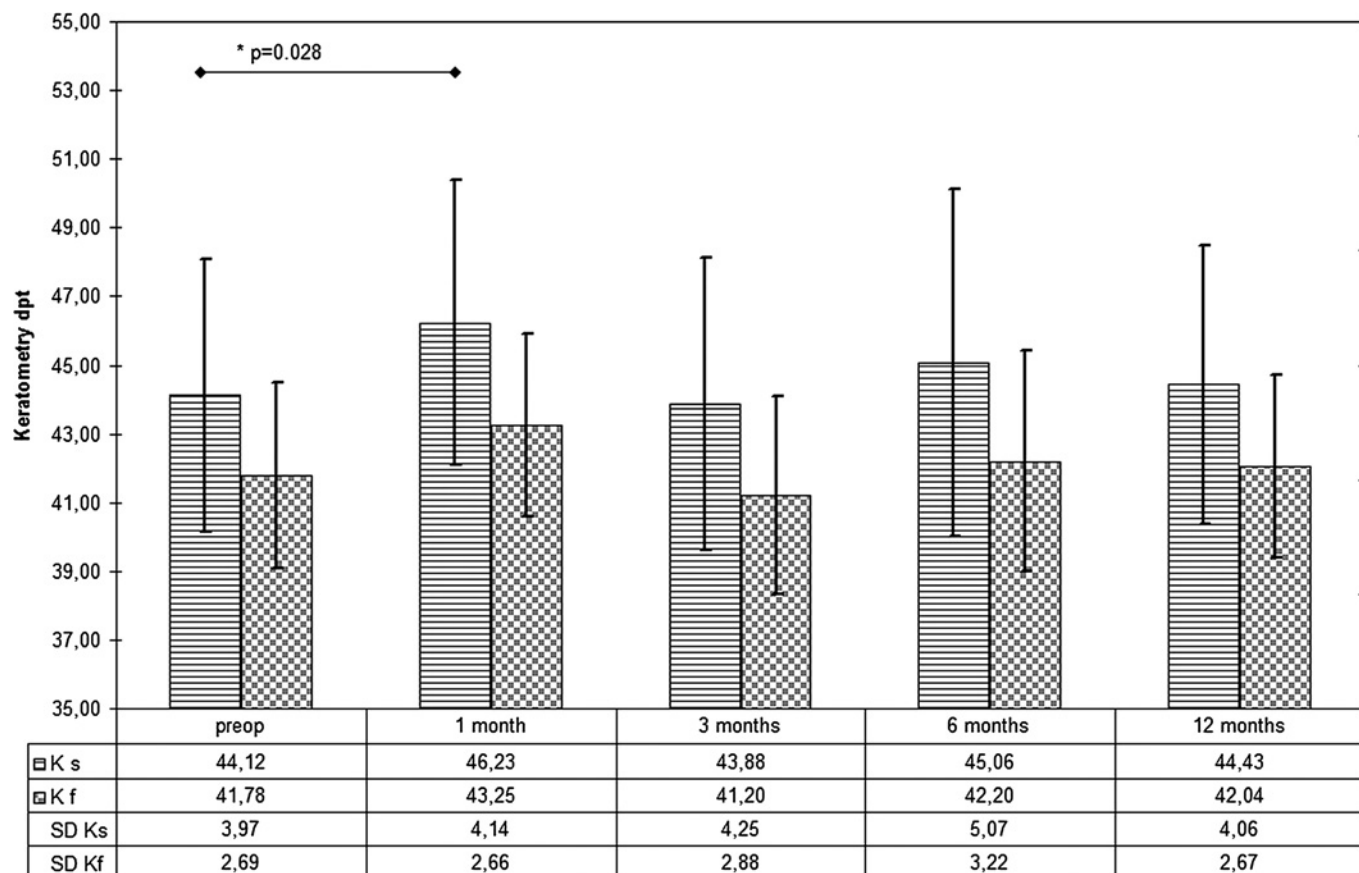

	preop	1 month	3 months	6 months	12 months
⊟ K s	44,12	46,23	43,88	45,06	44,43
⊡ K f	41,78	43,25	41,20	42,20	42,04
SD Ks	3,97	4,14	4,25	5,07	4,06
SD Kf	2,69	2,66	2,88	3,22	2,67

Figure 4 Changes in k readings during the first year. dpt, dioptre; Kf, minimum k-reading; Ks, maximum k-reading.

et al reported first about a successful treatment of a post-LASIK ectasia using corneal crosslinking back in 2005 in one patient with ectasia on both eyes.[9] In 2007, Hafezi *et al*[11] published the first results of corneal crosslinking in post-LASIK ectasia showing an arrest and even a partial reversal in the keratectasia.

Our results showed a worsening of both the uncorrected and the BSCVA in the first postoperative month (a non-significant loss of 1.5 lines in UCVA and of 0.5 lines in BSCVA). This change in visual acuity could be related to an increase in myopia and a consequent statistically non-significant increase in the spherical equivalent. This myopic shift would explain the decrease in visual acuity and could be, in our opinion, due to a modification in the corneal shape resulting from the compaction of the stromal collagen following the crosslink process. The increasing myopia goes along with increased topographic values (k-max, k-min, keratometric cylinder, SRI, SAI and KPI) reflecting a steepening of the cornea and an increase in an irregular astigmatism. A trace haze was present in 10 eyes which disappeared within the first three postoperative months and could also explain a slight myopic shift. After this period, the myopia and the spherical equivalent continuously diminished. The spherical equivalent improved significantly from the preoperative value as well as the first postoperative to the sixth postoperative month. There were some non-significant fluctuations in the manifest cylinder along with the corneal topography.

UCVA as well as BSCVA recovered after the third postoperative month and remained stable throughout the follow-up period of 12 months with a statistically significant increase in BSCVA. Parallel to these changes the corneal indices also provide hints about the corneal shape and ectasia existence/evolution. In our series, preoperative SRI and SAI were outside the normal range published by Burns *et al*,[23] revealing a corneal asymmetry compatible with post-LASIK ectasia.[8] KPI also showed preoperative values consistent with corneal ectasia (according to TMS-4 >0.24 ectasia suspect).

All three analysed indices regressed after the first postoperative month during the follow-up period. According to the index definitions of Burns *et al*,[23] the statistically significant reduction in KPI and statistically significant regression of the SRI support a regression of the corneal ectasia with a flattening of the cornea.

In our study, corneal crosslinking seems to be an effective option in the treatment of post-LASIK ectasia.

The stabilisation of VA and of the corneal curvature, and in some cases even an improvement in VA and reversal of the corneal ectasia, in our study correlates well with the results published by Kohlhaas and Hafezi.

There are, however, a few disadvantages to corneal crosslinking: thus far, researchers have not been able to monitor the long-term experience of patients; nor can they accurately predict the long-term effects of a single procedure.

Nevertheless, the results from the first 6 years of the crosslinking treatment of keratoconus are very promising. There are few reports of patients requiring a second crosslinking in the same eye.[18] Complications are very rare and include sterile infiltrates, stromal scars and haze. Corneal infection is a reported complication which is unlikely directly related to the crosslinking itself, since crosslinking acts as a bactericide and fungicide.[24]

Iatrogenic keratectasia remains a rather obscure subject. The underlying problem has not yet been fully understood, which makes keratectasia difficult to control. As we see in our cohort,

ectasia can present quickly after a refractive procedure, but it can also appear years after surgery. In our opinion, the most important step in the management of iatrogenic keratectasia is to monitor refractive patients regularly, even years after the laser procedure, in order to diagnose and try to treat such a complication at an early stage.

Corneal crosslinking is a promising procedure in the treatment of post-LASIK keratectasia, but we need to await the long-term results of a greater number of patients in randomised controlled trials in order to confirm its efficacy, safety and durability.

Competing interest None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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