ORIGINAL ARTICLE

Long-term Analysis of Epi-ON Corneal Collagen Cross-linking Outcomes in Corneal Ectasia

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Abstract

Aim and objective: To evaluate the 3-year follow-up clinical outcomes obtained in corneal ectasia using Epi-ON corneal collagen cross-linking (CXL).

Materials and methods: This study is a retrospective study enrolling 46 eyes from 32 patients with progressive corneal ectasia and treated with Epi-ON CXL in the period from September 2012 to April 2016. Two groups were differentiated according to the type of corneal ectasia: ectasia post-LASIK group (EPL, 12 eyes) and primary ectasia group (34 eyes). Two different platforms were used for the surgical protocol: VEGA CBM X LINKER platform (CSO, Firenze, Italy) and KXL (Avedro, Waltham, Massachusetts, USA). Visual, refractive, and corneal tomographic outcomes were evaluated during a 3-year follow-up.

Results: A statistically significant improvement in the logMAR corrected distance visual acuity (CDVA) was observed in the whole sample ($p < 0.001$) during the follow-up, with half of the sample improving one or more lines of CDVA. Likewise, only significant changes were detected in steepest keratometry ($p < 0.001$), corneal astigmatism ($p = 0.012$), and index of height asymmetry ($p = 0.021$), with a trend to increase. Regarding the comparison between groups, more significant improvement in CDVA was found in the EPL group compared to the primary ectasia group (-0.07 ± 0.09 vs -0.15 ± 0.14, $p = 0.028$). Likewise, a significant trend to more corneal thinning was observed in primary ectasia group ($p = 0.034$).

Conclusion: Epi-ON CXL is efficacious for stabilizing the progression of primary and iatrogenic ectasias for most cases, with significant improvement of visual acuity associated.

Keywords: Corneal collagen cross-linking, Corneal ectasia, Corneal tomography, Keratoconus, Pellucid marginal degeneration, Post-LASIK ectasia.

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Introduction

The classical definition of keratoconus considered this corneal disease as a progressive and noninflammatory corneal ectasia, leading on some occasions to corneal transplantation due to the absence of treatment to halt its progression.[1] However, this definition has been nuanced as a function of the new findings on the disease[2] because of its potential inflammatory nature.[3–5] In the same way, the prevalence of this corneal ectatic disease has been estimated to be 1/2,000 for many years,[1] but the development of new diagnostic tools has shown that this prevalence can be up to 10 times higher in certain regions.[6–9] This pathology is characterized by progressive stromal thinning and corneal ectasia causing irregular astigmatism and visual impairment.[10] It usually begins at puberty and progresses until the mid-third decade of life.[10] It is estimated that the mechanical stability of the cornea decreases by 40% in keratoconus, facilitating the conical protrusion of the cornea[11] and leading to keratoplasty surgery in up to 10–20% of patients.[12]

The CXL technique was described for the first time in 1998 as a potential treatment to halt the progression of keratoconus.[13] Since the "Dresden protocol" was presented in 2003, corneal collagen cross-linking (CXL) has become the treatment of choice for stopping the progression of keratoconus.[14] Until then, only treatments to correct the refractive errors and minimize aberrations associated to keratoconus were available, but not to halt the progression of the ectasia.[14] Photochemical cross-linking consists of the activation of a topically administered photosensitizer, typically riboflavin, by a source of ultraviolet light (UV-A) at 365 nm.[14] This process leads to the creation of oxygen radicals in the corneal stroma, which in turn induces the formation of permanent collagen cross-links through photopolymerization that results in an increase in corneal stiffness.[14] In multicenter prospective clinical trials, CXL has demonstrated its ability to stop the progression of keratoconus and corneal ectasia after refractive surgery.[15]

The initial CXL protocol has shown a high success rate and a low percentage of complications, although two main drawbacks were evident: the long surgical procedure time (>1 hour) and the need to remove the epithelium (more potential complications and long and unpleasant postoperative period for the patient).[15] Some variations of this protocol have appeared over the years to overcome these previous two limitations, including modifications in the duration of the treatment (standard vs accelerated), the

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light pattern used (continuous vs pulsed), the action against the corneal epithelium (Epi-OFF vs Epi-ON), and the use of an electric field (iontophoresis).[15] The aim of the current study was to evaluate the clinical outcomes obtained using Epi-ON CXL during 3 years of retrospective follow-up in eyes with primary and iatrogenic corneal ectasia.

Materials and Methods

Patients

This was a retrospective study enrolling patients with progressive corneal ectasia and treated with CXL in the period from September 2012 to April 2016 at the Eurocanarias Oftalmológica clinic in Las Palmas de Gran Canaria, Spain. All patients received and signed an informed consent before surgery. The study was conducted following the tenets of the Declaration of Helsinki and was approved by the ethics committee of the institution in which the investigation was conducted. Inclusion criteria for the study were diagnosis of keratoconus (KC),[10] pellucid marginal degeneration (PMD)[16] or post-laser *in situ* keratomileusis (LASIK) ectasia (EPL)[17] following the standard criteria, and ectasia progression was defined as a keratometric increase ≥1D in a period of 6 months.[10] Exclusion criteria included the age of 45 years or more in the KC group and ≥50 in PMD, follow-up of less than 3 years, previous implantation of intracorneal ring segments (ICRS), and rigid contact lens wear. Likewise, the presence of a minimum pachymetry of less than 400 µm was also considered as an exclusion criterion, as CXL surgery in eyes with very thin corneas has the additional risk of damaging the corneal endothelium.

Clinical Protocol

All patients enrolled in the study were examined preoperatively at 6 months, 1 year, and 3 years after CXL. The following clinical data were collected in each visit of the follow-up: manifest refraction, uncorrected (UDVA) and corrected distance visual acuity (CDVA), findings on slit lamp examination, and corneal morphologic parameters obtained with a rotating Scheimpflug camera (Pentacam, Oculus Optikgerate GmbH, Wetzlar, Germany). All participants who wore soft contact lenses were instructed to stop wearing them at least 3 days before the exams.

Surgical Procedure

All surgeries were carried out in the operating room under sterile conditions and in an environment rich in oxygen achieved through a continuous flow (100% at 10 cm from the operated eye). Oxybuprocaine hydrochloride 0.4% and tetracaine hydrochloride 0.1% drops were applied as preoperative local anesthesia. Due to the progressive improvement in riboflavin compositions and the optimization of surgical times because of the application of the Bunsen–Roscoe law, the surgical technique used was optimized according to the advances in this field, varying as follows:

- September 2012–November 2013, the VEGA CBM X LINKER platform (CSO, Firenze, Italy) was used following a standard treatment of continuous irradiation for 30 minutes at an energy of 3 mW/cm^2 prior to the imbibition of cornea with riboflavin (Ricrolin TE, riboflavin 5'-phosphate 0.1% + 15% dextran T-500) for another 30 minutes without removal of corneal epithelium.
- November 2013–June 2015, the KXL 1 platform (Avedro, Waltham, Massachusetts, USA) was used at an energy of 45 mW/cm^2 in pulsed mode (1 second ON, 1 second OFF) to perform an accelerated procedure of 5.2 minutes. First, a 0.25% hypotonic riboflavin with EDTA and benzalkonium chloride (ParaCel®, Avedro, Waltham, Massachusetts, USA) for 4 minutes was applied and after this, a second solution of 0.22% isotonic riboflavin with sodium chloride (VibeX Xtra®, Avedro, Waltham, Massachusetts, USA) was applied for 6 minutes as photosensitizer.
- June 2015 to the end of our study, the KXL 2 platform (Avedro, Waltham, Massachusetts, USA) was used, but maintaining the parameters used with the KXL 1.

As the aim of the current study was to know the efficacy of the Epi-ON CXL, no distinction was made between the variants of the Epi-ON technique.

Statistical Analysis

Statistical analysis of the results was done using the SPSS program v.26.0.0 for Windows (SPSS Inc., Chicago, Illinois, USA). According to Kolmogorov–Smirnov test, the distribution of most of the parameters evaluated followed a normal distribution, and then nonparametric statistical tests were applied. Differences between primary ectasia (KC-PMD) and EPL groups were assessed by means of Mann–Whitney *U* test, whereas differences between consecutive visits in each group were assessed with the Wilcoxon test. Likewise, the Spearman correlation coefficient was calculated to analyze the relationship between different variables.

Results

Analysis of the Whole Sample

A total of 46 eyes from 32 patients were included, whereas the distribution of the sample according to gender was as follows: 19 (59.37%) men and 13 (40.63%) women. A total of 12 eyes presented EPL and 34 KC or PMD. The mean age in the EPL group was 43.3 years (range: 35–52 years) years while in the KC-PMD group (primary ectasia), the mean age was 25.9 years (range: 7–50 years). Table 1 shows the preoperative and postoperative data (3 years) for all the parameters studied in the whole sample. Only statistically significant changes were observed during the 3-year follow-up in logMAR CDVA (p <0.001), the steepest keratometric reading (K2) (p <0.001), the magnitude of corneal astigmatism (p = 0.012), and the index of height asymmetry (IHA) (p = 0.021). Specifically, an improvement in CDVA and an increase in K2, corneal astigmatism, and IHA were found during the follow-up. There were no eyes worsening lines of CDVA, whereas half of the sample of eyes (50%) improved lines of CDVA (Fig. 1).

Comparison of Primary Ectasia and EPL Groups

Table 2 shows a summary of the clinical changes occurring during the 3-year follow-up in the different clinical parameters evaluated in the primary ectasia and EPL groups. As shown, more significant improvement with the follow-up was observed in the EPL group compared to the primary ectasia group (−0.07 ± 0.09 vs −0.15 ± 0.14, p = 0.028). Furthermore, significant differences between primary ectasia and EPL groups were found in minimal (MCT) (p = 0.034) and central corneal thickness (CCT) (p = 0.049), with a trend to a corneal thickening in the EPL group. No significant difference between groups was found in the change in the rest of parameters (p ≥0.260).

Complications

Postoperative complications related to the procedure were observed in two eyes (4.3%), with stromal turbidity that lasted 1 month and resolved with topical corticosteroid treatment.

Table 1: Summary of the preoperative and postoperative clinical outcomes obtained in the whole sample

Mean (SD) *Median (range)*	*Preoperative*	*Postoperative 6 months*	*Postoperative 12 months*	*Postoperative 3 years*	*p value*
Sphere (D)	−0.49 (2.00) −0.13 (−6.75–3.25)	−0.57 (2.01) 0.00 (−6.75–3.00)	−0.58 (1.99) 0.00 (−6.75–3.00)	−0.41 (2.17) 0.00 (−6.25–5.00)	0.270
Cylinder (D)	−2.75 (1.98) −2.13 (−9.00–0.00)	−2.60 (1.93) −2.25 (−7.75–0.00)	−2.75 (1.91) −2.25 (−7.50–0.00)	−3.02 (2.07) −2.63 (−8.00–0.00)	0.094
SE (D)	−1.87 (2.33) −1.38 (−9.75–1.75)	−1.87 (2.32) −1.31 (−10.50–1.75)	−2.15 (2.42) −1.81 (−10.50–1.88)	−1.92 (2.33) −1.50 (−10.00–3.13)	0.356
LogMAR CDVA	0.16 (0.19) 0.10 (0.00–0.70)	0.08 (0.11) 0.05 (0.00–0.40)	0.08 (0.13) 0.05 (0.00–0.70)	0.07 (0.14) 0.00 (0.00–0.70)	<0.001
K1 (D)	42.70 (3.02) 42.85 (36.6–53.9)	42.56 (2.95) 42.80 (36.7–53.4)	42.76 (3.00) 42.80 (36.30–52.70)	42.82 (3.09) 42.85 (36.80–53.00)	0.145
K2 (D)	46.20 (3.30) 45.40 (40.80–56.80)	46.32 (3.41) 45.60 (40.80–56.50)	46.53 (3.47) 45.70 (41.20–55.90)	46.68 (3.59) 46.00 (41.70–56.50)	<0.001
Kmax (D)	51.68 (5.07) 50.55 (45.00–70.4)	51.78 (5.07) 50.15 (45.20–69.00)	52.17 (5.26) 51.10 (44.20–68.90)	51.97 (5.19) 50.70 (43.70–68.70)	0.152
Corneal astigmatism (D)	3.50 (2.44) 2.60 (0.50–10.80)	3.73 (2.54) 2.90 (0.10–11.50)	3.75 (2.45) 3.05 (0.50–11.30)	3.86 (2.49) 3.40 (0.60–11.00)	0.012
MCT (µm)	487.2 (56.9) 492.0 (354.0–586.0)	487.5 (55.3) 483.0 (360.0–583.0)	484.8 (55.7) 477.5 (342.0–569.0)	484.3 (58.9) 480.5 (346.0–581.0)	0.083
CCT (µm)	503.3 (52.73) 508.0 (382.0–596.0)	503.9 (52.6) 497.5 (391.0–600.0)	503.1 (51.2) 496.0 (397.0–587.0)	502.5 (54.6) 499.5 (387.0–597.0)	0.285
ISV	69.1 (29.5) 60.5 (30.0–135.0)	69.9 (30.3) 59.0 (30.0–140.0)	70.3 (30.2) 60.5 (28.0–133.0)	68.6 (28.8) 59.0 (26.0–128.0)	0.334
IVA	0.78 (0.41) 0.62 (0.20–1.74)	0.79 (0.43) 0.60 (0.17–1.92)	0.79 (0.42) 0.62 (0.18–1.72)	0.76 (0.39) 0.59 (0.17–1.68)	0.074
IHA	26.12 (24.15) 20.75 (0.30–100.50)	24.43 (21.35) 18.55 (0.20–96.60)	23.24 (19.91) 17.15 (0.90–85.90)	32.16 (25.14) 23.55 (0.50–100.60)	0.021
IHD	0.09 (0.06) 0.07 (0.02–0.24)	0.09 (0.06) 0.07 (0.01–0.22)	0.10 (0.06) 0.07 (0.02–0.22)	0.09 (0.06) 0.07 (0.02–0.23)	0.319
CKI	1.02 (0.04) 1.02 (0.97–1.20)	1.02 (0.04) 1.02 (0.97–1.18)	1.02 (0.04) 1.02 (0.97–1.17)	1.02 (0.04) 1.01 (0.98–1.17)	0.458
Rmin	6.59 (0.59) 6.70 (4.79–7.50)	6.57 (0.59) 6.73 (4.89–7.47)	6.53 (0.61) 6.61 (4.90–7.63)	6.55 (0.61) 6.66 (4.91–7.73)	0.276

*SD, standard deviation; D, diopter; SE, spherical equivalent; CDVA, corrected distance visual acuity; K1, flattest keratometric reading; K2, steepest keratometric reading; Kmax, maximum keratometric reading; MCT, minimum corneal thickness; CCT, central corneal thickness; ISV, index of surface variance; IVA, index of vertical asymmetry; IHA, index of height asymmetry; IHD, index of height decentration; CKI, central keratoconus index; Rmin, minimum radius of curvature

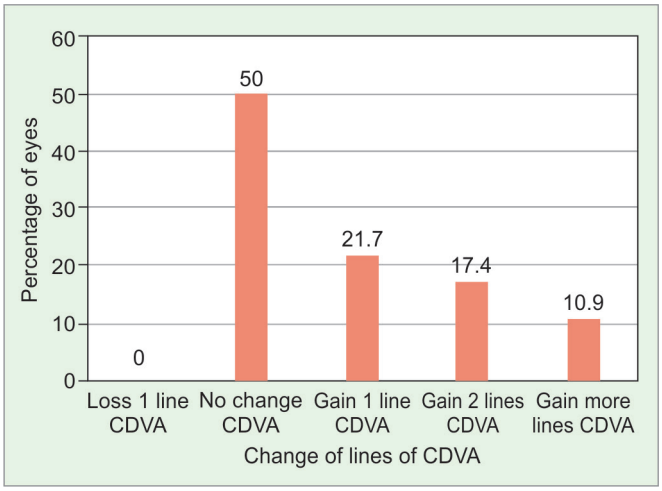

Fig. 1: Distribution of changes of lines of corrected distance visual acuity (CDVA) in the sample evaluated

Discussion

The main function of corneal epithelium is to protect the rest of the cornea and eye against external substances and agents, and riboflavin is a high molecular weight hydrophilic molecule that does not penetrate intact epithelium.[18] Many authors doubt about the efficacy of the effect of Epi-ON CXL mainly due to the lower level of penetration of riboflavin with this technique.[19,20] The riboflavin-soaked epithelium can limit the transmission of ultraviolet (UV) light to the stroma and attenuate the effect.[21] This attenuation of the Epi-ON CXL effect is well-known, with an increase in corneal stiffness of 64% after transepithelial procedures compared to an increase of 320% after the standard procedure using the same riboflavin and UV light irradiation pattern.[22] Besides this, another relevant point in accelerated Epi-ON CXL is the consumption of oxygen as it is higher due to the use of higher levels of energy.[23] A correct replacement of the oxygen consumed is necessary so that the photochemical reactions continue to be carried out throughout the treatment. With the objective of raising the oxygen concentration, two different

Table 2: Summary of the 3-year clinical changes obtained in the two subgroups of the current sample: primary ectasia group (34 eyes) and ectasia post-LASIK (EPL) group (12 eyes)

Mean (SD) *Median (range)*	*Primary ectasia group*	*Ectasia post-LASIK group*	*p value*
ΔSphere (D)	0.07 (1.06) 0.00 (−1.50–3.25)	0.13 (0.60) 0.25 (−0.75–1.50)	0.874
ΔCylinder (D)	−0.14 (1.50) 0.00 (−3.50–4.00)	−0.65 (0.91) −0.50 (−2.00–1.00)	0.280
ΔSE (D)	0.00 (0.95) −0.19 (−2.25–1.88)	−0.20 (0.71) −0.13 (−1.50–0.75)	0.509
LogMAR ΔCDVA	−0.07 (0.09) −0.05 (−0.37–0.07)	−0.15 (0.14) −0.10 (−0.35–0.00)	0.028
ΔK1 (D)	0.11 (0.78) 0.10 (−1.20–3.20)	0.14 (0.61) 0.15 (−1.20–1.30)	0.886
ΔK2 (D)	0.56 (1.31) 0.20 (−0.90–5.20)	0.26 (0.42) 0.20 (−0.40–0.90)	0.447
ΔKmax (D)	0.36 (2.13) 0.10 (−2.40–9.70)	0.08 (0.96) 0.05 (−1.40–2.30)	0.666
ΔCorneal astigmatism (D)	0.44 (1.17) 0.05 (−0.80–5.40)	0.14 (0.63) 0.20 (−0.80–1.10)	0.409
ΔMCT (μm)	−2.9 (12.8) −3.0 (−40.0–32.0)	5.8 (8.7) 6.0 (−6.0–19.0)	0.034
ΔCCT (μm)	−2.5 (10.0) −1.0 (−27.0–18.0)	3.9 (7.7) 3.5 (−7.0–18.0)	0.049
ΔISV	0.3 (9.2) −2.0 (−12.0–32.0)	−2.8 (3.8) −2.0 (−11.0–3.0)	0.277
ΔIVA	−0.02 (0.12) −0.04 (−0.28–0.35)	−0.03 (0.05) −0.04 (−0.14–0.05)	0.693
ΔIHA	2.89 (18.30) −1.00 (−43.00–67.8)	5.68 (12.33) 4.50 (−16.10–24.10)	0.627
ΔIHD	0.00 (0.01) 0.00 (−0.02–0.03)	0.00 (0.01) 0.00 (−0.02–0.02)	0.828
ΔCKI	0.00 (0.02) 0.00 (−0.03–0.12)	0.00 (0.01) 0.00 (−0.03–0.01)	0.260
ΔRmin	−0.03 (0.21) −0.01 (−0.75–0.24)	0.03 (0.07) 0.01 (−0.07–0.19)	0.335

*SD, standard deviation; D, diopter; SE, spherical equivalent; CDVA, corrected distance visual acuity; K1, flattest keratometric reading; K2, steepest keratometric reading; Kmax, maximum keratometric reading; MCT, minimum corneal thickness; CCT, central corneal thickness; ISV, index of surface variance; IVA, index of vertical asymmetry; IHA, index of height asymmetry; IHD, index of height decentration; CKI, central keratoconus index; Rmin, minimum radius of curvature

approaches have been developed: the use of oxygen dispensing sources near the eye during the treatment[24] and the use of the pulsed (on–off) protocols.[19,20] If the use of pulsed light pattern and hypotonic riboflavin formulated with benzalkonium chloride (BAC) that better penetrate the corneal stroma is combined with an oxygen-rich environment, the cross-linking effect may be sufficient to achieve topographic stability without the requirement of eliminating the corneal epithelium. In the current series, this combination has been used to perform Epi-ON CXL in a group of eyes with corneal ectasia, with an evaluation of clinical changes during a 3-year follow-up.

In our series, a significant improvement was observed during the follow-up after Epi-ON CXL. This is consistent with previous studies evaluating the long-term outcomes of accelerated Epi-ON CXL.[20,24–31] Specifically, in the current sample, there were no eyes worsening lines of CDVA, whereas half of the sample of eyes improved lines of CDVA. This improvement is mainly associated to the change in the level of corneal higher order corneal aberrations induced with the CXL treatment.[32,33] This change in the optical aberrations of the cornea with CXL should be the result of the modification of the corneal geometry generated by the CXL effect. However, in the current sample, no significant changes were found in corneal curvature and symmetry data, as reported in previous studies.[27,34–38] This may be explained by the significant variability observed in the outcomes achieved with this technique, with some samples including cases with ectatic cases of different severity. Indeed, some factors have been found to be related to a better effect with accelerated CXL. Zhang et al.[26] found by means of multiple linear regression that patients with thinner preoperative corneal thickness (≤450 μm) have decreasing postoperative average keratometry and increasing postoperative MCT after CXL. Likewise, these authors found that patients with posterior central elevation (PCE) >80 μm have decreasing postoperative average keratometry as well as postoperative PCE with CXL.[26] In the current study, cases of corneal ectasia with different levels of severity were considered in the analysis, with significant level of variability in the effect of CXL among them.

Despite the improvement in CDVA observed in the long term after CXL in our sample, significant increases were found in K2, the

magnitude of corneal astigmatism, and IHA that may be considered as compatible with ectasia progression.[10] Specifically, mean changes were found to be 0.48 D, 0.36 D, and 6.04 in K2, corneal astigmatism, and IHA, respectively. This suggests that although a successful outcome was achieved in most of cases, corneal changes persist at 3 years after surgery in some cases. Henriquez et al.[19] found in a comparative study that the keratoconus progression rate was 9.37% in a group of eyes undergoing accelerated Epi-ON CXL during a 5-year follow-up, whereas no progression was found in an Epi-off CXL group. Marafon et al.[27] found in another comparative study that 89.6 and 95.7% of the eyes were successfully treated with the traditional and accelerated CXL protocols, respectively.

When the analysis was performed separately depending on the type of ectasia, different trends were observed, with significant differences among primary ectasia and EPL groups in the visual and pachymetric changes occurring during the follow-up. More significant visual improvement was achieved in the EPL group as well as a less significant thickening of corneal thickness. This suggests a potentially more positive impact in post-LASIK ectasia, but it should be considered that more severe cases were included in the EPL group. To our knowledge, this is the first comparative analysis on the outcomes achieved with accelerated Epi-ON CXL in primary ectasia and EPL patients. This may be related to corneal structural differences between primary and iatrogenic ectasias leading to a different effect of CXL. It should be considered that preoperative CDVA is a significant prognostic factor for the visual outcome after CXL in keratoconus and EPL,[39] and cases with worse CDVA were included in the EPL group. More studies are needed to confirm these outcomes in future comparative trials.

One critical factor that should be considered and may have influenced our outcomes and the outcome of previous series is the eye rubbing habits. It should be considered that frequent eye rubbing is strongly linked to the progression of keratoconus.[40] Therefore, patients undergoing CXL should be advised about this and should be trained to avoid corneal stressing situations, such as eye rubbing, or pressure maintained during sleep in the prone position. For this reason, clinicians must control if these negative habits are maintained as they can influence significantly on the stability of the results achieved with CXL. Concerning the advantages of Epi-ON CXL over the Epi-Off procedures, it should be remarked that the absence of an iatrogenic corneal ulcer is accompanied by a completely painless postoperative period and a significant reduction in the risk of infection, especially in pediatric patients.

In conclusion, Epi-ON CXL is efficacious for stabilizing the progression of primary and iatrogenic ectasias for most cases, with significant improvement of visual acuity associated.

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