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ORIGINAL ARTICLE

Clinical Outcomes at 1 Year following Corneal Ectasia Treatment with Accelerated Transepithelial Cross-linking

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ABSTRACT

Objective: To assess the clinical outcomes in ectatic corneas following accelerated transepithelial cross-linking (CXL) over 1 year of follow-up.

Materials and methods: Twenty-one eyes diagnosed with progressive corneal ectasia (19 keratoconus, 2 post-laser *in situ* keratomileusis ectasias) in 14 patients aged between 26 and 69 years were enrolled. All cases were treated with accelerated transepithelial CXL using the Avedro KXL® system (Waltham, MA, United States). Changes at visual, refractive, corneal topographic, and corneal aberrometric level were evaluated over a 12-month follow-up period. The demarcation was also determined using optical coherence tomography (OCT).

Results: The mean depth of the demarcation line measured by OCT was 202.72 µm, varying between 153 and 230 µm. One month postsurgery, a change was noted at the limit of statistical significance in sphere ($p = 0.05$) and in spherical equivalent ($p = 0.05$). Likewise, a statistically significant difference was observed in corrected distance visual acuity (CDVA) ($p = 0.01$). There were no significant changes in either visual acuity or refraction between 1 and 6 months ($p \geq 0.35$). Although changes in trend were observed in corneal topographic and aberrometric parameters after surgery, none reached statistical significance ($p \geq 0.08$). A significant change was observed only in astigmatism of the posterior surface between 1 and 12 months ($p = 0.02$).

Conclusion: Accelerated transepithelial CXL may be a useful technique for the management of progressive corneal ectasia, as it is able to maintain the topographic and aberrometric profile of the cornea with no significant changes. Longer-term studies are required to confirm this finding

Keywords: Collagen, Corneal, Ectasia.

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INTRODUCTION

Corneal collagen cross-linking (CXL) is a method aimed at increasing the number of bonds between the collagen chains of the corneal stroma, thus inducing a change in the mechanical properties of the cornea.[1] This is achieved by instilling riboflavin on the cornea and subjecting it to ultraviolet A (UVA) radiation for a short period of time; this will activate oxygen radicals, strengthening the bonds between collagen lamellae, with a resulting increase in corneal stiffness.[1] The aforementioned technique has been shown to be effective in the field of corneal ectasia, preventing its progression and even regularizing the corneal surface in these cases.[1-13]

The need for epithelial debridement of the cornea to obtain a sufficient degree of riboflavin penetration and consequently a greater CXL effect was one of the main initial drawbacks of the CXL technique, as it prolonged the recovery and increased postoperative discomfort.[14-16] For this reason, new CXL protocols are being developed in order to avoid having to debride the corneal epithelium, such as the creation of intrastromal pockets for riboflavin infusion[17,18] or transepithelial CXL, either iontophoresis-assisted or using a benzalkonium chloride solution to increase the permeability of the corneal epithelium.[19-27] Although there is some experimental and clinical evidence of the effectiveness of accelerated transepithelial CXL, it is still limited. The aim of the present prospective, noncomparative study was to assess the visual, refractive, topographic, and aberrometric changes in the ectatic corneas after accelerated transepithelial CXL over 1 year of follow-up.

MATERIALS AND METHODS

Patients

This prospective, randomized study included a total of 21 eyes of 14 patients aged between 26 and 69 years. All patients belonged to the Corneal and Anterior Segment Unit of the Ophthalmology Department (OFTALMAR), Vithas Internacional Medimar Hospital (Alicante, Spain). The study inclusion criterion was the presence of keratoconus or progressive post-laser *in situ* keratomileusis (LASIK) ectasia: Central topographic steepening of more than 1D with refractive change of more than 0.50D in the last 6 months. The standard criterion for diagnosing

keratoconus was used: Corneal topography showing an asymmetric bow-tie pattern with or without inclined axes and at least one keratoconic sign on slit-lamp examination, such as stromal thinning, conic protrusion of the cornea at the apex, Fleischer's ring, Vogt's striae, or anterior stromal scarring.[28] Likewise, the following was used as a diagnostic criterion for post-LASIK ectasia: Noticeable corneal thinning on the biomicroscopic examination, unstable topographic steepening (more than 1.0D per 6 months of follow-up), progressive corneal thinning, reduced visual acuity, and unstable refraction (change of more than 0.50D in the spherical equivalent per 6 months of follow-up).[29] The exclusion criteria were previous eye surgery and the presence of any type of active eye disease. All patients were properly informed about their inclusion and signed an informed consent form. The study complied with the principles of the Declaration of Helsinki and was approved by the hospital ethics committee.

Examination Protocol

A complete ophthalmological examination was carried out preoperatively, which included measurement of manifest refraction, uncorrected (UDVA) and corrected distance visual acuity (CDVA), Goldmann applanation tonometry, anterior segment slit-lamp examination, corneal topography and aberrometry with the Sirius system (Costruzioni Strumenti Oftalmici, CSO, Florence, Italy), biometry (IOL Master v.4.3, Carl Zeiss Meditec, Jena, Germany), and eye fundus examination. Corneal optical aberrations were analyzed considering an analysis area of 6 mm in diameter. The following aberrometric parameters were calculated: High-order root-mean-square (RMS) error, astigmatism (Z_2^{-2}, Z_2^{2}), primary coma (Z_3^{-1}, Z_3^{1}), and primary (Z_4^{0}) and residual spherical aberration (higher order aberration, HOA – Z_3^{-1} + Z_3^{1} + Z_4^{0}).

Postoperatively, patients were reviewed 1 day, 1, 6 and 12 months postsurgery. The day after the surgery, a biomicrosopic examination of the cornea was carried out, as well as an analysis of the cornea by optical coherence tomography (OCT 3D-1000 system, Topcon), using the OCT software calipers to measure the depth of the area of highest reflectance that could be detected in the cornea at central level (corneal demarcation line) (Fig. 1). The same examination protocol as in the preoperative period was used at 1, 6, and 12 months.

Surgery

All operations were performed by the same expert surgeon (AA) under topical anesthesia, using the Avedro KXL CXL system (Waltham, MA, United States). After separating the eyelids with a blepharostat and applying the anesthesia, the procedure began with the instillation, every 90 seconds

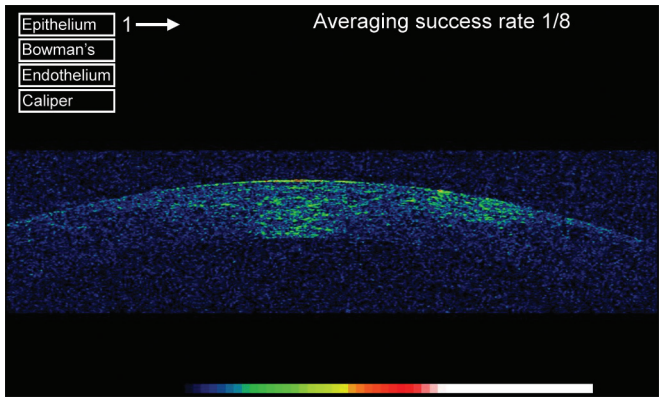

Fig. 1: Scan of the cornea obtained with the OCT system OCT 3D-1000 (Topcon), in which an area of higher reflectance associated with the treated area can be seen (line of demarcation)

for a total of 4 minutes, of dextran-free hypo-osmolar riboflavin drops containing agents to improve the epithelial permeability, including benzalkonium chloride (Paracel, Avedro, Waltham, MA, United States). A benzalkonium chloride-free 0.25% riboflavin solution (VibeX Xtra, Avedro, Waltham, MA, United States) was then instilled at the same rate for 6 minutes. Once these steps had been completed, UV radiation was applied for 2 minutes and 40 seconds, using a pulsed light protocol (2 seconds ON/1 second OFF). The total energy irradiated was 7.2 J/cm^2 and the UV power was 45 mW/cm^2. After irradiation, the cornea was rinsed with balanced saline solution. As postoperative treatment, the patient was instructed to apply one drop of antibiotic (Tobrex, Alcon Laboratories, Fort Worth, TX, United States) and epithelializing ointment (Oculos Epitelizante, Thea Laboratories, Clermont-Ferrand, France) every 8 hours and to use artificial tears.

Statistical Analysis

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) software for Windows version 19.0 (IBM, Armonk, NY, USA). Normal data distribution was evaluated using the Kolmogorov–Smirnov test. When the assumptions of normality were met, the Student's t test was used for paired samples to check the differences between visits. Otherwise, when normality assumptions were not met, the Mann–Whitney test was used to analyze the differences between follow-up visits. A p value of less than 0.05 was considered as statistically significant for all tests.

RESULTS

The study included a total of 21 eyes of 14 patients (12 men and 2 women) aged between 26 and 69 years (mean age: 46.6 years); there were 19 keratoconic eyes and 2 post-LASIK ectasias. Table 1 shows a summary of the visual and refractive results of the sample analyzed.

One month after the surgery, a change was noted at the limit of statistical significance in sphere (p = 0.05) and in spherical equivalent (p = 0.05), with no associated significant changes in cylinder (p = 0.89) or logMAR UDVA (p = 0.53). Likewise, a slight but statistically significant difference was observed in logMAR CDVA (p = 0.01). There were no significant changes in either visual acuity or refraction between 1 and 6 months (p ≥ 0.35).

Table 2 shows a summary of the corneal topography changes observed postoperatively. Although changes in trend can be observed 1 month after the surgery, none reached statistical significance (p ≥ 0.18). In contrast, a statistically significant increase was observed in the magnitude of the astigmatism of the posterior surface between 1 and 12 months after surgery. No statistically significant changes were observed in this period in the other topographic or pachymetric parameters (p ≥ 0.18).

Table 3 shows a summary of the corneal aberrometric changes observed postoperatively. Although some changes were noted, none reached statistical significance at 1 month postsurgery (p ≥ 0.09) or in the period between 1 and 12 months postsurgery (p ≥ 0.08).

Finally, the mean depth of the demarcation line measured by OCT varied between 153 and 230 µm, with a mean value of 202.72 µm (standard deviation (SD): 19.99; median: 203 µm).

Table 1: Summary of the visual and refractive outcomes in the analyzed sample

Mean (SD) Median (range)	*Preoperative*	*1 month*	*12 months*	*p-value preop–1 month*	*p-value 1–12 months*
LogMAR UDVA	0.61 (0.51)	0.41 (0.38)	0.29 (0.28)	0.14	0.53
	0.55 (0.05 to 1.30)	0.32 (0.05 to 1.30)	0.30 (0.00 to 0.70)		
LogMAR CDVA	0.34 (0.28)	0.21 (0.25)	0.23 (0.28)	0.01	0.80
	0.30 (0.00 to 1.00)	0.15 (0.00 to 1.00)	0.22 (0.00 to 1.00)		
Sphere (D)	–0.37 (2.95)	+0.34 (2.63)	–0.50 (1.99)	0.05	0.35
	0.00 (–9.00 to +3.25)	0.00 (–6.00 to +4.00)	–0.25 (–4.00 to +3.50)		
Cylinder (D)	–2.85 (1.95)	–3.16 (1.87)	–2.75 (2.14)	0.89	0.58
	–2.00 (–6.00 to 0.00)	–3.50 (–6.00 to 0.00)	–2.50 (–6.00 to 0.00)		
Spherical equivalent (D)	–1.86 (2.92)	–1.24 (2.30)	–1.88 (2.05)	0.06	0.44
	–1.00 (–11.63 to +1.00)	–0.88 (–7.25 to +1.75)	–1.88 (–5.50 to +1.50)		

Table 2: Summary of corneal topographic and pachymetric outcomes in the analyzed sample

Mean (SD) Median (range)	*Preoperative*	*1 month*	*12 months*	*p-value preop–1 month*	*p-value 1–12 months*
KMa (D)	48.49 (3.22)	49.41 (4.65)	47.22 (1.93)	0.55	0.18
	48.57 (44.27 to 53.70)	47.54 (45.06 to 59.90)	46.98 (44.88 to 51.19)		
ACA (D)	3.51 (1.24)	4.39 (1.68)	4.65 (2.40)	0.26	0.76
	3.82 (0.10 to 5.10)	4.46 (1.26 to 6.80)	3.82 (2.36 to 6.80)		
KMp (D)	7.14 (0.90)	7.55 (1.00)	7.13 (1.03)	0.26	0.73
	7.26 (4.96 to 8.48)	7.26 (6.09 to 9.01)	6.87 (5.89 to 8.93)		
PCA (D)	1.13 (0.79)	1.02 (0.44)	1.73 (0.92)	0.92	0.02
	1.02 (0.23 to 3.94)	0.99 (0.22 to 1.85)	1.48 (0.94 to 4.11)		
Qa	–0.79 (0.44)	–0.95 (0.41)	–0.84 (0.39)	0.20	0.50
	–0.69 (–1.92 to –0.11)	–0.84 (–1.58 to –0.43)	–0.72 (–1.52 to –0.30)		
Qp	–0.85 (0.67)	–1.13 (0.64)	–1.17 (0.71)	0.33	0.88
	–0.73 (–2.09 to –0.09)	–1.01 (–1.97 to –0.16)	–0.93 (–2.47 to –0.45)		
CCT (µm)	469.05 (46.55)	463.29 (54.75)	471.90 (48.72)	0.60	0.69
	478.00 (383 to 541)	447.0 (379 to 557)	490.00 (365 to 514)		
MCT (µm)	446.55 (47.86)	443.14 (58.87)	454.90 (49.69)	0.22	0.61
	450.00 (378 to 538)	422.50 (366 to 546)	468.50 (356 to 511)		
X position MCT (mm)	–0.01 (0.61)	0.08 (0.65)	–0.07 (0.49)	0.25	0.56
	0.16 (–0.89 to 0.71)	0.15 (–0.72 to 1.29)	–0.06 (–0.77 to 0.61)		
Y position MCT (mm)	–0.72 (0.36)	–0.49 (0.52)	–0.57 (0.53)	0.18	0.72
	–0.71 (–1.26 to –0.06)	–0.53 (–1.24 to 1.03)	–0.59 (–1.36 to 0.63)		
Corneal volume (mm^3)	55.50 (4.44)	55.81 (4.42)	55.47 (2.24)	0.18	0.82
	54.90 (47.80 to 62.90)	54.70 (49.50 to 66.80)	55.60 (51.80 to 58.80)		

KMa: Anterior mean keratometry; ACA: Anterior corneal astigmatism in the 3-mm central area; KMp: Posterior mean keratometry; PCA: Posterior corneal astigmatism in the 3-mm central area; Qa: Asphericity of the anterior corneal surface in the central 8-mm area; Qp: Asphericity of the posterior corneal surface in the central 8-mm area; CCT: Central corneal thickness; MCM: Minimal corneal thickness

Table 3: Summary of the corneal aberrometric outcomes in the analyzed sample

Mean (SD) Median (range)	*Preoperative*	*1 month*	*12 months*	*p-value pre-op–1 month*	*p-value 1–12 months*
Anterior corneal surface					
Total RMS (μm)	4.01 (1.38)	4.97 (1.41)	4.49 (1.13)	0.53	0.11
	3.88 (1.72 to 5.92)	4.82 (3.12 to 7.28)	4.35 (2.86 to 6.36)		
HOA RMS (μm)	2.92 (1.25)	3.43 (1.42)	3.12 (1.20)	0.23	0.43
	2.51 (1.38 to 5.44)	3.37 (2.13 to 5.37)	3.15 (1.42 to 4.87)		
Astigmatism (Z_2^{-2}, Z_2^{2}) RMS (μm)	2.57 (1.16)	3.45 (1.11)	3.02 (1.17)	0.82	0.20
	2.34 (1.02 to 4.34)	3.50 (1.98 to 4.92)	3.04 (0.63 to 4.45)		
Primary coma (Z_3^{-1}, Z_3^{1}) RMS (μm)	2.60 (1.30)	3.09 (1.39)	2.81 (1.17)	0.17	0.39
	2.31 (0.93 to 5.21)	2.94 (1.85 to 5.01)	2.83 (1.18 to 4.57)		
Primary spherical aberration (Z_4^{0}) (μm)	0.46 (0.41)	0.48 (0.36)	0.36 (0.35)	0.70	0.08
	0.32 (0.10 to 1.42)	0.42 (0.09 to 1.01)	0.22 (0.01 to 0.93)		
Residual (HOA – Z_3^{-1} + Z_3^{1} + Z_4^{0}) RMS (μm)	1.12 (0.32)	1.35 (0.43)	1.22 (0.42)	0.59	0.59
	1.10 (0.48 to 1.56)	1.18 (0.88 to 1.94)	1.25 (0.53 to 1.98)		
Posterior corneal surface					
Total RMS (μm)	0.99 (0.43)	1.24 (0.55)	1.30 (0.68)	0.66	0.29
	0.98 (0.40 to 1.62)	1.13 (0.41 to 2.00)	1.23 (0.52 to 2.56)		
HOA RMS (μm)	0.80 (0.37)	1.06 (0.55)	0.88 (0.44)	0.92	0.18
	0.74 (0.33 to 1.57)	0.86 (0.39 to 1.87)	0.80 (0.37 to 1.50)		
Astigmatism (Z_2^{-2}, Z_2^{2}) RMS (μm)	0.51 (0.38)	0.59 (0.28)	0.89 (0.62)	0.09	0.98
	0.53 (0.05 to 1.08)	0.65 (0.13 to 0.96)	0.66 (0.37 to 2.33)		
Primary coma (Z_3^{-1}, Z_3^{1}) RMS (μm)	0.42 (0.32)	0.50 (0.21)	0.41 (0.31)	0.35	0.99
	0.39 (0.03 to 1.03)	0.60 (0.27 to 0.83)	0.39 (0.06 to 1.12)		
Primary spherical aberration (Z_4^{0}) (μm)	0.15 (0.12)	0.20 (0.10)	0.19 (0.16)	0.97	0.63
	0.13 (0.04 to 0.36)	0.25 (0.07 to 0.32)	0.14 (0.04 to 0.49)		
Residual (HOA – Z_3^{-1} + Z_3^{1} + Z_4^{0}) RMS (μm)	0.58 (0.37)	0.86 (0.62)	0.70 (0.41)	0.60	0.18
	0.56 (0.20 to 1.49)	0.60 (0.28 to 1.85)	0.53 (0.35 to 1.41)		

DISCUSSION

In this study, we observed that the accelerated transepithelial CXL technique induces changes at the limit of statistical significance in the spherical defect and spherical equivalent. Thus, changes in the mechanical properties of the cornea induced by CXL produce a change in the optical properties of the cornea, eventually affecting the refractive level. This is consistent with the findings reported in other series evaluating the results of transepithelial CXL, either by iontophoresis or accelerated.[19-27] Similarly, in line with all previous studies on transepithelial CXL,[19-27] a significant improvement in CDVA was observed after surgery that remained throughout the entire 12-month follow-up period. Lesniak and Hersh,[24] in a prospective study, evaluated a similar technique and found a mean improvement in CDVA of 0.83 Snellen lines. In our study, the mean improvement in CDVA was slightly better: Approximately one logMAR line of visual acuity. Koppen et al[27] also detected an improvement in CDVA at 6 and 12 months after transepithelial CXL surgery using standard UV radiation (3 mW/cm^2) and instillation of a benzalkonium chloride solution to improve epithelial permeability.

As regards topographic changes after CXL, central flattening of the anterior corneal surface was observed in our series, which did not reach statistical significance. No significant changes were noted either in the curvature of the posterior corneal surface during the 12-month follow-up period or in the asphericity of the anterior or posterior surface. A nonstatistically significant change in trend toward more negative asphericity values was observed for both surfaces. Other studies have evaluated changes in the maximum keratometry after different modalities of transepithelial CXL.[19-27] Lesniak and Hersh[24] found a mean reduction of 0.9D in the maximum keratometry in a prospective study that evaluated the results of a similar CXL technique than that used in our study over a 6-month period. It should be borne in mind that this study included keratoconus cases that were more advanced than in our series, so the mean keratometry was higher. However, a statistically significant change was observed in the magnitude of the astigmatism of the posterior surface between 1 and 12 months after surgery, causing an increase in this value. This could be indicative of more long-term changes in the corneal structure after CXL. In fact, variability was observed in the topographic changes from one case to another, which suggests that after the accelerated transepithelial CXL technique, complex changes occur at the structural level of the cornea that cannot be simply characterized with

geometric parameters of the anterior corneal surface. The different degrees of riboflavin penetration from one eye to another may also have played a crucial role in the variability of the CXL effect. More complex studies are therefore required that characterize the *in vivo* changes at the biomechanical level of the cornea structure, as have already been studied *ex vivo*.[20,30]

The central and minimum pachymetry underwent changes, but they did not reach statistical significance. A nonsignificant trend toward a reduction in pachymetric values was observed 1 month after the surgery, with thickening at 12 months. Other authors have reported this pachymetric reduction in the initial transepithelial CXL postoperative period, even finding statistical significance.[31] These changes reflect the structural modifications that occur in the cornea after the CXL procedure. Nawaz et al[31] compared two groups of patients with keratoconus who underwent conventional CXL with epithelial debridement and transepithelial CXL and found that there was an increase in the central pachymetry 6 months after the surgery in both groups.

With respect to corneal aberrations, as with the topographic parameters, there was wide interpatient variability, with no statistically significant changes. Filippello et al[23] reported a significant change in high-order corneal aberrations 18 months after surgery in progressive keratoconus patients treated with a variant of transepithelial CXL. In contrast, Caporossi et al[21] did not find changes in the comatic aberration after applying the same variant of transepithelial CXL at 12 months after surgery. The same authors reported an increase in this series in the spherical aberration at 24 months postsurgery.

Finally, the corneal demarcation line measured by OCT had a mean depth of 202.72 µm. This value is consistent with the degree of riboflavin penetration measured in experimental studies that have evaluated the effect of transepithelial CXL.[15,32] It should be considered that the demarcation line measured by OCT after CXL represents the area of cornea treated and must be in relation with the level of penetration of riboflavin. Bouheraoua et al,[32] in a comparative study, found that the mean depth of the demarcation line detected with OCT was 184.2 ± 38.9 µm after accelerated transepithelial CXL, and 212 ± 36.5 µm after transepithelial CXL by iontophoresis. Evidently, this area of cornea treated is less than that achieved by conventional CXL with epithelial debridement.[32] Therefore, longer-term studies continue to be necessary to confirm the potential stabilization of the cornea in progressive keratoconus.

In summary, accelerated transepithelial CXL could be a potentially useful technique for the management of progressive corneal ectasia, as it can maintain the topographic and aberrometric profile of the cornea without significant changes for a period of 12 months after the procedure. Future studies are warranted that show the corneal biomechanical changes that occur *in vivo* with the use of this technique. This procedure could induce marked refractive changes during the first month following surgery and even in some cases up to the third postoperative month. These must therefore be taken into account when prescribing a definitive optical correction in these patients.

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