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Keratoconus management with partial topography-guided PRK combined with high-fluence CXL (Athens Protocol): results according to phenotype classification

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Keratoconus management with partial topography-guided PRK combined with high-fluence CXL (Athens Protocol): results according to phenotype classification

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ABBREVIATION LIST

PRK – photorefractive keratectomy;

t-PRK – partial topography-guided photorefractive keratectomy;

CXL – corneal collagen cross-linking;

BSCVA – best spectacle corrected visual acuity;

K1 – flat axis keratometry;

K2 – steep axis keratometry;

KMax – max simulated keratometry;

D – dioptre;

HPCM – hydroxypropyl methylcellulose;

UVA – ultraviolet A.

ABSTRACT

Purpose: To evaluate the efficacy of the Athen's Protocol concerning visual, refractive and topographic outcomes in patients with different preoperative topographic characteristics.

Setting: Department of Ophthalmology in Centro Hospitalar da Universidade de Coimbra, Coimbra, Portugal

Design: Retrospective study

Methods: Patients preoperatively divided according to cone location and axis coincidence underwent simultaneous, same-day, partial topography-guided photorefractive keratectomy (t-PRK) and corneal collagen cross-linking (CXL). Patients were followed for a minimum of 3 months postoperatively. Study parameters included best spectacle corrected visual acuity (BSCVA) and manifest refraction sphere, cylinder, and spherical equivalent. Flat, steep and maximum keratometry values were measured at baseline and at first, sixth and twelfth months after surgery.

Results: Regarding the visual outcome, mean BSCVA significantly improved from 0.44 ± 0.25 preoperatively to 0.27 ± 0.28 logMAR ($P<0.01$) after the procedure. The mean improvement in BSCVA was not significantly different when comparing both coincident and non coincident groups directly ($p=0.716$). BSCVA improvement was more evident in the central (0.43±0.24 to 0.24±0.15), followed by paracentral (0.46±0.25 to 0.36±0.27) and pericentral cases (0.27±0.12 to 0.20).

Concerning the topographic outcomes, mean K1 declined from 46.25±3.96 D preoperatively to 45.77±3.75 D ($p=0.031$), mean K2 declined from 50.87±4.09 D preoperatively to 48.85±4.40 D ($p=0.002$) and mean KMax declined from 55.13±4.91 D preoperatively to 52.99±5.05 D ($p=0.045$).

In regards to the refractive outcomes, mean values of the spherical equivalent measures increased from a preoperative value of -2.54 ± 2.27 D to -3.62 ± 2.81 D ($p=0.044$), the refractive sphere greatly declined from -0.94 ± 2.28 D preoperatively to -2.78 ± 2.60 D ($p=0.000$) and the refractive cylinder declined significantly from 3.50 ±2.06 D to 2.32 ± 1.49 D ($p=0.012$). The mean increase in the spherical component was not significantly different

between the coincident and non coincident groups (p=0.81), as well as the decrease in the cylindrical component (p=0.782).

Conclusion: Simultaneous PRK and CXL was an effective treatment in the approach of keratoconus patients. Patients with central cone appear to show a more significant improvement when compared to the paracentral and pericentral counterparts. Coincidence of the axis appears not to be relevant regarding the outcomes.

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KEYWORDS

Keratoconus; Cornea; Crosslinking; Athens Protocol.

INTRODUCTION

Keratoconus is a progressive, bilateral condition characterized by biomechanical instability, thinning and protrusion of the corneal stroma.[1] It is a common cause for visual impairment in the general population, with a varying but significant prevalence[2]. Loss of visual acuity occurs primarily from irregular astigmatism and myopia and secondarily by corneal scarring.

Corneal collagen cross-linking (CXL) is a recently introduced surgical treatment that is currently the only method capable of stabilizing the pathological progression of the ectasia.[3,4] While successful in addressing the biomechanical weakening of the stroma, it is less effective in correcting the optical deterioration induced by an irregular cornea. A new treatment alternative has emerged that uses a combination of CXL and excimer laser surface ablation to offer keratoconus patients both biomechanical stability and functional vision rehabilitation.[5]

Another treatment modality that offers the prospect of visual rehabilitation in keratoconus patients is intracorneal ring implantation.[6] The visual and refractive outcomes have been shown to differ depending on different preoperative morphological characteristics, namely the location of the cone and the relation between topographic and refractive axis.[7] Preoperative characteristics are therefore taken into consideration when deciding if and what type of intracorneal ring segments to implant.

There are several studies evaluating combined CXL and simultaneous topography guided photorefractive keratectomy.[8,9,10] However, to the best of our knowledge, none of them distinguishes among different preoperative morphologies. We designed a retrospective study on the visual, refractive and topographic results after applying the Athen's Protocol to each of the phenotypes. The results should help future decision-making when, facing with a patient with keratoconus, picking the appropriate procedure according to the phenotype that the patient presents.

METHODS

Patients

Patients who underwent simultaneous, same-day, partial topography-guided photorefractive keratectomy (t-PRK) and corneal collagen cross-linking (CXL) between July 2017 and December 2018 were included in this retrospective, interventional, non-controlled study.

Key inclusion criteria were: documented progression of keratoconus or contact lens intolerance and unsatisfactory best spectacle corrected visual acuity. Progression of keratoconus was defined as front maximal or mean keratometry steepening of >1 diopter (D); decrease in central corneal thickness >5% or 20 µm; increase of posterior elevation >15 µm; increase of manifest myopia, astigmatism or spherical equivalent >1 D; decrease of one Snellen line of best corrected visual acuity. All patients had central corneal pachymetry ≥ 400 µm and an expected residual corneal stromal bed thickness superior to 350 µm.

Patients were divided among different morphologies or phenotypes based on two baseline features.

1. Cone Location. The thinnest point on the corneal pachymetry map, as charted with the Pentacam rotating Scheimpflug system (Oculus, Wetzlar, Germany), was noted and its distance from the centre of the pupil measured both on the vertical and horizontal axis. Cases were classified as central, paracentral or pericentral based on whether this distance was inferior to 0.8 mm, between 0.8 mm and 1.6 mm, or superior to 1.6 mm.

2. Axis coincidence. The difference between the axis of the refractive cylinder and the flattest corneal meridian as assessed in the Pentacam tomographer was measured. Cases were classified as either coincident (Figure 1) or non-coincident (Figure 2) when that difference was inferior or superior to 30 degrees, respectively.

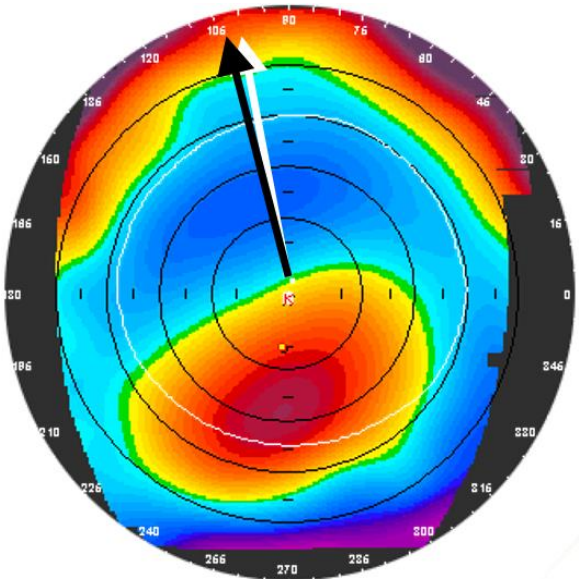

Figure 1 – Coincident axis keratoconus (white arrow labels the topographic axis; black arrow labels the refractive axis).

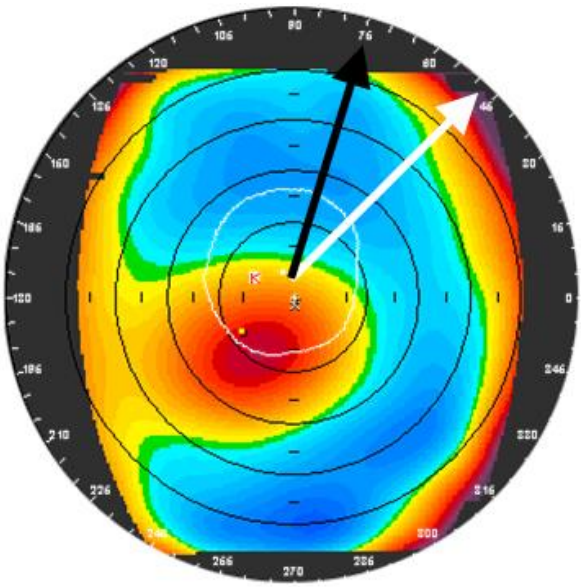

Figure 2 – Non-coincident axis keratoconus (white arrow labels the topographic axis; black arrow labels the refractive axis).

The nature of the disease, the proposed surgical treatment and the possible postoperative complications were fully explained to all patients preoperatively. The tenets of the Declaration of Helsinki were followed, and all patients gave their informed consent.

The exclusion criteria defined for this study were previous corneal or intraocular surgery, a history of herpetic keratitis, diagnosed autoimmune disease, systemic connective tissue disease or history of delayed epithelial healing, known endothelial cell dysfunction, cataract, a history of glaucoma or retinal disease, neuro-ophthalmic disease, or a history of ocular inflammation.

Surgical Technique

The surgical devices used in this study included the KXL Crosslinking System (Avedro Inc., Burlington, MA, USA) and the Wavelight Allegretto Wave Eye-Q Excimer Laser System (Alcon Laboratories, Fort Worth, TX, USA). All t-PRK procedures were performed using the proprietary T-CAT software from the Wavelight Allegretto eye-Q laser system.

Centration onto the pupil was performed and followed by epithelial debridement of 50 µm on the central 6.5 mm zone via the trans-epithelial treatment mode. Partial t-PRK calculation was performed beforehand, aimed at correcting up to 70% of astigmatism and some of the sphere component, always with the concern of not exceeding 50 µm ablation in planned stromal removal. Corneal ablation of the stromal tissue via t-PRK was performed with a 5.5 mm optical zone. After t-PRK, a disposable triangular sponge spear was soaked with 0.2 mg/ml mitomycin C solution and applied onto the de-epithelialized corneal surface for 20 seconds. Balanced salt solution was then used to thoroughly wash the deepithelized corneal surface. Accelerated CXL was performed by soaking the exposed stroma with isotonic riboflavin 0.1% with saline and hydroxypropyl methylcellulose (HPMC) (VibeX RapidTM, Avedro Inc.). Instillations were made every 2 minutes, with a total soaking time of 10 minutes. UVA irradiation was performed for 10 minutes using 10 mW/cm^2 of power to deliver a total energy dose of 6 J/cm^2. All patients were then treated postoperatively with topical ofloxacine 3mg/ml (Floxedol, Laboratórios Edol, Portugal) for 1 week and fluorometholone acetate 1% (FML Liquifilm; Alcon, USA) after epithelial healing for 1.5 months, tapered gradually.

All patients were examined on the third postoperative day to ensure complete re-epithelization. Then, patients were followed up at the end of the first, sixth and twelfth postoperative months.

Outcome Measures

Patients were followed for a minimum of 3 months postoperatively. Complete examinations were made at 3, 6, and 12 months. Study parameters included best spectacle corrected visual acuity (BSCVA) and manifest refraction sphere, cylinder, and spherical equivalent. Visual acuity was assessed using a Snellen chart and then converted to logMAR values before statistical analysis. Flat, steep and maximum keratometry values were measured at baseline and the postoperative assessments and taken from the Scheimpflug topography data (Pentacam, Oculus, Wetzlar, Germany).

Statistical Analysis

The statistical analysis was performed with IBM SPSS Statistics, version 21.0 (IBM Corp., Armonk, USA). Qualitative and quantitative data were presented as either number and percentage and mean and standard deviation. Normality was checked using the Kolmogorov–Smirnov test. For non-normally distributed data, Wilcoxon test was used. For normally distributed data, *t*-tests were used. A P value of less than 0.05 was regarded as proof of statistical significance

RESULTS

Our study included 53 eyes of 53 patients (23 female and 30 male) with a mean follow-up time of 12.53 ± 8.03 months (range: 3.10-33.47months). Table 1 shows patient demographics. All patients were successfully submitted to simultaneous partial topography guided PRK, followed by accelerated CXL, with no intraoperative or postoperative complications.

Of the 53 enrolled eyes, 29 were coincident and 24 non-coincident. Regarding cone location, 24 eyes had central cones, 26 paracentral cones and 3 had pericentral cones.

TABLE I. Patient Demografics

Characteristic	Value
Eyes	53
Age, years	33,11±12,59 [18 to 93]
Sex (male/female)	30/23
Thinnest point, µm	464,98±50,44 [303 to 623]
Central Cornea Thickness, µm	496,30±52,09 [327 to 633]
Spherical Equivalent, D	-2,54±2,27 [-9,00 to 1,25]
Refractive Sphere, D	-0,94±2,28 [-7,00 to 4,00]
Refractive Cylinder, D	3,50±2,06 [0,00 to 10,00]
K1, D	46,25±3,96 [37,1 to 58,6]
K2, D	50,87±4,09 [42,8 to 60,9]
KMax, D	55,13±4,91 [46,6 to 66,8]

Data shown as n or mean ± SD [range]; D = dioptre; K1 = flat axis keratometry; K2 = steep axis keratometry; KMax = max simulated keratometry.

Visual Outcome Analysis

Mean BSCVA significantly improved from 0.44 ± 0.25 preoperatively to 0.27 ± 0.28 logMAR (P<0.01) after the procedure. The safety index (ratio of postoperative to preoperative monocular BSCVA) for the surgery was 1.5.

Looking at the coincident group, mean BSCVA improved from 0.45 ±0.26 D to 0.29 ± 0.25 logMAR (p=0.001). On the non-coincident group, mean BSCVA improved from 0.42 ± 0.2 to 0.27 ± 0.14 logMAR (p=0.005). The mean improvement in BSCVA was not significantly different when comparing both groups directly (p=0.716).

Analizing eyes by cone location showed us that the BSCVA improvement was more evident in the central (0.43±0.24 to 0.24±0.15), followed by paracentral (0.46±0.25 to 0.36±0.27) and pericentral cases (0.27±0.12 to 0.20).

Refractive Outcome Analysis

The mean spherical equivalent increased from a preoperative value of -2.54 ± 2.27 D to a postoperative value of -3.62 ± 2.81 D (p=0.044). This was probably due to an increase in the refractive sphere, from -0.94 ± 2.28 D to -2.78 ± 2.60 D (p=0.000). On the other hand, the refractive cylinder declined significantly from 3.50 ±2.06 D to 2.32 ± 1.49 D (p=0.012).

The increase in the spherical component was noted both in coincident (from -0.88 ± 0.47 to -2.66 ± 0.52 D, p=0.002) and non-coincident eyes (from -1.65 ± 0.47 to -3.70 ± 0.68 D, p=.036), and the mean increase was not significantly different between both groups (p=0.81). The decrease in the cylindrical component followed a similar pattern, with both coincident eyes (from 3.36 ± 0.36 to 2.47 ± 0.33 D, p=0.059) and non-coincident eyes (from 3.55 ± 0.48 to 2.48 ± 0.44 D, p=0.157) showing a decrease in refractive astigmatism, and again the mean reduction was not significantly different between both groups (p=0.782).

The changes in refractive parameters across different cone locations are displayed in Table 2. The spherical component of refraction became more myopic on all types of cone location. A reduction in the cylindrical component was noted in both central and paracentral cones but, strikingly, not on pericentral cones. Both mean sphere and mean cylinder change were not significantly different across cone location categories (p=0.808 and p=0.782, respectively).

TABLE II. Refractive Parameters by cone location

Location	Occasion	Parameter	Mean	Range
Central	Preoperative	Cylinder	3,14±0,42	[1,00-8,50]
		Sphere	-1,43±0,43	[-7,00-1,50]
	Postoperative	Cylinder	2,30±0,30	[0,00-6,00]
		Sphere	-3,14±0,52	[-8,00-1,00]
Paracentral	Preoperative	Cylinder	3,41±0,41	[0,00-6,00]
		Sphere	-0,88±0,67	[-6,50-4,00]
	Postoperative	Cylinder	2,59±0,51	[0,50-7,00]
		Sphere	-2,91±0,74	[-8,00-2,00
Pericentral	Preoperative	Cylinder	3,08±1,37	[0,75-5,50]
		Sphere	0,00±1,26	[-2,50-1,50]
	Postoperative	Cylinder	3,17±0,93	[2,00-5,00]
		Sphere	-2,75±2,77	[-6,00-2,75]

Data shown as D; D = dioptre.

Topographic Outcome Analysis

Considering all eyes, mean K1 declined from 46.25±3.96 D preoperatively to 45.77±3.75 D (p=0.31). Mean K2 declined from 50.87±4.09 D preoperatively to 48.85 ± 4.40 D (p=0.002). Mean KMax declined from 55.13±4.91 D preoperatively to 52.99±5.05 D (p=0.045).

Considering only eyes with coincident axis, mean K1 changed from 45.45 ± 3.94 to 45.62 ± 3.54 D (p=0.082). Mean K2 changed from 50.09 ± 3.84 to 48.80 ± 4.13 D (p=0.119). Mean KMax changed from 53.74 ± 4.41 to 53.25 ± 5.42 (p=0.767).

Considering only eyes with non-coincident axis, mean K1 changed from 47.31 ± 3.73 to 46.38 ± 4.32 D (p=0.016). Mean K2 changed from 51.99 ± 4.20 to 49.38 ± 5.12 (p=0.005). Mean KMax changed from 57.13 ± 4.99 to 53.17 ± 5.08 (p=0.006).

Preoperative and postoperative topographic parameters across the different cone locations are displayed in table 3. Mean change in K1, K2 and KMax was not significantly different across the 3 cone locations (p=0.191, p=0.089, and p=0.052, respectively).

TABLE III. Topographic Parameters by cone location

Location	Occasion	Parameter	Mean	Range
Central	Preoperative	K1	47,9±3,88	[42,6-58,6]
		K2	52,33±4,11	[44,6-60,9]
		KMax	56,03±4,63	[48,5-66,8]
	Postoperative	K1	46,61±3,56	[40,4-55,8]
		K2	49,51±4,48	[43,0-60,5]
		KMax	52,71±4,87	[46,2-63-4]
Paracentral	Preoperative	K1	45,46±3,35	[37,1-52,2]
		K2	50,22±3,75	[42,8-58,6]
		KMax	55,2±5,08	[46,6-63,4]
	Postoperative	K1	45,31±4,13	[36,7-52,5]
		K2	48,6±5,00	[38,8-56,5]
		KMax	53,72±6,04	[45,4-63,6]
Pericentral	Preoperative	K1	40,67±1,23	[39,3-41,7]
		K2	46,2±0,52	[45,9-46,8]
		KMax	49,367±1,86	[47,3-50,9]
	Postoperative	K1	44,67±4,26	[39,9-48,1]
		K2	48,1±3,14	[45,3-51,5]
		KMax	53,9±1,37	[52,4-55,1]

Data shown as D; D = dioptre; K1 = flat axis keratometry; K2 = steep axis keratometry; KMax = max simulated keratometry.

DISCUSSION

The purpose of the Athen's Protocol in keratoconus patients is to improve both the function and the structure of their corneas. In this study, we evaluated the visual and topographic outcomes of 53 eyes with keratoconus submitted to the procedure.

Concerning the visual outcome, mean BSCVA greatly improved in our study group. While there was no significant statistic difference between the coincident and the non coincident groups, we found that the patients with central keratoconus showed a more relevant improvement in comparison to the paracentral and pericentral counterparts, with the last having the least improvement.

These results suggest that patients with central keratoconus benefit the most of the application of the Athen's Protocol as their BSCVA will improve more when compared to the patients with other cone locations. Yet, we should not discard that all the groups benefited from the procedure. Young patients (less than 24 years) usually have more central cones and better responses to CXL, so our results are in agreement with this previous knowlege.[11]

In regards to refractive outcomes, both the spherical equivalent and the refractive sphere increased from the preoperative value, while the refractive cylinder declined significantly. This increase in sphere was unexpected, but may be due to two reasons. On one side, after corneal regularization it is easier to refract the patient, who is more likely to improve vision when offered a more negative sphere, while before surgery it is often indifferent to change sphere in 1, 2 or 3 D. On the other side, the topography-guided excimer ablation removes tissue in the cornea periphery, to regularize the cornea. This removal is not compensated by a deeper ablation in the cornea center for safety reasons, as ablations in the cornea center are limited to 50 µm or less, depending on the residual stromal bed. Again, there was no significant difference between coincident and non coincident groups. Comparing the cone location groups, we find that patients with central or paracentral cone showed a reduction in the cylindrical component, while patients with pericentral cones did not.

Concerning topographic outcomes, we noted that mean K1, K2 and Kmax values declined considerably. While patients with coincident axis demonstrated less significant changes on their topographic evaluations, patients with non-coincident axis showed significant declining in all the 3 parameters. Concerning the cone location, patients with central cone presented the most significant improvements in the K1, K2 and KMax

measures, while the paracentral patients showed less impressive improvements and the patients with the pericentral cone presented a worsening of all the 3 parameters.

This suggests that patients with the central location of the cone gain the most benefits in terms of topographic stability while the patients with the paracentral cone show less impressive improvements. Patients with pericentral cone demonstrate a worsening in their keratometry, which make us think that the Athen's Protocol is not as effective, as it appears to destabilize the cornea. This could prove crucial to the assessment of keratoconus patients with pericentral cone, as the Athen's Protocol could even become ill-advised in cases where the potential benefit in visual acuity may not justify the worsening of topographic parameters.

In conclusion, it appears that the visual, refractive and topographic outcomes of patients submitted to the Athen's Protocol vary according to the location of their cone. Further studies are needed in order to determine whether or not there is a need to improve the treatment methods in order for patients to achieve satisfying visual, refractive and topographic results independently of the cone location.

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