RESEARCH ARTICLE

Efficacy of Combined Phototherapeutic Keratectomy, Wavefront-optimized Photorefractive Keratectomy and Corneal Collagen Crosslinking in the Management of Progressive Keratoconus over One-year Follow-up: Modified Athens Protocol

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Abstract

Purpose: Keratoconus is a degenerative, ectatic corneal disorder. Recently, corneal crosslinking (CXL) as a stabilizing procedure has been combined with other procedures to improve visual and refractive outcomes as in Athens and Cretan protocols. The aim of the study is to present the efficacy and safety of a modified Athens protocol over 1-year follow-up.

Materials and methods: The study is a retrospective descriptive one with a total of 43 eyes (36 patients) with progressive keratoconus who underwent combined transepithelial phototherapeutic keratectomy (PTK), partial wavefront-optimized photorefractive keratectomy, and corneal collagen CXL. Visual, refractive, pachymetric and keratometric preoperative and postoperative follow-up data at 1 month, 3 months, 6 months, and 1 year were taken from patients' medical records.

Results: The mean uncorrected distance visual acuity (UDVA) improved from (0.33 ± 0.19) preoperatively to (0.64 ± 0.27) at 1 year postoperatively and the mean corrected distance visual acuity (CDVA) from (0.62 ± 0.21) to (0.80 ± 0.20). At 1-year postoperative visit, the mean spherical and cylindrical values changed significantly from (−2.10 ± 2.45) to (−0.34 ± 2.26) and from (−3.50 ± 1.85) to (−1.23 ± 1.02), respectively. The mean steep and flat *K* readings significantly decreased from (50.97 ± 4.46) to (47.58 ± 5.61) and from (47.08 ± 4.02) to (44.84 ± 4.47), respectively. The mean K_{max} also decreased from (56.27 ± 6.40) preoperatively to (51.22 ± 7.94) postoperatively. The thinnest corneal thickness mean was (462.49 ± 36.17 µm) preoperatively and (388.21 ± 56.64 µm) postoperatively.

Conclusion: Our modified Athens protocol has shown to be safe and efficacious in the management of progressive keratoconus. Impressive improvements in visual, refractive, and keratometric values were noted. This approach offers a more tissue saving protocol than the original Athens protocol with less alteration to the surface of the cornea, which may offer more predictability and less refractive surprises.

Keywords: Athens protocol, Cretan protocol, Crosslinking, Efficacy, Keratoconus.

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Introduction

Keratoconus is a degenerative ectatic disorder characterized by progressive corneal protrusion and paracentral corneal thinning leading to impairment in visual function.[1] It is considered the most common primary corneal ectatic disease.[2] In the last 2 decades, photochemical crosslinking (CXL) has been developed to arrest disease progression, improve corneal keratometry, and reduce corneal irregular astigmatism.[3] Crosslinking -plus procedures, which have been proposed by many ophthalmologists, proved to be effective in further improvement of the refractive errors associated with keratoconus. The Cretan and Athens protocols use the phototherapeutic keratectomy (PTK) to remove the epithelium and regularize the surface of the cornea.[4] The Athens protocol makes an additional normalization of the corneal surface and partial correction of refractive errors by topography-guided photorefractive keratectomy (topo-guided PRK).[5–11] In this article, the results of our modified Athens protocol, which is PTK, partial wavefront-optimized rather than topo-guided PRK, and CXL in the management of progressive keratoconus over 1-year follows-up are shown.

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Materials and Methods

This is a retrospective descriptive study of a total of 43 eyes of 36 patients (median age 26 years, range 18–35) with progressive keratoconus grades I–III on Amsler–Krumeich classification. The data were collected retrospectively from the patients' records at the Department of Ophthalmology, An-Najah National University Hospital after the approval of the study by An-Najah National University IRB Committee. These patients underwent same-day PTK, partial wavefront-optimized PRK, and CXL between November 2015 and December 2016.

The diagnosis of progressive keratoconus was based on slit lamp examination, corneal tomography, keratometry, corneal pachymetry, and subjective refraction. Preoperative data and follow-up data at 1, 3, 6 months, and 1-year postoperatively were taken from the patients' medical records.

Measurements and Analysis

Preoperative and postoperative evaluation included uncorrected distance visual acuity (UDVA) and corrected distance visual acuity (CDVA) in decimals. Cylindrical and spherical values were measured using subjective refraction. Flat, steep, mean, and maximum keratometric values (*K*1, *K*2, K_m, and K_{max}) and pachymetric (thinnest corneal thickness) corneal measurements using Pentacam Scheimpflug imaging device (Pentacam, Oculus, Wetzlar, Germany).

Descriptive statistics were performed using the Statistical Package for Social Sciences (SPSS Statistics V.22.0, SPSS Inc., Chicago, Illinois, USA). We considered *p* values less than 0.05 statistically significant. The visual acuity is represented in decimals and keratometric values in diopters (D). Results were reported as mean ± standard deviation and range as minimum to maximum.

Inclusion Criteria

The criteria set out before the study were clinical diagnosis with progressive keratoconus and a minimum age of 18. Patients with systemic diseases (collagen vascular diseases and diabetes mellitus), previous eye surgery or corneal scar, chemical injury or delayed corneal epithelial healing, and pregnancy or lactation were excluded from the study. Progression of keratoconus was defined by an increase in $K_{max} \geq 2D$, $K_{max} - K_{min} \geq 1D$, $K_m \geq 0.75D$, pachymetry ≥2% decrease in CCT, corneal apex power >1D and manifest refraction spherical equivalent (MRSE) >0.5D over 6 months.

Surgical Technique

All procedures were performed at An-Najah National University Hospital by the same surgeon (MMS) under sterile conditions. Topical anesthesia was applied by proxymetacaine HCL 0.5% eye drops. Then, transepithelial PTK ablation at a depth of 50 µm using an optical zone of 7 mm and transitional zone of 1.25 mm was used to remove the corneal epithelium, followed by up to 70% wavefront-optimized PRK laser ablation; the degree of correction and the optical zone were modified so that the remnant stromal bed did not go below 350 µm. The optical zone ranged from 5.5 mm to 6.0 mm. Subsequently, mitomycin C 0.02% solution was applied over the ablated corneal surface for 20 seconds using a cellulose sponge. It was followed by copious irrigation with 30 mL of balanced salt solution. Thereafter, riboflavin 0.1% sodium phosphate solution was instilled repeatedly every 3 minutes for 30 minutes. The surgeon used the blue light of the slit-lamp to monitor the presence of riboflavin in the anterior chamber and saturation of the corneal stroma. Corneal thickness was measured just before the ultraviolet light irradiation to ensure that the corneal thickness exceeded 400 µm. If the thickness was below 400 µm, dextran-free hypotonic riboflavin was used to swell the cornea. The cornea was irradiated for 30 minutes by 3 mW ultraviolet-A light of mean 370 nm wavelength. At the end of the procedure, a bandage contact lens was applied, and it was removed around day 7 postoperatively when the epithelial layer was healed. Postoperative medications included topical gatifloxacin 0.3% four times daily for 7 days and dexamethasone 0.1% four times daily tapered over 3 weeks. The patients were instructed to protect their eyes from the natural light with sunglasses.

Results

Visual Acuity Changes

Preoperative and postoperative UDVA and CDVA are presented in Table 1. Both showed significant improvement 1 year after the procedure. Mean UDVA improved from 0.33 ± 0.19 to 0.49 ± 0.25 at 1 month. Further improvement to 0.61 ± 0.28 was noticed at 3 months. Minimal improvement to 0.64 ± 0.27 was noticed thereafter at 1 year.

Mean CDVA improved from 0.62 ± 0.21 to 0.68 ± 0.22 at 1 month. Additional improvement to 0.79 ± 0.22 was noticed at 3 months. Minimal improvement to 0.80 ± 0.20 was noticed thereafter at 1 year.

Keratometric Outcomes

The mean steep *K* readings showed significant reductions from 50.97 ± 4.46 preoperatively to 48.65 ± 4.95 at 1 month postoperatively. Over the next year, follow-up showed minimal changes toward stability as following 47.97 ± 4.96 at 3 months, 47.68 ± 5.24 at 6 months, and 47.58 ± 5.61 at 1 year. The flat K_{mean} readings also showed significant reduction from 47.08 ± 4.02 preoperatively to 45.68 ± 4.08 at 1 month postoperatively, minor changes were noted at 3 months 45.30 ± 4.13 and up to 1 year 44.84 ± 4.47. The K_{mean} readings exhibited significant improvement from 48.94 ± 4.15 preoperatively to 47.11 ± 4.41 at 1 month postoperatively.

Table 1: Visual acuity data of participants over 1-year follow-up

Parameters	*Preoperative (43 eyes)*	*1 month (43 eyes)*	*3 months (43 eyes)*	*6 months (37 eyes)*	*1 year (34 eyes)*
UDVA					
Mean ± SD	0.33 ± 0.19	0.49 ± 0.25	0.61 ± 0.28	0.64 ± 0.26	0.64 ± 0.27
Gain/loss	–	+0.16	+0.28	+0.31	+0.30
CDVA					
Mean ± SD	0.62 ± 0.21	0.68 ± 0.22	0.79 ± 0.22	0.79 ± 0.21	0.80 ± 0.20
Gain/loss	–	+0.06	+0.17	+0.17	+0.20

CDVA, corrected distance visual acuity; SD, standard deviation; UDVA, uncorrected distance visual acuity

Changes were minimal at 3 months 46.63 ± 4.41 and reached 46.11 ± 5.01 at 1 year. $K_{max\ mean}$ readings preoperatively were 56.27 ± 6.40 and showed a significant change to 51.50 ± 8.24 at 1 month postoperatively. Small changes were noticed over the next year 51.22 ± 7.94, as shown in Table 2.

Corneal Thickness

As a result of laser ablation used during PTK and PRK, a significant reduction in the thinnest corneal thickness mean of 84.5 µm was noticed at 1 month postoperatively. However, it slightly increased over the 1-year follow-up, as illustrated in Table 3.

Refractive Outcomes

A significant improvement in cylindrical and spherical equivalents was noticed at a 1-month visit, postoperatively. The mean changes of cylindrical and spherical values were (change: +1.54 ± 1.69) and (change: +1.86 ± 3), respectively, with gradual improvement over the subsequent visits, as shown in Table 4.

Discussion

Keratoconus is a progressive noninflammatory biomechanical weakness of corneal collagen which is characterized by thinning and steepening that leads to abnormal topographic findings and visual function impairment.[1] Corneal cross linking was developed to provide corneal stability, halt progression of corneal ectasia, and reduce the refractive and keratometric irregularities. The Cretan protocol was introduced by Kymionis et al. They showed that transepithelial PTK to remove the corneal epithelium has a positive regularizing and smoothing effect on the corneal surface because it uses masking and neutralizing effect of the epithelium with minimal stromal ablation. A follow-up of 23 eyes over 24–56 months after PTK and CXL by Kymionis et al. revealed improvement in UDVA, CDVA, and keratometric readings without intraoperative or postoperative complications.[4] However, Kanellopoulos and Binder described the management of corneal ectasia after LASIK with combined, same-day, topography-guided partial transepithelial PRK, and collagen CXL: the Athens protocol.[5] We believe that combining the PTK, which alters the topography of the ectatic cornea and the topo-guided PRK, which also modifies the topography of the cornea may lead to unwanted refractive surprises in some cases. Furthermore, topo-guided PRK sacrifices more corneal tissue compared with the wavefront-optimized ablation. Therefore, in our modified Athens protocol, we use the effect of the transepithelial PTK (the Cretan protocol) to make some regularization of the keratoconic cornea with the advantage of minimal tissue ablation, and the wavefront-optimized PRK with additional tissue saving to decrease the refractive errors of the keratoconic patients. We believe that our modified Athens procedure will be beneficial as a rehabilitation procedure for patients with anisometropia, patients who want to decrease rather than to eliminate their dependency on glasses and patients who want to improve their uncorrected and corrected visual acuity. It should not be used as a refractive procedure for patients with high expectations who want to achieve spectacle independency, which may cause disappointment for these patients.

Visual Acuity Changes

Based on our results, there was a significant improvement in UDVA, starting at 1 month, continuing at 3 months and 6 months postoperatively with a noticeable positive gain, reaching an average gain of three lines at 1 year. At 12 months, 91.2% of eyes gained at least one line (47.1% of eyes gained ≥3 lines and 26.5% of eyes gained ≥5 lines). The same pattern of improvement was noted in CDVA: 70.6% of eyes gained at least one line, 41.2% of eyes gained ≥3 lines, and 14.7% of eyes gained ≥5 lines. Overall, the average gain was two lines at 1 year.

Two of 43 eyes reported a loss of one line in UDVA, yet gain in the CDVA was still obtained. Four of 43 had a loss of one line in the CDVA, with an improvement in the UDVA. One eye had a loss of two lines in both UDVA and CDVA. This may be attributed mostly to corneal haze. This complication has frequently been reported in some studies. It can be explained by the use of CXL and its physiological wound healing and corneal depth changes postoperatively with keratocyte loss.[12] The patient might not

Table 2: Anterior keratometry (*K*) measured by the Scheimpflug device

Parameters	*Preoperative (43 eyes)*	*1 month (43 eyes)*	*3 months (43 eyes)*	*6 months (37 eyes)*	*1 year (34 eyes)*
Steep *K* (D) mean ± SD	50.97 ± 4.46	48.65 ± 4.95	47.97 ± 4.96	47.68 ± 5.24	47.58 ± 5.61
Flat *K* (D) mean ± SD	47.08 ± 4.02	45.68 ± 4.08	45.30 ± 4.13	44.88 ± 4.15	44.84 ± 4.47
K_{mean} (D) mean ± SD	48.94 ± 4.15	47.11 ± 4.41	46.63 ± 4.41	46.26 ± 4.69	46.11 ± 5.01
K_{max} (D) mean ± SD	56.27 ± 6.40	51.50 ± 8.24	51.53 ± 7.57	51.27 ± 7.55	51.22 ± 7.94

D, diopters; SD, standard deviation

Table 3: Thinnest corneal thickness

Parameters	*Preoperative (43 eyes)*	*1 month (43 eyes)*	*3 months (43 eyes)*	*6 months (37 eyes)*	*1 year (34 eyes)*
Thinnest corneal thickness mean ± SD	462.49 ± 36.17	378.05 ± 48.95	376.88 ± 50.81	386.51 ± 54.02	388.21 ± 56.64

SD, standard deviation

Table 4: Refractive outcomes

Parameters	*Preoperative (43 eyes)*	*1 month (43 eyes)*	*3 months (43 eyes)*	*6 months (37 eyes)*	*1 year (34 eyes)*
Sphere mean ± SD	−2.10 ± 2.45	−0.24 ± 2.46	−0.43 ± 2.71	−0.42 ± 2.53	−0.34 ± 2.26
Cylinder mean ± SD	−3.50 ± 1.85	−1.96 ± 1.25	−1.74 ± 1.54	−1.29 ± 1.17	−1.23 ± 1.02

SD, standard deviation

require specific treatment or sometimes need flourometholone eye drops (low dose corticosteroids) with vitamin C. However, considering a stromal haze, an expectant normal finding post-CXL has been controversial.[13]

Keratometric Changes

Based on our keratometric results mentioned above, we found a statistically significant improvement in the steep, flat and steepest K, noticing the major decline at 1 month postoperatively, with a minimal yet continuous decline at 3 months, 6 months, and 1 year. This is an anticipated result of corneal anterior surface normalization done by PTK and PRK.

Pachymetric Changes

The postoperative corneal thickness, demonstrated by the thinnest corneal thickness, experienced a great reduction, which would be expected due to tissue excimer ablation of the corneal stroma. At 1 month, due to the epithelization process occurring at the corneal cellular level, a nadir thinnest would still not be expected. It is noteworthy, however, to mention that the main reduction was at 3 months because of halted epithelization process and tissue shrinkage and remodeling. However, corneal thickness was increasing progressively after 3 months as a result of the stromal reflectivity and density modification between the anterior and intermediate part of the cornea associated by CXL.[14]

Refractive Changes

According to refractive outcomes, there were significant improvements in mean spherical and cylindrical values from (-2.10 ± 2.45) to (-0.34 ± 2.26) and (-3.50 ± 1.85) to (-1.23 ± 1.02), respectively, after 1-year follow-up. This would be mostly as a result of partial correction by PRK and the flattening effect of cross linking.

Conclusion

Based on our study, the majority of cases demonstrated potentially promising refractive, keratometric and topometric results over 1-year follow-up after the use of the combination of PTK, wavefront-optimized PRK and CXL as a safe and effective therapeutic intervention in treating mild to moderate irregular keratoconic corneas. This combined approach is a viable option for keratoconic progression and improve corneal regularity and offer a temporary or permanent alternative to keratoplasty.

Additional studies for a longer period of follow-up may be warranted to confirm the efficacy and stability of cases treated with this combined approach.

Declarations

Ethics Approval and Consent to Participate

Ethical approval was granted by An-Najah National University, IRB ethical committee.

Consent for Publication

The manuscript does not contain any person's data in any form.

Availability of Data and Material

Based on the ethical approval from An-Najah National University, IRB ethical committee, data will be kept confidential, and we can only submit the findings.

Authors' Contributions

Mohammad M Shehadeh has made substantial contributions to the conception and design of the study, acquisition of data, analysis and interpretation of the data, and drafting of the manuscript. Jamal Qaddumi has made substantial contributions to data collection and interpretation, and drafting the manuscript. Mohammad T Akkawi has made substantial contributions to the conception and design of the study, acquisition of data, analysis and interpretation of the data, and drafting of the manuscript. Ahmad R Soboh and Dima Sadi have made substantial contributions to the conception and design of the study, the acquisition of data, the analysis and interpretation of the data, and the drafting of the manuscript. Deyab R Khloof and Ammar A Aghbar have made substantial contributions to the conception and design of the study, the acquisition of data, the analysis and interpretation of the data, and the drafting of the manuscript. All authors have given final approval of the version to be published.

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