Complications of Combined Topography-Guided Photorefractive Keratectomy and Corneal Collagen Crosslinking in Keratoconus

Michelle Cho, M.D.¹
Anastasios John Kanellopoulos, M.D ¹,²
New York University School of Medicine, Department of Ophthalmology, New York, NY ¹
Laservision.gr Institute, Athens, Greece ²
2nd Annual ISRS Special Crosslinking Session
Corneal Crosslinking Discussion – Where We Are and What’s Next?

Supported by avedro
Financial interests

• Alcon/Wavelight
• Bausch & Lomb
• Revision Optics
• Seros Medical
• Avedro
• Ocular Therapeutix
CXL: a Photooxidative reaction
courtesy E. Spoel, MD

- Photodynamical reaction Typ 2

- RF + UV $\rightarrow {^1RF}^*$ $\rightarrow {^3RF}^*$ $\rightarrow$

- $^{3}O_2 \rightarrow {^1}O_2$ (Singulet-oxygen)

- Production of radicals

- Oxidative dissemination
Biochemical reaction

Kanellopou
Introduction of riboflavin in a femto-pocket

**Collagen Cross-linking in Early Keratoconus With Riboflavin in a Femtosecond Laser-created Pocket: Initial Clinical Results**

Anastasios John Kanellopoulos, MD
Decrease of UV-intensity

courtesy E. Spoel MD
Visual rehabilitation of ECTASIA

- Spectacles, Contacts, INTACS, DALK, PK!
- CXL
  - Combined technique: CXL+tgPRK
  - Implantation of phakic IOLs in cases with high residual myopia and/or anisometropia
  - CXL prior to a phakic IOL will produce a more stable ground for calculating the refractive error
- other
We introduced: Higher fluence CXL: 6, 7, 9, 10 and 12mW/cm²

AAO 2008: CXL for 15 minutes utilizing 7mW/cm² fluence

Shorter duration, higher ultraviolet A irradiation (UVA) fluence collagen cross-linking (CCL) for keratoconus (KCN)

A. John Kanellopoulos, MD
From: New York University School of Medicine, Manhattan Eye, Ear and Throat Hospital, New York, NY, USA
LaserVision.gr Institute, Athens, Greece

Background:
We have presented our experience over the last 6 years in using this entry in its standard form in past AAO meetings. With goal to shorten the duration and potentially increase efficacy we opted to study a model of CCL of higher UVA light intensity (from 3mW to 7 mW/cm²) and the same adjacent 0.1% topical riboflavin sodium phosphate solution.

Objective To evaluate the safety and efficacy of higher UVA fluence and shorter duration for collagen cross-linking in KCN.

Design: Prospective, randomised comparative case series.

Methods: 15 patients with bilateral keratoconus were included. All cases were evaluated for UCVA, BSCVA, refraction, keratometry changes (K), topography changes, endothelial cell changes and corneal clarity. All eyes received CCL with topical 0.1% riboflavin solution drops and in regard to UVA they were randomized for each patient: 15 eyes were CCL with 7mW/cm² for 15 minutes and the 15 contra lateral eyes with 3mW/cm² for 30 minutes. Mean follow up was 1.5 years.

Results:
The mean improvement of UCVA was 0.2 to 0.4, BSCVA improved from 0.4 to 0.7.
The average change of spherical equivalent was 1.5D reduction in myopia, the average change in cylinder was 2.1D reduction. The average highest keratometry was 51.2D pre-op and changed to 48.5D post-op There was no statistical difference in the means in the 2 groups.

Conclusions
Shorter duration, higher UVA fluence-CCL appears to be as safe and as effective in stabilization of ectasia in KCN.
It may cause less cell toxicity due to lesser cornea dehydration (less time) and shorter exposure of keratocytes and endothelial cells to UV light along with riboflavin. Further studies are needed to validate this data.
Introduced Prophylactic CXL in PRK and LASIK
4 years after iLASIK+CXL
Variable UV fluence: Avedro
1-30mW/cm²
Topo-guided partial PRK

1-Topolyzer: Placido disc topography
2-Pentacam (Oculyzer)
3-Pentacam HD (oculyzer II)-Refractive suite
4-Vario (placido disc + pupil sensor + iris recognition + limbal landmarks recognition)

WaveLight® FS200
Femtosecond Laser

WaveLight® EX500
Excimer Laser

WaveLight® Refractive Suite
The Athens Protocol:
PTK > topoPRK > MMC > CXL (7mW/cm² x 15 min)

340mOsm 0.1% riboflavin sodium phosphate

7mW/cm² for 15 minutes
Oxygen Depletion Over 30 Minutes

Depletion and gradual replenishment of dissolved oxygen below a 100 µm thick corneal flap, saturated with 0.1% RF during 3 mW/cm² UVA irradiation at 25 ºC.
The Athens Protocol
7-years

Stability of Simultaneous Topography-guided Photorefractive Keratectomy and Riboflavin/UVA Cross-linking for Progressive Keratoconus: Case Reports

Ronald R. Krueger, MD, MSE; A. John Kanellopoulos, MD
Comparison of Sequential vs Same-day Simultaneous Collagen Cross-linking and Topography-guided PRK for Treatment of Keratoconus

Anastasios John Kanellopoulos, MD

Kolozsvári et al
IOVS 2002;43:2165-2168

JRS Sept 2009
Combined same-day tgPRK and CXL appear to be superior to the rehabilitation of KCN and ectasia

- One procedure
- Less PRK-associated scarring
- Better riboflavin penetration
- Less shielding of UV by Bowman’s wider CXL area
- Redistribution of cornea’s strain (biomechanics)
- No need to remove cross-linked cornea
- Underscore refraction
26y/o pilot, from UCVA 20/60 to 20/15
postLASIK ectasia:
Difference: pre- and post- treatment
Bilateral LASIK ectasia treated with topoPRK+CXL:
Short and long term complications of combined topography guided PRK and CXL (the Athens Protocol) in 412 keratoconus eyes (2-7 years follow-up)

Anastasios John Kanellopoulos, MD
Director, Laservision.gr Institute, Athens, Greece
Clinical Professor NYU Medical School, NY
Financial Interests: Alcon. Wavelight
From UDVA 20/20 to 20/40 over 4 years with a 2.5D hyperopic shift
Unknown Possible Long Term CXL

- Cataracts
- Conjunctival squamous cell carcinoma
- Long Term Dry Eyes due to UV A Damage to ocular surface
- Progressive thinning
- Poor glaucoma management
• **Introduction:**

  • Corneal collagen crosslinking (CXL) has become a new addition to the armamentarium for the treatment of keratectasias, in particular keratoconus and post—LASIK ectasia. CXL with the use of riboflavin (vitamin B2) and ultraviolet A (UVA) irradiation cross links the collagen fibers in the corneal stroma thereby strengthening and biomechanically stabilizing the cornea (1). This is especially useful in keratoconus (KC) where progressive corneal thinning and steepening leads to myopia and irregular astigmatism (2). Promoting a new approach for the treatment of KC, CXL has become a viable option in addition to the established treatments available including spectacle correction, rigid gas permeable contact lenses, intrastromal corneal ring segments (3) and penetrating keratoplasty (4).
• The goal of introducing topography-guided photorefractive keratectomy as a component to the CXL procedure is to normalize the corneal surface and to decrease the irregular astigmatism (5). The synergistic effect of combined topography-guided photorefractive keratectomy and collagen crosslinking (tgPRK-CXL), the Athens Protocol, may provide further improvement in visual acuity than with CXL alone (6).
References:

Purpose

• The purpose of this study is to demonstrate the common early and late complications associated with tgPRK-CXL in keratoconus patients. The primary outcome measures in this prospective cohort study are the presenting complications and the resulting corrected-distance visual acuity post tgPRK-CXL.
Surgical Procedure

- Following the completion of this procedure, a bandage contact lens was placed. The postoperative regimen consisted of topical ofloxacin (Allergan Inc, Irvine, CA) four times a day for 10 days, prednisolone acetate 1% (Pred Forte, Allergan) four times a day for 60 days, and oral Vitamin C 1000mg daily for 60 days. Sunglasses were highly recommended to protect from all natural light. The bandage contact lens was removed at approximately day 5 following complete reepithelialization.
Surgical Procedure

- Topographic data from the proprietary WaveLight customized platform (Topolyzer) served as the basis for the topography-guided PRK. The resulting topographic data were drawn from an average of eight topographies with the following parameters: zero postoperative asphericity, no tilt correction, and a 5.5 mm optical zone. The goal was to treat 70% of cylinder and the remaining amount of sphere up to a maximum of 70%, so as not to exceed 50 μm in stromal removal.

- Next riboflavin sodium phosphate ophthalmic 0.1% solution (Priavision, Merlo Park, CA) was applied topically every 2 minutes for 10 minutes. Four diodes emitting UVA light of approximately 370 nm wavelength (365 to 375 nm) and 3 mW/cm² radiance at 2.5 cm was projected onto the corneal surface for 30 minutes. During this time, riboflavin solution was applied topically every 2 minutes with the aid of a Keracure timing device (Priavision).
The surgical procedure was performed in a single institution by the same surgeon (A.J.K) under sterile conditions. Following placement of an aspirating lid speculum (Rumex, St Petersburg, FL), 20% alcohol solution was placed within a 9-mm titanium LASEK trephine (Rumex) for 20 seconds after which the epithelium was removed with a dry Weck-cell sponge. The laser treatment was then applied. Mitomycin C 0.02% solution in a soaked cellulose sponge was placed on the ablated tissue for 20 seconds followed by irrigation with 10 mL of chilled balanced salt solution.
Results

- CDVA from 20/100 to 20/50. Early complications: 65% pain (Day 1),
- Ectasia Regression: 1.2% ectatic progression requiring retreatment. None required a corneal graft.
- The complications encountered were delayed epithelial healing, postoperative pain, epithelial scarring, transient stromal haze, and progression of ectasia. (20%).
Results-details

• Epithelial healing occurred in 75% of cases by day 4, 15% by day 5, and 10% by day 10. No significant pain on postoperative day 1 was reported in 45% of the cases, moderate pain in 25%, and severe pain in 30%. Salzmann-like epithelial scarring, seen in 25% of the cases, persisted for an average of one month. The epithelial scar resolved with lubrication (30%), lubrication and bandage contact lens (BCL) (25%), autologous serum administration in addition to lubrication and BCL (25%), or surgical removal
Results 2

- At 6 months post-procedure, 12 of the 412 cases had persistent subepithelial corneal scarring, but none that necessitated penetrating keratoplasty. Transient stromal haze was noted in 15% of the cases, which resolved by month 6 in 95% of these cases (8 of 412 cases showed stromal haze past month 6). Seven of 412 cases showed signs of ectatic progression, for which 2 required penetrating keratoplasty, 4 required repeat CXL, and 1 elected no treatment. One case with ectatic progression had undergone pregnancy out of 7 total pregnancies of the 412 cases.
OCT evaluation
2 months after AP
Late stromal scar
Late stromal scar-resolving
AP15mos
3 months later (lotemax, Autologous)
2 weeks out-delayed epitheliazation
2 weeks later (1 month postop)
Early haze (2 months-gone after 6 months)
Delayed epithelial healing
Delayed epithelial healing with haze OD simple AP, OS after K scar from CL
Regression of effect and application of 2\textsuperscript{nd} Athens Protocol with $\frac{1}{2}$ of the CXL time (7mW/cm\(^2\) for 8 minutes)

1\textsuperscript{st} Athens Protocol

2\textsuperscript{nd} Athens Protocol
2nd treatment
2 treatments, now 320um, 20/40 with -5 SCL
Delayed healing
1 month
I month-Salzman’s-like deposit
2 weeks-delayed healing with heaped-up white margins
2 months-PRK scar
2 months-PRK anterior stromal scar
2 weeks-elevated epi scar
Video

Short and long term complications of combined topography guided PRK and CXL (the Athens Protocol) in 412 keratoconus eyes (2-7 years follow-up)

Anastasios John Kanellopoulos, MD
Director, Laservision.gr Institute, Athens, Greece
Clinical Professor NYU Medical School, NY
Healing delay-day4-ok on 1 month

PRK-like haze 1 year after, in heavy sunbathing improved with steroids

Week 2

Week 2
Salzmann's-like nodule(s) can persist to 3 months postop

Delayed epithelial healing with white spots

Haze

Faint Scar and white spot
Conclusions

Like any surgical procedure, combined topography-guided photorefractive keratectomy and corneal collagen crosslinking (the Athens Protocol) has its own set of complications. The main early complications noted were postoperative pain, delayed epithelial healing, and Salzmann-like epithelial scarring.

A significant percentage of patients experienced moderate to severe pain on postoperative day one after the Athens Protocol. This is most likely due to removal of the epithelium, much like the individual procedures PRK and CXL (7). A PTK (50 micron, 6.5mm diameter) was used to aid in the epithelium removal. However, recent studies have shown that there is no increase in postoperative pain with the use of alcohol in PRK (8). Topical nonsteroidal anti-inflammatory drugs (NSAIDs) have been successful with pain management in traditional surface ablation procedures. Due to the nature of the keratoconic corneas and increased risk of delayed epithelial healing and perforation, topical NSAIDs were avoided (9).
Conclusions

• Delayed epithelial healing was reported if the epithelium did not heal completely after 5 days post procedure. After CXL alone, the mean epithelial healing time was found to be 3.25 days, ranging from 1 to 8 days (10). Our study found 10% of cases that did not heal completely by day 10. The PRK component may be contributing to the delay. These patients were observed closely to monitor for signs of additional corneal thinning or infection.

• Salzmann-like epithelial scarring, which persisted for an average of one month, was found in a significant percentage of cases. The epithelial scar resolved with lubrication (30%), lubrication and bandage contact lens (BCL) (25%), autologous serum administration in addition to lubrication and BCL (25%), or surgical removal (20%). 2.9% of cases had persistent subepithelial corneal scarring beyond six months that did not respond to the various interventions. However, none of these cases necessitated penetrating keratoplasty. It is well known that CXL is cytotoxic to keratocytes (11), and confocal microscopy may be helpful in determining the composition of this epithelial scarring for further prevention.
Conclusions 3

• Notable late complications were stromal haze, and ectatic progression. Only a small percentage of cases (3.8%) demonstrated stromal haze past month six in this study. Permanent corneal haze after CXL alone has been reported (12). Other studies have reported posterior linear stromal haze formation after combined photorefractive keratectomy and collagen crosslinking (13). However, these studies did not include mitomycin C in their surgical protocol. Mitomycin C was used in this study since it has been shown to modulate corneal wound healing and to reduce corneal haze formation post PRK (14).

• The Athens Protocol was unable to halt the progression of keratoconus in a few cases (1.2%). Repeat CXL was required to treat this ectatic progression. Another study of simultaneous topography-guided PRK and CXL revealed no topographic or clinical signs of keratoconus progression post procedure (15). There are small differences between the two surgical procedures, and further studies are required to determine the causative factors for ectatic progression.
Conclusions 4

• The strengths of this study are the large cohort of patients and the long-term follow-up for a relatively novel procedure. This enabled us to present the late complications associated with this procedure. The main limitation is the observational study design, which does not include a control group. Generalizability is also limited since the study took place at a single clinical site. The effect of the Athens Protocol in advanced keratoconus with corneal thickness less than 350 μm is unknown at this time.

• The Athens Protocol, combined topography-guided photorefractive keratectomy (with the Alcon/Wavelight platform) and corneal collagen crosslinking, is a promising technique to halt the progression of keratoconus and to provide improved, functional vision. The early complications associated with this procedure are postoperative pain, delayed epithelial healing, and Salzmann-like epithelial scarring, while the late complications are subepithelial corneal scarring, stromal haze, and ectatic progression. Techniques to manage the various complications are discussed with further studies necessary to control, manage, and prevent additional complications.
IK after, dog bite

CXL + ABTs
Severe scar of the cornea
BCVA 20/200,
Lamellar or PK?
From 20/200 to 20/40!
Conclusions-ectasia management

• CXL is an effective means of ectasia stabilization
• We are using: Higher fluence, shorter/pulsed expo time
• Athens Protocol: topo-guided partial PRK+CXL stable with long term follow-up is our standard choice in ALL cases
• Prophylactic CXL may become a customised biomechanic modulator in LASIK
AAO/ISRS meeting in Athens!

• December 17th
• The ISRS didactic course
• Live surgery and commentary in LASIK, Athens Protocol, CXL and femto cataract surgery

• Please contact:
• Helen@laservision.gr

Kanellopoulos MD
Thank you