PARTIAL TOPOGRAPHY-GUIDED PHOTOREFRACTIVE KERATECTOMY FOLLOWED BY CORNEAL CROSS LINKING IN THE MANAGEMENT OF PROGRESSIVE KERATOCONUS: OUR INITIAL TEN-MONTH RESULTS

Igor Knezović1, Mirna Belovari Višnjić2 and Hrvoje Raguž3

1Department of Ophthalmology, Dubrava University Hospital, Zagreb; 2Department of Ophthalmology, Čakovec General Hospital, Čakovec; 3Knezović Vision Group Eye Center, Zagreb, Croatia

SUMMARY – The aim was to assess the results achieved in keratoconic corneas submitted to the combined partial topography-guided photorefractive keratectomy (TG-PRK) and corneal cross linking (CXL) procedure performed on the same day. Four patients underwent this treatment of one eye. Corneal epithelium removal was performed by 50-micron phototherapeutic keratectomy. Then, partial TG-PRK laser treatment was applied (Wavelight Allegretto, Eye Q, 400Hz), followed by corneal collagen cross-linking (CXL, 3 mW/cm²) for 30 minutes using 0.1% topical riboflavin solution. Outcome measurements included uncorrected distance visual acuity (UCDVA), best spectacle corrected distance visual acuity (BSCDVA), manifest refraction spherical equivalent, keratometry, corneal high order aberration values, and corneal tomography. At the end of 10-month follow up, all eyes showed improvement in BSCDVA of 1-5 lines on Snellen chart. All other investigated parameters showed significant improvement as well. One eye showed some topographic improvement, but no improvement in UCDVA. No corneal haze, prolonged epithelial healing or endothelial cell loss occurred. During 10-month follow up, the same-day combined TG-PRK and CXL appeared to offer tomographic improvement and better visual acuity in keratoconus patients.

Key words: Keratoconus; Photorefractive keratectomy; Topography-guided photorefractive keratectomy; Corneal diseases – surgery; Corneal cross-linking

Introduction

A number of treatments, for example, corneal collagen cross linking (CXL)1, intrastromal corneal ring segment implantation2, conductive keratoplasty3, and phakic intraocular lenses4 can be included in the management of keratoconus patients. In the last decade, corneal collagen cross linking has shown promising results in the treatment of keratoconus by slowing down or halting its progression5. This procedure is also useful in the treatment of postoperative LASIK ectasia as a noninvasive treatment that delays the need of penetrating keratoplasty6. One of the latest therapeutic treatments includes the same-day simultaneous topography-guided photorefractive keratectomy (TG-PRK) and corneal collagen CXL procedure, also known as Athens protocol7,8. This treatment, especially if done as a same-day procedure, achieves corneal biomechanical stability and better visual rehabilitation8. Results of this combined procedure are best evident in patients with highly irregular corneas who are not adapted to contact lens wear.

Patients and Methods

The time span of this procedure, which was performed on one eye in four patients, lasted from August
2013 until May 2014. All study patients were male, mean age 31.16±4.27 years. In each patient, the procedure consisted of partial TG-PRK followed by corneal CXL. Prior to the procedure, all study patients signed the informed consent form accepting the terms of the procedure. The criteria set out before the study were second and third stage keratoconus according to Amsler Krumeich classification, preoperative best spectacle corrected distance visual acuity (BSCDVA) of 0.4 on each eye, and corneal thickness more than 450 microns at the thinnest location. Exclusion criteria were first and fourth stage keratoconus, previous trauma or surgical procedure on the eye, and disease status that could delay the cornea healing process. During a 6-month period before the procedure evaluation, keratoconus progression was marked as one or more of the following changes: increase ≥0.5 D in manifest refraction spherical equivalent (MRSE) and increase ≥1D in anterior sagittal curvature corneal topographic maps. All patients were intolerant to contact lens wear. Also, 3 weeks before the procedure and just before the surgery, eye examination was performed. The following measurements were performed to complete evaluation of keratoconic corneas: endothelial cell microscopy, axial length scans automated keratometry, anterior spectral domain optical coherence tomography and corneal tomography, providing the best treatment for each individual patient.

The Wavelight Allegro Oculyzer (Alcon Laboratories Inc., Fort Worth, Texas, USA) provides an accurate three-dimensional view of the cornea and separate approach to refractive surgery using a rotation Scheimpflug camera in all meridians. Objective determination of corneal topography, 3D analysis of anterior chamber, overall pachymetry, tomographic analysis, and lens density measurement are also included in this examination. The Oculyzer software compares the measurements of corneal asymmetry indices with the mean and standard deviation of a normal population. In our study, the following parameters were especially monitored: index of surface variance (ISV), index of vertical asymmetry (IVA), index of height asymmetry (IHA) and index of height decentration (IHD). ISV marks standard deviation of individual corneal sagittal radii from the mean curvature; normal value is less than 37%; IVA is the mean difference between superior and inferior corneal curvature expressed in mm; a value greater than 0.32 is pathologic; IHA is the mean difference between height values superior minus height values inferior with horizontal meridian as mirror axis expressed in μm, and a value greater than 21 is pathologic; IHD provides the degree of decentration in vertical direction, calculated on a ring with 3-mm radius; it is expressed in μm and pathologic value is greater than 0.016.

Non-contact, high magnification image capture of the endothelium is enabled by a specular microscope CEM 530 (Nidek Co. Ltd. Japan), which provides observation of the shape and size of the cells. Also, apart from conventional central and peripheral specular microscopy, this microscope also has a unique function of capturing paracentral images, which automatically gives complete analysis in two seconds.

Measurement of the following six values in 10 seconds is enabled by the optical biometer axial length scan (AL scan, Nidek Co. Ltd., Japan): corneal curvature radius, pupil size, axial length, anterior chamber depth, white-to-white distance, and central corneal thickness.

Analysis of the anterior eye segment with a resolution of 3 microns is enabled by spectral-domain optical coherence tomography (SOCT Copernicus, Optopol Technology S.A., Zawiercie, Poland). The tomography records pachymetry maps and measures corneal epithelial thickness.

Surgical technique

Wavelight Allegretto Eye Q 400 Hz excimer laser device was used for conducting phototherapeutic keratectomy (PTK) and TG-PRK. After these procedures, we conducted corneal collagen CXL using a CXL device, wavelength 370 nm (CSO VEGA CMB X Linker, Florence, Italy).

The first step to prepare the patient for this combined procedure was to apply the topical anesthetic oxybuprocaine hydrochloride 0.4% eye drops; then PTK was performed on the central 7.0 mm zone with 50 micron ablation depth for epithelium removal. Partial TG-PRK was performed on a 5.5 optical zone (OZ), desired refraction was settled to save the corneal tissue and keep residual stroma within a boundary of 380–400 microns before corneal CXL treatment.

Corneal haze was prevented by applying mitomycin C 0.02% on the stromal surface for a period of
30 seconds. When applied on the cornea, this anti-
neoplastic agent regulates fibroblast proliferation and
myofibroblast formation, which is responsible for cor-
neal haze after PRK\textsuperscript{15,16}.
Riboflavin solution 0.1% (Sooft, Italy) was applied
over the corneal surface every 2 minutes during a 20
minute period to allow its absorption throughout the
corneal stroma into the anterior chamber, which was
confirmed by slit lamp biomicroscopy.
After corneal alignment, collagen CXL was ap-
plied on the corneal surface for 30 minutes (UvA 370
nm light at the irradiance of 3.0mW/cm\textsuperscript{2}). Riboflavin
was applied every 2 minutes during UvA exposure.
Before the CXL and every 5 minutes during the pro-

cedure, ultrasound pachymetry measurement was per-
formed. If the corneal thickness was reduced to less
than 380 microns, a balanced salt solution was applied
on its surface to swell the cornea. Postoperatively, a
bandage soft contact lens was placed on the eye for 3-5
days and was removed after epithelium regeneration.
Anti-inflammationoary eye drops were administered after
the procedure according to our protocol. The patients
applied antibiotic eye drops five times a day for seven
days and corticosteroid eye drops four times a day for
the first two weeks. After the first two weeks, the pa-
tients gradually reduced the corticosteroid eye drops
every fourteen days for the next few weeks.

\begin{table}
\centering
\begin{tabular}{|l|c|c|c|c|c|c|}
\hline
 & N & Mean & Std. Deviation & Minimum & Maximum & Percentiles \\
\hline
& & & & 25th & 50th (Median) & 75th \\
\hline
UCDVA (decimal) & 4 & 0.1625 & 0.09465 & 0.10 & 0.30 & 0.1000 0.1250 0.2625 \\
BSCDVA (decimal) & 4 & 0.6250 & 0.17078 & 0.40 & 0.80 & 0.4500 0.6500 0.7750 \\
MRSE (D) & 4 & -3.2500 & 1.56791 & -5.25 & -2.00 & -4.8750 -2.8750 -2.0000 \\
MeanK (D) & 4 & 49.3500 & 2.61087 & 46.20 & 52.30 & 46.7750 49.4500 51.8250 \\
Kmax (D) & 4 & 55.4000 & 4.70956 & 49.40 & 60.70 & 50.7250 55.7500 59.7250 \\
ISV & 4 & 83.5000 & 11.09054 & 70.00 & 97.00 & 73.0000 83.5000 94.0000 \\
IVA (mm) & 4 & 0.7050 & 0.30293 & 0.43 & 1.10 & 0.4500 0.6450 1.0200 \\
IHA (µm) & 4 & 34.5250 & 14.42460 & 17.50 & 30.00 & 29.0000 34.5000 47.5000 \\
IHD (µm) & 4 & 0.0600 & 0.02676 & 0.03 & 0.09 & 0.0325 0.0640 0.0835 \\
Coma0 & 4 & -0.1638 & 0.12782 & -0.17 & 0.52 & -1.2273 0.2670 0.4690 \\
Coma90 & 4 & -1.8920 & 1.02315 & -2.91 & -0.91 & -2.8380 -1.8740 -0.9640 \\
Spherical aberration & 4 & -0.5598 & 0.11697 & -0.69 & -0.42 & -0.6715 -0.5625 -0.4453 \\
ECC (cell/mm\textsuperscript{2}) & 4 & 2708.0000 & 101.28179 & 2583.00 & 2820.00 & 2607.0000 2714.5000 2802.5000 \\
UCDVA1 (decimal) & 4 & 0.5250 & 0.21717 & 0.30 & 0.80 & 0.3250 0.5000 0.7500 \\
BSCDVA1 (decimal) & 4 & 0.8250 & 0.17078 & 0.60 & 2.00 & 0.6500 0.8500 0.9750 \\
MRSE1 (D) & 4 & -1.7500 & 0.95743 & -3.00 & -1.00 & -2.7500 -1.5000 -1.0000 \\
MeanK1 (D) & 4 & 46.9250 & 2.37960 & 44.00 & 49.40 & 44.5250 47.1500 51.8000 \\
Kmax1 (D) & 4 & 51.9621 & 2.0113 & 49.30 & 52.20 & 51.3020 50.6700 49.2600 \\
ISV1 & 4 & 66.2500 & 11.98263 & 51.00 & 80.00 & 54.5000 67.0000 77.2500 \\
IVA1 (mm) & 4 & 0.4450 & 0.26715 & 0.19 & 0.80 & 0.2175 0.3950 0.7225 \\
IHD1 (µm) & 4 & 0.0283 & 0.01650 & 0.00 & 0.04 & 0.0115 0.0340 0.0393 \\
Coma01 & 4 & -0.2940 & 0.79095 & -1.48 & 0.18 & -1.1063 0.0580 0.1663 \\
Coma901 & 4 & -1.3975 & 1.25194 & -2.80 & -0.04 & -2.6100 -1.3775 -0.2050 \\
Spherical aberration1 & 4 & -0.1370 & 0.38632 & -0.54 & 0.39 & -0.4610 -0.1970 0.2470 \\
ECC1 (cell/mm\textsuperscript{2}) & 4 & 2693.5000 & 80.06039 & 2612.00 & 2802.00 & 2625.2500 2680.0000 2775.2500 \\
\hline
\end{tabular}
\caption{Descriptive statistics}
\end{table}
Results

The patients were followed up and examined for a 10-month period during the study. Preoperative and postoperative visual and refractive data are summarized in Table 1.

Visual acuity and refraction

Both uncorrected distance visual acuity (UCDVA) and BSCDVA were significantly improved ten months after the procedure. The mean value of UCDVA increased from 0.1625 to 0.5250, while the values of BSCDVA improved from 0.6250 to 0.8250. MRSE decreased from -3.2500 to -1.7500.

Keratometric values

These values were monitored before the procedure and at the end of 10-month follow up as the mean keratometric value (Mean K) and maximal keratometric value (K max). Comparison of the Mean K and K max before the procedure and at the end of follow up yielded statistically significant changes in both Mean K and K max toward normal keratometric values (Table 1).

Corneal indices

The corneal indices observed were ISV, IVA, IHA and IHD. All data on the corneal indices were taken by rotating Scheimpflug camera (Wavelight Allegro Ocuzyner, Germany). The information displayed in Table 1 clearly shows that all measures changed and normalized during the period of observation. However, these changes were considerably more pronounced in the elevation based indices (IHA and IHD) as compared with the surface based indices.

Fig. 1. Pre- and postoperative Scheimpflug tomography (anterior sagittal curvature map): right eye – patient 1.

Fig. 2. Pre- and postoperative Scheimpflug tomography (anterior sagittal curvature map): left eye – patient 2.
Aberrometric results

The corneal high order aberrations (CHOA) presented as coma 0, coma 90, and spherical aberration. The results measured with the Wavelight Allegro Oculyzer showed improvement toward ideal corneal values according to Zernike analysis, except for coma 0 \textsuperscript{17,18}.

Topographic results

Topographic improvement was analyzed in the anterior sagittal curvature topographic view using the Wavelight Allegro Oculyzer (Figs. 1, 2, 3 and 4). Each figure consists of three images: preoperative topography image on the left panel; postoperative image on the mid-panel, showing remarkable topographic normalization; and a difference map between preoperative and postoperative keratometric values on the right panel. The profile of customized topography-guided excimer laser ablation is clearly visible.

Healing process and patient subjective satisfaction

No severe complications were reported after the treatment. All patients indicated some degree of pain during the first two days after the procedure and mild discomfort during the first month. Complete reepithelialization occurred within five days in all cases. No prolonged healing, corneal haze, infection or systemic adverse events were recorded.

Discussion

Modern diagnostic devices have enabled precise diagnosis and the opportunity for correction of irregular astigmatism, which is particularly pronounced
in patients with keratoconus. The main problems in keratoconus patients are corneal biomechanical instability and poor quality of vision, so the treatment of keratoconus represents a big challenge to many corneal surgeons worldwide. One of the first studies dealing with this topic, published by Kanellopoulos and Binder in 2007, presented CXL with sequential TG-PRK as an alternative to penetrating keratoplasty. Results showed significant clinical improvement and corneal stability over more than one-year of follow up. The following imperfections of this approach were observed: the central superficial part of the stiffened cross linked cornea was removed with PRK, thus reducing the benefits of CXL, and the corneal ablation rate after CXL was different in cross linked corneas with unpredictable refractive results compared to PRK in virgin corneas. In 2009, Kanellopoulos published a study comparing sequential with same-day CXL and TG-PRK. This study found the same-day procedure to be superior to the sequential procedure in progression of keratoconus and better visual rehabilitation. In the same year, Kymionis et al. reported on the results of TG-PRK immediately followed by CXL as an efficient treatment to manage this problem. In 2012, Tuwairqui and Sinjab evaluated 1-year visual and refractive outcome and patient satisfaction after simultaneous CXL combined with TG-PRK in the eyes with low-grade keratoconus. Corneal topography showed improvement in all treated eyes and overall better experience in visual outcome and rehabilitation. In our study, we evaluated the results of partial TG-PRK immediately followed by CXL in the eyes with moderate grade (stage II-III) keratoconus. Partial TG-PRK was performed to provide better postoperative visual acuity, but also to spare the thinned corneal tissue. The role of CXL is to provide better corneal biomechanical stability and halt the progression of keratoconus. BSCDVA and corneal topography parameters were significantly improved ten months after the procedure in all eyes, however, with different degrees. After removal of the Bowman layer with PTK and partial TG-PRK, imbibition of the corneal tissue with riboflavin is faster and UV A irradiation is more homogeneous, so we believe that the CXL after TG-PRK can be more effective than usual. Corneal compressive forces are redistributed, resulting in decreased corneal power on the apex, which can be explained by topography normalization. In their study published in June 2014, Hammer et al. proved tightening of the corneal tissue by more than 100% and efficacy of more than 95% after CXL. In our study, demarcation line visualized on the spectral-domain anterior segment optical coherence tomography was more pronounced centrally in comparison with the nasal and temporal depth, which is consistent with the study by Kymionis et al. published in 2013 (Fig. 5).

Combined, same-day partial topography-guided excimer laser treatment followed by corneal collagen CXL proved to be an effective, safe and increasingly predictable therapeutic option for keratoconic and highly aberrated corneas during 10-month follow up. This procedure provided significant improvement in UCDVA, BSCDVA, keratometric and topographic normalization, as compared to CXL alone.

References

4. Sedaghat M, Ansari-Astaneh MR, Zarei-Chanavati M,


Sažetak

PARCIJALNA TOPOGRAFSKI VODENA FOTOREFRAKTIVNA KERATEKTOMIJA I KORNEALNI CROSS LINKING U LIJEČENJU PROGRESIVNOG KERATOKONUSA: NAŠI POČETNI DESETOMJESEČNI REZULTATI

I. Knezović, M. Belovari Višnjić i H. Raguž

Cilj je prikazati kliničke rezultate kod rožnica s keratokonusom liječenih parcijalnom topografski vodenom fotorefrakтивnom keratektomijom (engl. topography-guided photorefractive keratectomy, TG-PRk) i rožničnim kolagenim “cross linking” (CXL) u kombiniranom istodnevnom postupku. U ovaj postupak na jednom oku su bila uključena četiri bolesnika. Za uklanjanje rožničnog epitela je primijenjena fototerapijska keratektomija, 50 mikrona. Nakon toga je primijenjena parcijalna TG-PRk (Wavelight Allegretto, Eye Q, 400 Hz) te rožnični kolageni CXL (3 mW/cm²) kroz 30 minuta uz primjenu 0,1% otopine riboflavina. Izlazna mjerenja su pratila nekorigiranu vidnu oštrinu na daljinu, najbolje korigiranu naočalnu vidnu oštrinu na daljinu, manifestni refrakcijski sferni ekvivalent, keratometriju, rožnične aberacije višeg reda i rožničnu tomografiju. Kod svih očiju je zabilježeno poboljšanje najbolje korigirane naočalne vidne oštrine na daljinu (1-5 redova na Snellenovim optotipima) tijekom i na kraju desetomjesečnog praćenja. Ostali istraživani parametri su također pokazali značajno poboljšanje. Na jednom oku je zabilježeno topografsko poboljšanje, bez poboljšanja nekorigirane vidne oštrine na daljinu. Nije zabilježeno zamućenje rožnice, produljeno cijeljenje epitela niti gubitak endotelnih stanica. Kombinirani istodnevni postupak parcijalne TG-PRk i rožničnog kolagenog CXL rezultirao je topografskom normalizacijom i boljom vidnom oštrinom kod bolesnika s keratokonusom tijekom desetomjesečnog praćenja.

Ključne riječi: Keratokonus; Fotorefraktivna keratektomija; Topografski vodena fotorefraktivna keratektomija; Kornealne bolesti – kirurgija; Kornealni “cross linking”