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Course IC-99

Successful Cross-Linking: Patient Selection, Management of Complications, Long-Term Follow-Up, and Understanding Corneal Response to Treatment

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20 September 2011
14.30 – 16.30
Room 2
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ADDRESSES

*Special thanks to Pietro Rosetta, MD*
*Ophthalmology Dept. – Istituto Clinico Humanitas*
I. Patient selection

Collagen Cross Linking

TRADITIONAL USE

PROGRESSIVE CORNEA ECTASIA

- Keratoconus
- Pellucid Marginal Degeneration
- Post iatrogenic ectasia

RECENTLY...
- CXL and corneal infection
- CXL with INTACTS
- CXL and PTK

Collagen Cross Linking

in progressive corneal ectasia

AIM

1. How to diagnose ectasia
2. How to assess progression of ectasia in KC, PMD, ectatic corneas
3. Inclusion CXL criteria
4. Exclusion CXL criteria

1. HOW TO DIAGNOSE ECTASIA
ectasia or pseudo-ectasia?

Interlocking relationships on Holladay Report

- Risk Factor or Hot Spots: RED on RED
- Coincidence of hot spots:
  Maximum curvature – max ant. & post. elevation - minimum pachymetry

ECTASIA RED on RED

PSEUDOECTASIA RED on BLUE
1. HOW TO DIAGNOSE ECTASIA
ectasia or pseudo-ectasia?

- Coincidence and displacement of maximum ant. & post. Elevation
  Anterior elevation values > 12-15 μ
  Posterior elevation values > 20 μ
- Eccentricity of thinnest point
- Map patterns (eccentric, asymmetric pattern/hot spots)

Interlocking relationships on Holladay Report

Holladay report
Normal cornea

- Thinnest point located centrally
- Thicker nasally and superiorly
- Flatter nasally
- Pachymetry gradient is predictable
- Map patterns

ASTIGMATISM: typical pattern!

PSEUDOECTASIA

Highest curvature does not correspond to thinnest cornea

Cicatrix
Perforating wounds
Host-donor interface

IRREGULAR ASTIGMATISM

Post refractive ablation
Corneal thinning corresponds to highest curvature point.

**ECTASIA**

Steepest, thinnest, most elevated points coincidence.

**HYPERCURVATURE**

**PELLUCID MARGINAL DEGENERATION**

RED on RED

**POST LASIK ECTASIA**

RED on RED

**TAKE HOME MESSAGE 1.**

**HOW TO DIAGNOSE ECTASIA**

- Interlocking relationships are a safer and more sensitive tool for ectasia diagnosis than single maps
- **ECTATIC CORNEA**
  - RED on RED
- **NON ECTATIC CORNEA**
  - BLUE on BLUE

**2. HOW TO ASSESS ECTASIA PROGRESSION**

- Slit lamp: subjective but not repeatable
- Endothelium and Vogt striae: late changes
- Confocal microscopy: not sensitive
- Refraction: HOA, and LOA
  - Ectasia outside the pupillary area does not change refraction: false negative
  - Progression of myopia: false positive

These are not reliable indicators of ectasia progression

**How can progression be monitored?**

- Follow up with DIFFERENTIAL MAPS
  - Curvature: Tangential map
  - Elevation: Elevation Maps
  - Thickness: Pachymetry Map

... Method: to evaluate change

**ABSOLUTE VALUE**  **PATTERN**
When differential maps are not available we should compare pattern & absolute value & indices.

**2001**

- Pattern change
- Increased cone area
- Absolute keratometry change

**TANGENTIAL MAP**

- Pattern variation
- Increase in elevation

**ANTERIOR ELEVATION MAP**

**POSTERIOR ELEVATION MAP**

**PACHYMETRY MAP**

- Thickness reduction
- Pattern variation
TAKE HOME MESSAGE 2
Only progression indicates ectasia

- Single topographic map is not a safe diagnostic instrument
- Differential maps allow soon progression assessment
- Differential maps allow earlier ectasia diagnosis in borderline cases
- Early diagnosis is important for successful application of cross linking

WHAT TO DO IN CASE OF DOUBTFUL ECTASIA?

FALSE POSITIVE = WARPAGE

SUSPECT KERATOCONUS  RED on RED

WHAT TO DO IN CASE OF DOUBTFUL ECTASIA?

TOPO AND TOMOGRAPHIC INDICES
- Corneal Navigator OPD
- Belin Ambrosio Indices PENTACAM
- Corneal Hysteresis ORA

BELIN /AMBROSIO INDICES

BFS
Enhanced BFS
Difference Elevation Maps
<6  6-12  >12
**TAKE HOME MESSAGE**

**EARLY DIAGNOSES IS IMPORTANT!**

- Avoid PK, DALK.
- Soon CXL.
- Preserve best VA.
- Preserve good CL tolerance.

**3. CXL TO TREAT OR NOT TO TREAT**

**INCLUSION CRITERIA**

- Ectatic corneal disease
- Ectasia progression documented by serial differential corneal topographies and optical pachymetries
- pt’age over 9 years
- signed informed consent
- Adequate corneal thickness

**CORNEAL THICKNESS**

at its thinnest point

- at least 400 µ in degenerative ectatic corneal diseases
- At least 380 µ in most severe cases
- At least 350 µ in post refractive ectasia

**4. EXCLUSION CRITERIA**

**ABSOLUTE**

- Loss endothelial cell count
- Severe corneal opacities
- pregnant or nursing ♀

**RELATIVE**

- history HSV, HZV
- severe eye dryness
- corneal infections
- autoimmune diseases
- previous ocular surgery
- poor compliant pt

...REMEMBER

- First stages KC and pediatric patients have better topographical and visual recovery.
- CL tolerance
- CCT/Kmax

Thank you for your attention!

Elena Albé
Istituto Clinico Humanitas

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II. Surgical Technique

Organized Surgical Approach

- Check-list
  - Eye
  - Patient data
- Activities by:
  - Attending physician
  - Nurse
  - Surgeon
- Alert
- Same-day control of clinical situation
- Antipain meds 30 min before CXL

Surgical Approach - Sterility

- Day Surgery
- Sterile conditions in the operating suite
  - Preop disinfection
  - Scrub
- Surgical gown and gloves
- Disposable medication
- Single-set surgical instruments
- Patient draping

Preoperative Medications

- 2% Pilocarpine drops
  - Pilocarpine reduces the thermal and photochemical Ultraviolet A (UVA) light irradiation potentially harmful to the lens and retina
  - Amount of light rays reaching the retina is proportional to the square of the pupil diameter
  - I.e., 6 mm pupil = 36 units, 4 mm pupil = 16 units, 2 mm pupil = 4 units
  - Topical anesthesia with two applications of 4% lidocaine drops and oxybuprocaine hydrochloride 0.2%

Available UVA Devices

- UV light from a solid-state UVA source
- UV-X™ System Peschke Meditrade GmbH, Huenenberg, Switzerland
  - The UV-X™ System was developed by Theo Seiler, MD and Eberhard Spoerl, PhD (Zuerich / Dresden).
  - It consists of a radiator which emits highly homogenized UV-light at 365 nm and a table mount.
  - Irradiance of 3 mW/cm² or 5.4 J/cm²

Available UVA Devices

- UV light from a solid-state UVA source
  - VEGA CBM X Linker, Oofta HT, Montegiorgio, Italy
  - Diode UV-A emitting source with a wavelength of 370 nm, with diaphragm, fixation point, double light aiming system, LCD camera

Standard Surgical Procedure

- Corneal epithelium is abraded in a central, 9-mm diameter area with an Amoils brush.
- Photosensitizing riboflavin 0.1% solution (10 mg riboflavin-5-phosphate in 20% dextran-T-500 10 ml solution) is applied onto the cornea every minute for 30 minutes to achieve adequate penetration of the solution
- Using a slit lamp with the blue filter, presence of riboflavin in the anterior chamber is confirmed before UV irradiation
Surgical Procedure
• A calibrated UVA meter (LaserMate-Q; Laser 2000, Messlingen, Germany) used before treatment to check the irradiance at a 1.0 cm distance. Laser λ = 370±5 nm, Power 3 mW/cm² (= 5.4 J/cm²)
• UV source exposition for 30 minutes
  • Leave untreated zone of at least 1.5 mm from the limbus (stem cells protection)
  • Do not shorten treatment time
  • Do not use home-made solutions
  • Surface must remain moist to avoid haze formation
  • Riboflavin solution is applied again, but only once every 5 minutes
  • Focusing is very important: out-of-focus can result in dangerous or ineffective dosage

Postoperative Medication
• Cyclopentolate 2% eyedrops
• Levofloxacin eyedrops
• Soft bandage contact lens until re-epithelialization is complete.
  • Topical levofloxacin 4 times daily for 7 days
  • Dexamethasone 0.15% drops 3 times daily for 20 days
  • 0.15% sodium hyaluronate drops 6 times daily for 45 days
  • Oral aminoacid supplement

Postoperative Period
• 1, 3, 6, 12 month-controls
• Complete ophthalmological examination
• Corneal topography
• Pentacam
• Haze monitoring
• 0.15 % sodium hyaluronate drops
• CL use is allowed one month after surgery if corneal epithelium appears healthy and regular

Good Medical Practice
• Accurate preoperative patient information (i.e., course of visual acuity)
• Standardized informed consent
• In Italy, one IC for the whole nation, approved by the national ophthalmological society (SOI)
  • Documenting ectasia progression over at least 6 month-period:
    • Corneal topography
    • Pentacam

Good Medical Practice
• Documenting Surgery
  • Surgical logbook
  • Surgical report
  • Use of product adhesive labels (i.e, riboflavin)
• Documenting follow-up:
  • Visual Acuity
  • Corneal topography
  • Pentacam

Thank you for your attention!

Ophthalmology Department
Istituto Clinico Humanitas
University of Milan, Italy
III. Topo-aborrometric, refractive and pachymetric analysis of Keratoconics eyes undergoing CXL

Long term result of CXL

Part 1

Cross-linking (CXL) technique

- 2% Pilocarpine drops (protection of lens and retina)
  - The light reaching the internal structures of the eye is decreased by the square of the reduction of the pupil diameter
  - (For example: a 6-mm pupil = 36 units, a 4-mm pupil = 16 units, 2-mm pupil = 4 units)
- Antipain meds 30 min before CXL.
- Oxybuprocaine hydrochloride 0.2% + Lidocaine 5 min before CXL.

Cross-linking (CXL) technique

- Laser test (UVA meter)
- Laser λ 370 ± 5 nm
- Power 3 mW/cm² (= 5.4 j/cm²)
- Calibration should be extremely precise: +/- 0.1 mW/cm²
- Focusing is very important
  - out-of-focus can result in dangerous or ineffective dosage

Diaphragm adjusts size of treatment area

Laser plus camera enabling monitoring of focus, beam size and corneal surface

Monitor with view of cornea, beam, and treatment time
Cross-linking (CXL) technique

- A 9-mm central epithelial abrasion with Amoils brush
- Riboflavin 0.2% solution, 2 drops every minute for 30 minutes (commercially available®)
  - Do not be tempted to shorten treatment time
  - Do not use home-made solutions
  - Surface must remain moist to avoid haze formation
- Riboflavin absorption check (anterior chamber flare)
- UVA irradiation, leaving an untreated zone of at least 1.5 mm from the limbus (stem cells protection)
- Riboflavin again, 1 drop every 2-3 minutes during treatment

At the end of treatment
- Cyclopentolate 0.5%
- Hyaluronic acid + antibiotics (till re-epithelization)
- Bandage contact lens

Demographic

- 545 treated eyes
- Preop evaluated eyes: 344
  - 28 pediatric
  - 21 ectatic (lasik, prk, intacs)
  - 3 PMD
  - age@OP average: 30 years (from 10 to 67)
  - sex: female 27.1%, or 95 eyes
  - male 72.4%, or 254 eyes

  - pre SR equiv: mean -3.95 D ± 4.35 D (from -24.75 to 5.50)
  - pre SR sph: mean -2.49 D ± 4.20 D (from -23.00 to 6.00)
  - pre SR cyl: mean -2.92 D ± 1.97 D (from -10.00 to 0.00)

Defocus equivalent-%

Change in BSCVA - % “Safety”

Refractive outcome refractive variation / preop
**BSCVA - %**

- 1 m (200)
- 6 m (100)
- 1 y (170)
- 2 y (70)
- 3 y (70)

**BSCVA over time**

**Achieved Correction SEQ over time**

- "STABILITY"

**Pentacam**

- Chamber volume mm³

**Anterior chamber dept mm**

- Mean cyl
**OPD corneal navigator %**

<table>
<thead>
<tr>
<th></th>
<th>KCS</th>
<th>KC</th>
<th>PMD</th>
<th>PKP</th>
<th>KS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRE XL (351)</td>
<td>6.64</td>
<td>32.03</td>
<td>15.10</td>
<td>0</td>
<td>17.33</td>
</tr>
<tr>
<td>POST 3 M (160)</td>
<td>9.72</td>
<td>32.6</td>
<td>12.1</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>POST 6 M (282)</td>
<td>0</td>
<td>32</td>
<td>0</td>
<td>0</td>
<td>23</td>
</tr>
<tr>
<td>POST 1 Y (170)</td>
<td>0.3</td>
<td>35.95</td>
<td>0</td>
<td>0</td>
<td>5.03</td>
</tr>
<tr>
<td>POST 2 Y (48)</td>
<td>0.27</td>
<td>34.78</td>
<td>0</td>
<td>0</td>
<td>3.7</td>
</tr>
<tr>
<td>POST 3 Y (19)</td>
<td>0.18</td>
<td>35.2</td>
<td>0</td>
<td>0</td>
<td>3.7</td>
</tr>
</tbody>
</table>

**K max 3-5-7 mm**

**K min 3-5-7 mm**

**Ambrosio's Indexes**

- **ISV**: Index of Surface Variance—this index is elevated in all types of irregularity of the corneal surface (astigmatism, warpage, etc.).
- **IVA**: Index of Vertical Asymmetry: this index is elevated in case of oblique astigmatism, in keratoconus, or in ectasia.
- **KI**: Keratoconus Index increases with severity of central KC.
- **IHA**: Index of Height Asymmetry: this index is analogous of IMA, this index but it is more sensitive.
- **IHD**: Index of Height Decentration: this index is analogous to Keratoconus.
- **Rmin**: Minimum Sagittal curvature in 8 mm zone.
- **TKC**: Topographical Keratoconus Classification only based on anterior corneal data.

**Tecnique, intra-operative findings, and post-operative regimen**

**Intra-operative findings**

Why dealing with intra-operative findings?

- To understand the real shape of the cornea without the masking effect of the epithelium.
- To determine the changes occurring after epithelial removal.
- To document the changes induced by CXL.
- To explain why topography and BCVA do deteriorate during the first 3 months after CXL.
Why these late cone changes?

- The epithelium in a keratoconic cornea is arranged according to the law of surface tension: thinner at the apex and thicker at the edge of the cone.
- This masks the real (keratoconic) shape of the stroma.

Why these late cone changes?

- After any epithelial abrasion, the physiological rearrangement of the layers takes weeks to complete.
- Only when the epithelium is back to normal, and its masking function is re-established, does the flattening effect of CXL begin to appear (at about 3 mos).
Other intra-operative findings

- Apparent corneal thinning
- Biomechanical changes

BSCVA is better even if there is an apparent corneal thinning

<table>
<thead>
<tr>
<th>Pre CXL</th>
<th>1 mos post CXL</th>
<th>6 mos post CXL (nat)</th>
</tr>
</thead>
<tbody>
<tr>
<td>474 µ</td>
<td>-176 µ</td>
<td>+94 µ</td>
</tr>
</tbody>
</table>

Reduction of the elevation anterior of the keratoconus overtime

Differential elevation anterior map: -14 µ

Reduction of the area/power of the keratoconus overtime

Differential tangential map: -9.6 D

Pachymetry distribution 6 mos after CXL

Differential Pachymetry relative map

+22.8%

Apparent corneal thinning

“Thinning” is only temporary because:

- Riboflavin solution contain dextran that together with the exposure to air of the denuded cornea dehydrates the stroma
- Collagen fibers and lamellae are packed by CXL
**Corneal thickness normalization**
- Epithelium takes weeks to return to normal thickness
- Stroma rehydrates
- Increase of fiber diameter due to CXL
- Corneal thickness can even increase with time (1-2 years)
- Pachymetry map shows a more physiological distribution with time

**Return to normal thickness**
- Normalization of pachymetry distribution 18 mos after CXL

**Fluctuation of the corneal thickness**
- Fluctuation of pachymetry from pre op to 6 mos after CXL

**Return to normal thickness:** minimal thickness decrease(-9µ) and early regularization (+28µ) after 4 mos
Normalization of pachymetry distribution 1 year after CXL

<table>
<thead>
<tr>
<th>Pre-CXL relative pachymetry</th>
<th>Post-CXL relative pachymetry</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>OS</td>
</tr>
</tbody>
</table>

Normalization of pachymetry distribution only 3 mos after CXL

-8 % at only 3 mos post CXL!!

Biomechanical properties of cornea (ORA)

<table>
<thead>
<tr>
<th></th>
<th>pt</th>
<th>CH</th>
<th>CRF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>185</td>
<td>0.89±1.0</td>
<td>11±3.6</td>
</tr>
<tr>
<td>Moderate</td>
<td>397</td>
<td>1.07±0.4</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>156</td>
<td>10.8±2.4</td>
<td>10.8±2.4</td>
</tr>
</tbody>
</table>

Biomechanical improvement immediately after CXL

Results

CRF (Corneal Resistance Factor)

<table>
<thead>
<tr>
<th></th>
<th>PRE XL WITH EPI</th>
<th>PRE XL Wout EPI</th>
<th>POST XL Wout EPI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PRE XL Wout EPI</td>
<td>POST XL Wout EPI</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9,42</td>
<td>14,15</td>
<td>9,05</td>
</tr>
</tbody>
</table>

Statistical significances

<table>
<thead>
<tr>
<th></th>
<th>PRE XL WITH EPI</th>
<th>PRE XL Wout EPI</th>
<th>POST XL Wout EPI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pt</td>
<td>CH</td>
<td></td>
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<td></td>
</tr>
<tr>
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<td>1.03±0.4</td>
<td>1.03±0.4</td>
</tr>
<tr>
<td>Severe</td>
<td>156</td>
<td>10.8±2.4</td>
<td>10.8±2.4</td>
</tr>
</tbody>
</table>

Results

CH (Corneal Hysteresis)

<table>
<thead>
<tr>
<th></th>
<th>PRE XL WITH EPI</th>
<th>PRE XL Wout EPI</th>
<th>POST XL Wout EPI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PRE XL Wout EPI</td>
<td>POST XL Wout EPI</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10,32</td>
<td>15,18</td>
<td>9,68</td>
</tr>
</tbody>
</table>

Statistical significances

Reduction of the area/power of the keratoconus overtime

1 mos post-op

-3.55 D

3 mos post

-4.15 D

6 mos post

-5.17 D

12 mos post

-4.08 D

24 mos post

-6.61 D

CXL over time: from keratoconus to irregular astigmatism

Differential map from pre cxl to 24 mos post cxl

1.0 -2.25@7

0.9 -0.75 -2.00@20

0.9 -2.50@15

Differential Tangential map

From pre to 1 yrs post cxl

-3.42 D
BSCVA is better with minimal decrease of the curvature

<table>
<thead>
<tr>
<th>Pre cxl</th>
<th>1 mos post cxl</th>
<th>3 mos post cxl</th>
<th>6 mos post cxl</th>
<th>9 mos post cxl</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.4 -3.00 sph</td>
<td>0.4 -15.25 (-5.25)</td>
<td>0.5 con -16sf -4.50@40</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

52.9 D                    55.2 (+2.1) D | 51.8 (-0.9) D | 52.4 (-0.5) D

Differential tangential map: only – 0.5 D!!!

( Differential Tru net power map +1.1D )

pt n° 154

Curvature reduction of keratoconus post Cxl over time

<table>
<thead>
<tr>
<th>Pre cxl</th>
<th>6 mos post cxl</th>
<th>1 yrs post cxl</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2 -23sf -3.50 @65</td>
<td>0.4 -15.25 (-5.25) @65</td>
<td>0.5 con -16sf -4.50@40</td>
</tr>
</tbody>
</table>

54.42 D 46.59 D 43.19 D

Differential axial map -11,23D

Reduction of the TRUE NET power of the keratoconus overtime

<table>
<thead>
<tr>
<th>Pre cxl</th>
<th>1 mos post cxl</th>
<th>3 mos post cxl</th>
<th>6 mos post cxl</th>
</tr>
</thead>
<tbody>
<tr>
<td>49.3 D</td>
<td>48.8 D</td>
<td>46.0 D</td>
<td>46.3 D</td>
</tr>
</tbody>
</table>

pt n° 75

Differential map from pre op cxl to 2 yrs post cxl

Coma reduction overtime

<table>
<thead>
<tr>
<th>Pre cxl</th>
<th>1 mos post cxl</th>
<th>3 mos post cxl</th>
<th>6 mos post cxl</th>
<th>12 mos post cxl</th>
<th>24 mos post cxl</th>
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</thead>
<tbody>
<tr>
<td>LWF/CornHO</td>
<td>1.685 µ</td>
<td>1.096 µ</td>
<td>1.029 µ</td>
<td>1.079 µ</td>
<td>1.013 µ</td>
</tr>
</tbody>
</table>

pt n° 75

coma reduction of the 44.57 %

Reduction of elevation anterior map over time of the keratoconus

<table>
<thead>
<tr>
<th>Pre cxl</th>
<th>3 mos post cxl</th>
<th>6 mos post cxl</th>
<th>1 yrs post cxl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Differential Elevation anterior map -8 micron</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reduction of elevation posterior map over time of the keratoconus

<table>
<thead>
<tr>
<th>Pre cxl</th>
<th>3 mos post cxl</th>
<th>6 mos post cxl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Differential Elevation posterior map -19+ micron</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

pt n° 250
Reduction of elevation anterior map over time of the keratoconus

Reduction of pachimetry map over time of the keratoconus post cxl with expansion

Reduction of area/power over time of the keratoconus post cxl with expansion

Lasik: zo ricentrata molto visibile con riduzione dell’ametropia

Pentacam Nucleus Staging

Cirrus vs Pentacam

Staging example
Keratoconus

- Keratoconus is a degenerative disorder of the eye in which structural changes within the cornea cause it to thin and change to a more conical shape than its normal gradual curve.
- The exact cause of the kc is uncertain, but has been associated with detrimental enzyme activity within the cornea and with disorder of thyroid (altered value of T3, T4, FTSH) and hipofisy.

Study

Total 91 asintomatic pts

- 65, 9% male (8,3 % altered value)
- 34, 1% female (16,12 % with altered value)

- Patologies checked:
  - Struma plurinodulare
  - Tiroidite cronica su base autoimmunitaria
  - Tiroidite cronica con noduli solidi
  - Iperplasia nodulare dx/sx
  - Tiroidite (assenza di noduli)
  - Noduli isoeccogeni

Conclusions

- FT3- pg/ml (tri-iodo-tironina)= 1%
- FT4 ng/dl (tiroxina) = 1%
- TSH micro U/L (thyroid stimulating hormone) = 4,39%

- Ab HTG UI/ml = 5,49%
- HTG ng/ml (normal value)
- Ab Rec TSH U/L (value normal)
- AbTPO UI/ml = 8,79%

Thank you for your attention

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IV. Corneal Cross-Linking for Ectasia After Excimer Laser Refractive Surgery: One-Year Results

Causes of Ectasia

- Flap thicker than planned
- Insufficient bed thickness
- LASIK flap cuts 200 million stromal fibers (PRK 5 millions)
- Interface inflammation/infection, S.O.S. etc.
- Pre-operative overlook of risk factors

Cross-Linking and Ectasia After Refractive Surgery

- Patients that underwent refractive surgery
- After looking for a permanent solution for an unpleasant situation, such as high myopia...
- ...find themselves with an even worst life quality!
- Instability and an apparently endless progression of bad visual acuity, heading towards PK...
- Often these patients come to our office when CXL is not anymore possible, due to extreme corneal thinning
- Astonished and diffident patients ...
A Growing Phenomenon?

- Effects are visible only over the long period
- Inefficient interpretation of topography maps
- Unsufficient use of pachymetric maps during patient evaluation
- Wide-diameter flap e O.Z. (large pupil) sever a larger number of fibers

Materials And Methods

**INCLUSION CRITERIA**

- Corneal thickness of at least 350μm, at thinnest point
- Age: 30 to 59
- Signed informed consent.
- Ectatic cornea (post-LASIK, post-PRK)

**EXCLUSION CRITERIA**

- History of HSV, HZV
- Severe eye dryness
- Corneal infections
- Corneal opacities
- Autoimmune diseases
- Poorly compliant pt
- Pt wearing RGP CL 4 weeks before baseline examination.

**Materials And Methods**

13 eyes with ectasia after refractive surgery
- 3 prk
- 10 lasik

9 patients: 6 women, 3 men, mean age 42.2 years

- Pre Sph: mean: +4.0D ± 4.4D (from +18.5 to +3.50)
- Pre Cyl: mean: +0.8D ± 4.9D (from +16.0 to -6.00)
- Pre Pri: mean: +3.0D ± 3.6D (from +5.50 to +1.50)

- Ectasia progression documented in the last 6 months by:
  - Differential topography
  - Scheimpflug optical pachimetry
- Minimal corneal thickness: 350 μm
- MEAN CTT: 412 microns
- Follow up: 1, 3, 6 and 12 months.

**Change in BSCVA - % “Safety”**

- Month (eyes) - 1 (18)
- 3 (16)
- 6 (20)
- 12 (18)

**BSCVA over TIME**

- Pre op
- 1 m
- 3 m
- 6 m
- 1 y
- 1.5 y
Achieved Correction over time - SE - “STABILITY”

Cross-Linking and Ectasia After Refractive Surgery

Results

UCVA: unchanged
preop BCVA 0.75
3 mos: 0.9 (p<.05), SE: reduced at 6 mos (p > .05)
6 mos: Subjective UCVA improvement
6 to 12 mos continuous improvement in BCVA

3 mos postoperatively:
Klyce CVP, LogMAR and SRC indexes increased (p<.05)
SDP index decreased (p<.05)

6 mos postoperatively:
Ambrosio IVA index increased
KCI index, on the opposite, was significantly decreased

12 mos:
mean corneal coma, SA and high order astigmatism were decreased (p > .05)

Indexes of Ambrosio

- ISV: index surface variance—this index is elevated in all types of irregularity of the corneal surface (astigm, warpage, etc).
- IVA: Ind of vertical Asymmetry: this index is elevated in case of oblique astigmatism, in kc or in ectasia.
- KCI: kc index
- CKI: center keratoconus index: increases with severity of central kc
- IHA: ind of Height Asimmetry: this index is analogous of IVA, this index but it is more sensitive
- IHD: index of Height Decentration is elevated in keratoconus
- Rmin: Minimum Sagittal curvature in 8 mm-zone
- TKC: topographical Keratoconus Classification only based on anterior corneal data

Pentacam Optical Pachymetry

- PUPIL CENTER
  - PRE 437 ± 45.48 µm
  - POST 3 m 404 ± 65.89 µm
  - POST 6 m 368 ± 64.35 µm
  - POST 12 m 352 ± 35.55 µm
- THINNEST POINT
  - PRE 427 ± 27.33 µm
  - POST 3 m 309 ± 66.42 µm
  - POST 6 m 342 ± 86.69 µm
  - POST 12 m 442 ± 63.61 µm

Cross-Linking and Ectasia After Refractive Surgery

Optical Pachymetry with Pentacam

3 mos
- Mean central pupil pachymetry and mean pachymetry at the thinnest corneal point were decreased (p < .05)
- total corneal volume at was decreased (p < .05)
- Corneal thickness at 0 and 2 mm: decreased (~9.0%) (p<.05)

At 4 months the STEEPEST POINT curvature value is greatly reduced

-5.99D of flattening

Post-la sik
**2001**
- Case 13: 35 y.o. woman, Physician
- VOD 20/20 -4.00 D
- VOS 20/20 -4.00 D
- 2001, OU successful LASIK
- All went well for two years, then...

**2003**
- Progressive decrease in VA, with return to spectacle use.

**2005**
- VOD 20/25 -0.75 -1.00 (65)
- VOS 20/35 -1.50 -3.25 (110)
- Pentacam:
  - 2nd order topographical astigmatism
  - Normal pachimetry
  - OD 12 µm suspect elevation on altimetric map
- Contact lens correction

**2008**
- VOD 20/30 -3.00 -3.75 (80)
- VOS 20/40 -2.75 -3.75 (95)
- OD apparent central corneal thinning
- LAC withdrawal
- Pentacam
- OPD

**LE, 2005 vs. 2008**
Cross-Linking and Ectasia After Refractive Surgery

Case 13. LE, 04.03.2005, first examination, four years after LASIK for -4.00 -0.50 (125). BSCVA is 20/35 with -1.50 -3.25 (110).

LE, 09.03.2008, immediately before cross-linking, BSCVA is 20/50 with -2.75 -6.00 (95). Note worsening of ectasia.

LE, 04.07.2009, 6 months after cross-linking, BSCVA is 20/30 with -2.50 -4.00 (105). Note central flattening.
Cross-Linking and Ectasia After Refractive Surgery

Upper right, LE 04.03.2005, first examination, the cross indicates a central point with 43.01 D of curvature. Upper left, LE 09.03.2008, immediately before cross-linking, the same, cross-marked, point now has 47.17 D of curvature. Differential map showing that the progression of ectasia was of 4.15 D.

Upper right, 09.03.2008, immediately before cross-linking, the cross is on the central point with 47.17 D of curvature. Upper left, 04.07.2009, 6 months after cross-linking, the same, cross-marked, point now has 43.90 D of curvature. Differential map shows that ectasia regressed of 3.27 D.

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Conclusions 1

- Perform regular topo- and tomographic examinations using differential maps
- Always suspect that a LASIK patient may develop ectasia at some future point
- Perform CXL early, before cornea becomes too thin, with greatest refractive changes

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Conclusions 2

- No complications
- All patients display stability
- OZ apparently recentered
- Mild reduction of refractive error
- Improvement continues long after CXL
- Corneas thinner than 400 μ are still treatable

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Complication and failure rates after corneal crosslinking
Tobias Koller, MD, Michael Mrochen, PhD, Theo Seiler, MD, PhD

PURPOSE: To evaluate the complication rate of corneal crosslinking (CXL) for primary keratectasia and to develop recommendations for avoiding complications.

SETTING: Institut für Refraktive und Ophthalmochirurgie, Zurich, Switzerland.

METHODS: In a prospective study, eyes with verified progressive keratectasia had standard CXL. Preoperative and 6- and 12-month postoperative examinations included corrected distance visual acuity (CDVA), slitlamp evaluation, applanation tonometry, and Scheimpflug imaging (Pentacam). Statistical analysis included analysis of variance and the Mann-Whitney U test to detect risk factors for complications.

RESULTS: The study evaluated 117 eyes of 99 patients; approximately 90% completed the 12-month follow-up. The complication rate (percentage of eyes losing 2 or more Snellen lines) was 2.9% (95% confidence interval, 0.6%-6.5%). The failure rate of CXL (percentage of eyes with continued progression) was 7.9%. Age older than 35 years and a preoperative CDVA better than 20/25 were identified as significant risk factors for complications. A high preoperative maximum keratometry (K) reading was a significant risk factor for failure. Sterile infiltrates were seen in 7.8% of eyes and central stromal scars, in 2.8%.

CONCLUSIONS: Results indicate that changing the inclusion criteria may significantly reduce the complications and failures of CXL. A preoperative maximum K reading less than 58.00 diopters may reduce the failure rate to less than 3%, and restricting patient age to younger than 35 years may reduce the complication rate to 1%.

PATIENTS AND METHODS

Study Design

This study enrolled eyes with progressive keratocasias. Progression of keratocasias was verified by repeated Scheimpflug imaging over at least 6 months (range 6 months to 2 years). Progression was accepted if the increase in the maximum K reading exceeded 1.0 diopter (D), which equals 3 standard deviations (SD).6 Second eyes were treated no earlier than 6 months after first eyes. Only eyes with mild to moderate keratocasias (maximum K value <65.00 D; corneal thickness >400 μm) were included. Because of the broad overlap of the diagnoses of pellucid marginal degeneration and keratocasias, no distinctions were made between the 2 clinical entities. Eyes with preoperative corneal opacities were not accepted because Scheimpflug photography may give false results in such cases. Additional exclusion criteria were ocular pathology other than keratocasias, especially the cornea guttata or other endothelial irregularities, history of recurrent erosions, age younger than 18 years, actual or intended pregnancy, not available for follow-up examinations for 1 year, and connective tissue disease. The Ethikkomitee des Kantons Zürich approved the study protocol. All patients provided informed consent.

Examinations

Patients were examined preoperatively, in the early postoperative period (at 1 to 3 days [until epithelial healing]) and 1, 6, and 12 months postoperatively. At all follow-up visits except the early postoperative, a standard examination was performed consisting of autorefractometry and autokeratometry ( Humphrey Model 599, Carl Zeiss Meditec), corneal topography (Orbscan II, Bausch & Lomb), Scheimpflug imaging (Pentacam 70700, Oculus), manifest refraction using the logging technique, uncorrected (UDVA) and with spectacle corrected (CDVA) distance visual acuity, applanation tonometry, and slit lamp evaluation of the anterior and posterior segments of the eyes. The haze in the anterior stroma was graded on a scale used after photorefractive keratectomy (PRK).10 This scale was used even though corneal opacity after CXL is not located strictly subepithelially but also extends into deep stroma. At the 1-month follow-up examination, the depth of the demarcation line was estimated at the stiplamp as the percentage of central corneal thickness (CCT).11 The maximum K reading was recorded as the mean of 3 Scheimpflug measurements. The threshold of significant difference for the Scheimpflug maximum K readings was 1.00 D (3 SD of the reproducibility).6 To calculate the mean values and for comparisons, visual acuities were converted to the logMAR scale.

The complication rate was defined as the percentage of eyes with a loss of 2 or more Snellen lines of CDVA at the 12-month follow-up compared with preoperatively. The failure rate of CXL was defined as the percentage of eyes with an increase in the maximum K reading of more than 1.00 D over the preoperative value.

Patients using rigid contact lenses were asked not to wear them for at least 3 weeks before the preoperative examination and for 1 month after treatment. The lenses were also removed at least 3 weeks before each follow-up examination.

Surgical Technique

Topical anesthesia of the cornea was obtained using oxybuprocaine and tetracaine drops, alternating every 3 minutes for 15 minutes. After a lid speculum was inserted, a 9.0 mm diameter corneal abrasion was made. Then, riboflavin 0.1% drops were instilled every 3 minutes for 30 minutes. The riboflavin drops were prepared immediately before treatment by mixing aqueous riboflavin 0.5% solution with dextran T-500 20% solution. Next, central corneal pachymetry was performed using ultrasonic. In eyes with a CCT (without epithelium) less than 400 μm, additional riboflavin 0.1% drops without dextran (hypocomatric drops) were applied until the thickness exceeded 400 μm. The eyes were then inspected at the slitlamp to ensure that the riboflavin had penetrated the aqueous (blue light). After this, the eye was irradiated for 30 minutes with ultraviolet-A light with an irradiance of 3 mW/cm² (UV-X, Peschken Meditec). During irradiation, the cornea was moistened every 3 minutes with riboflavin 0.1% drops and oxybuprocaine drops at the patient's discretion. At the end of the procedure, ofloxacin 0.3% ointment was applied and the eye was patched. The patient was asked to use the antibiotic ointment 5 times a day for 3 days. After epithelial healing, the patients used topical fluorometholone 2 times a day for 1 week. For eyes with sterile infiltrates during the early postoperative phase, dexamethasone drops were prescribed 5 times a day for 1 week, after which the drops were tapered over the following 2 weeks.

Statistical Analysis

All calculations were performed with WinSTAT for Excel (R. Finch Software). Variables were described as the mean, SD, and 95% confidence interval (CI). A 1-factor analysis of variance (ANOVA) was performed and included the following variables: age, preoperative maximum K reading, change in the maximum K reading between preoperatively and 12 months postoperatively (change in maximum K reading), preoperative CDVA, and change in CDVA (lines lost) between preoperatively and 12 months postoperatively. The ANOVA was followed by multiple comparisons using the Scheffé test. The same variable was compared between different follow-up times using the Wilcoxon rank-sum test. Comparison of a variable between 2 groups (eg, preoperative CDVA in the total group and in the failure group) was by the Mann-Whitney U test. The odds ratio (OR) of a risk factor and its CI were calculated using the standard algorithm for a 2 × 2 table. A P value less than 0.05 was considered statistically significant.

RESULTS

One hundred seventeen eyes of 99 patients were evaluated. The demographic data showed a strong skew toward male patients (62.2%) and left eyes (58.1%). Of the 117 eyes enrolled in the study, 105 completed the 1-year follow-up, yielding a dropout rate of 10.3%.

Epithelial healing was complete within a mean of 3.25 ± 1.4 days (range 1 to 8 days; 95% CI, 2.6). At the 1-month examination, virtually all eyes had anterior stromal haze with a mean grade of 0.78 ± 0.42 (range 0 to 2); the mean grade decreased to 0.18 ± 0.28 at 6 months and 0.06 ± 0.18 at 12 months. The demarcation line in the deeper stroma was visible at the 1-month examination in 84% of eyes at a mean depth of 62% ± 17% of CCT (range 25% to 100%; 95% CI, 32%–93%). The mean preoperative corneal thickness over the pupil
Table 1. Analysis of variance post hoc multiple comparisons

<table>
<thead>
<tr>
<th>Variable</th>
<th>CDVA Lost</th>
<th>Change in Max K</th>
<th>Preop Max K</th>
</tr>
</thead>
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<tr>
<td>CDVA</td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>CDVA lost</td>
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<td></td>
</tr>
<tr>
<td>Change in max K</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preop max K</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CDVA = corrected distance visual acuity; Max K = maximum keratometry reading

The 1-factor ANOVA showed a highly statistically significant interaction between the variables of age, preoperative maximum K reading, change in maximum K reading, and lines of CDVA lost. The post hoc multiple comparisons showed the influence of the preoperative maximum K reading and age on all other parameters (Table 1).

Of the 105 eyes, 3 lost 2 Snellen lines of CDVA from preoperatively to 1 year postoperatively, yielding a complication rate of 2.9% (95% CI, 0.6%-8.5%). Although initial comparison of the complication subgroup and the total group indicated that age, preoperative CDVA, and preoperative maximum K reading were predictive parameters, the only statistically significant differences between the 2 groups were in mean age (37.7 years versus 29.2 years; \( P = .029 \)) and preoperative CDVA (0.98 versus 0.53; \( P = .012 \)). An age older than 35 years and a preoperative CDVA better than 20/25 were identified as risk factors. The OR was 13.14 for age and 18.18 for CDVA and the 95% CI, 1.3-132.7 and 1.78-185.8, respectively. Introducing an age limit of 35 years as an inclusion criterion would have reduced the complication rate in these patients to 1.04% (95% CI, 0.03%-5.40%). No morphologic or optical reason for the visual loss could be determined.

Regarding efficacy, 8 eyes (7.6%; 95% CI, 3.3%-14.7%) had an increase in the maximum K reading of 1.00 D or more during the first postoperative year (Table 2), indicating failure of the CXL treatment. There were differences between the failure subgroup with the total group in sex (women: 62.5% versus 38.8%; \( P = .048 \)), preoperative CDVA (0.39 versus 0.55; \( P = .16 \)), and preoperative maximum K reading (61.30 D versus 55.00 D; \( P = .04 \)); however, only the differences in the preoperative maximum K reading and sex were statistically significant. The OR for the risk factor of maximum K reading greater than 58.00 D was 5.32 (95% CI, 1.19-23.79) and for female sex, 3.11 (95% CI, 0.7-13.7). Changing the inclusion parameter for maximum K reading from less than 65.00 D to less than 58.00 D would have reduced the failure rate to 2.8% (95% CI, 0.6%-8.5%).

Sterile infiltrates occurred in 7.6% of eyes. A stromal scar developed in 3 eyes (2.9%) (Figure 1). The sterile infiltrates resolved within 4 weeks with treatment of corticosteroids 4 times a day. None of the complications resulted in a significant loss of CDVA. In all cases with stromal scars, the UDVA increased significantly. The scars faded appreciably within the first postoperative year, and the corresponding flattening in topography decreased (Figure 2). No parameter evaluated was identified as a predictor of these complications. There were no other complications requiring medical or surgical intervention.

**DISCUSSION**

Since the introduction of CXL in 1996, several clinical studies have found the treatment to be efficacious in stopping the progression of keratoconus (Seiler T, et al. IOVS 1996; 37:ARVO Abstract 4671). However, the patient groups in these studies were too small to allow conclusions about the real efficacy and safety of the technique.
procedure. Single cases with complications after CXL in the literature\textsuperscript{4-11} are important but do not allow an estimation of the complication rate.

In refractive surgery, a complication is defined as a loss in CDVA of 2 or more Snellen lines\textsuperscript{15} at an appropriate time after surgery (6 months or 1 year). A refractive surgical procedure is considered safe if this complication rate is lower than 5%.\textsuperscript{16} In our study, the complication rate was 2.9% but with a relatively high 95% CI (0.6%-8.5%) because of the small group size (N = 105). Refractive surgery is elective; therefore, a high safety standard is mandatory and appropriate. However, because at present CXL is the only option for halting or reversing the progression of keratocastasia, the treatment should no longer be considered elective.

Risk factors for visual loss after CXL seem to be (1) age over 35 years and (2) a CDVA of 20/25 or better. Fortunately, these parameters do not characterize the typical CXL patient because most candidates are in the third decade of life and are motivated to have the treatment because of substantial visual loss. From a strategic viewpoint, it may be that the earlier CXL is performed, the better for the patient because the treatment's primary aim is to stop the progression of keratocastasia. A CDVA of 20/25 or better as a risk factor contradicts this strategy because at this early stage, CDVA is usually still good; thus, the patient will not risk losing visual acuity. In contrast, the other risk factor—age over 35 years—is not a strategic obstacle because patients older than 35 years have usually known about their disease for many years. In addition, in the future, such patients may have CXL much earlier in life. Establishing an upper age limit of 35 years would have reduced the complication rate in this study to 1.04% (95% CI, 0.03%-5.40%), a rate that characterizes a very safe procedure. (Compare this with the 3% adverse reaction rate for general anesthesia in children.\textsuperscript{17})

Although failures are not considered complications, they may have an impact on the complication rate. In our study, the only identified risk factor for failure was a maximum K reading greater than 58.00 D. Indeed, limiting the preoperative maximum K reading to 58.00 D or less would have reduced the failure rate to 2.8%. Such a limitation would have had no effect on the complication rate. The 2.8% failure rate is significantly higher than rates for CXL reported in the literature, which range from 0\textsuperscript{4,13,14} to 1\textsuperscript{3,15,16}.\textsuperscript{15}
There has been discussion of whether haze is a normal finding after CXL and whether the haze affects vision. Although haze occurs after CXL, it usually decreases from grade 0.78 to 0.06 during the first postoperative year. The haze after CXL differs from the haze after PRK in stromal depth. Whereas haze after PRK is strictly subepithelial, haze after CXL extends into the anterior stroma to approximately 60% depth, which is on average equal to an absolute depth of 30 μm. The nature of this haze is unclear but we associated it with the depth of CXL and loss of keratocytes. Evaluation of the depth of sufficient CXL may become important in the future in terms of a potential surface ablation treatment to regularize irregular astigmatism. More studies, including confocal microscopy, are necessary to elucidate this.

None of our patients had a severe complication; however, several presentations at professional meetings reported such complications. In cases of corneal infection after CXL, contact with the infectious agent likely occurred during the early postoperative period rather than during surgery because CXL not only damages keratocytes, it also kills bacteria and fungi. This effect is used to advantage when CXL is performed for infectious keratitis. In our study group, epithelial healing took up to 8 days; it may take longer in some cases, for example in patients with atopic disease. During epithelial healing, the cornea is vulnerable to infection and melting. The use of amnion in addition to bandage contact lenses may shorten the time to healing. One complication in our study—central stromal scarring—had a beneficial aspect; that is, it resulted in significant flattening of the cornea and a large improvement in UDVA. During the follow-up, the strong flattening effect regressed as the scar faded.

In summary, CXL appears to be a safe treatment that would yield a complication rate of approximately 1% if certain inclusion parameters (eg, patient age less than 35 years, CDVA <20/25) were respected. Also, the efficacy of CXL would likely increase if the treatment were limited to eyes with a maximum K reading of less than 58.00 D. More studies are necessary to identify rare complications and to establish a list of indications regarding patient age, diagnosis (pseudocylindrical degeneration versus keratoconus), and the stage of keratokone.

REFERENCES


VI. Pediatric Patients: Two Years Results

**PEDIZAR PATIENTS 2 YEARS RESULTS**

E Albé MD, P Vinciguerra MD, S. Trazza

I have no financial interest to disclose

---

**PK Complications in Pediatrics**

- Expulsive Choroidal Hemorrhage 2-3%
- Wound leak or dehiscence 1-10%
- Inadvertent lens loss 1-2%
- Corneal ulcer and/or infection 4-9%
- Endophthalmitis 2%
- New onset glaucoma 5-9%
- Cataract 2-7%
- Retinal Detachment 3-5%
- Phthisis 4-13%

**Demographic**

- number of eyes: 57 stage II KC (Amsler-Krumeich Classif)
- Age average: 14 years (from 9 to 18)

- female: 22.8% or 13 eyes
  male: 77.2% or 44 eyes

- pre SR equiv: mean -3.75 D + 3.74 D (from -3.75 to 2.00)

- KC progression documented by serial differential corneal topographies and optical pachymetries.

- Controlateral not treated eyes stage I-II used as control.

---

**Regulator del Diaphragma**

- 2% Pilocarpine drops and antipain meds 30 min before CXL.
- Oxybuprocaine hydrochloride 0.2% 5 min before CXL.
- LASER TEST UVA meter
  - Laser: 370±5 mm
  - Power: 3 mW/cm² (+ 5.4 j/cm²)

- RICROLIN riboflavin 0.1% solution instillation each minute for 30 min

- Riboflavin check absorption in anterior chamber (flare).
- UVA Light Corneal irradiation 8M CSO 7.5 mm Ø.
- RICROLIN instillation 6 times of 5 min each
- Bandage soft CL application and levofloxacin eyedrops

---

**PROGRESSION OF KC**

- PZ 12 years
- NO CXL
- NO CL fitting

**AFTER**

4 MONTHS...

-186 MICRON!!!
SAFETY:

ENDOTHELIAL CELL COUNT

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Change in BSCVA% SAFETY

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CORRECTION

sphere and cylinder

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SEQ correction over time

STABILITY

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RESULTS

PENTACAM TOMOGRAPHY

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FASTER RECOVER Peds/ADULTs 1 year instead of 2

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<th>Time (years)</th>
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<th>3m</th>
<th>12m</th>
<th>24m</th>
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</thead>
<tbody>
<tr>
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<td>2193</td>
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<td>1100</td>
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COMA REDUCTION

<table>
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<th>POST XL 2 y</th>
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<tr>
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</table>

OPD CORNEAL NAVIGATOR KLYCE INDEXES

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>Pre</th>
<th>POST XL 6 m</th>
<th>POST XL 2 y</th>
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<tr>
<td>CDI</td>
<td>3201</td>
<td>2992</td>
<td>2193</td>
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</table>

EQUAL BEHAVIOUR Peds/ADULTs
RESULTS

TOPOGRAPHY

Results of topography analysis showing changes over time. The graphs indicate improvements in corneal surface irregularities and reductions in corneal power asymmetry and wavefront aberrations.

Conclusions

- CXL is indicated for PEDs with progressive KC.
- CXL appears to be effective in improving UCVA and BSCVA, reducing corneal asymmetry and corneal wavefront aberrations at two years follow-up.
- CXL is a safe treatment for KC, with faster reepithelialization and faster recovery of CCT in pediatric patients.
- Careful screening and closer follow-up are needed in pediatric patients to avoid faster and more dramatic progression of the disease.

Thank you for your attention!

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VII. Evaluation of Crystalline Lens Opacity Induced by Corneal Cross-Linking with Scheimpflug Imaging

**Evaluation of Crystalline Lens Opacity Induced by Corneal Cross-Linking with Scheimpflug Imaging**

F1 Camesasca, P Vinciguerra, S Trazza

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IRCCS Istituto Clinico Humanitas
Rozzano, Milano, Italy

Chairman: Prof. P. Vinciguerra

I have no financial interest to disclose

Corneal Cross-linking (CXL):
- stabilizes progressive keratoconus
- inhibits some physiopathological mechanism of corneal ectasia
- increases biomechanical strength of cornea of 300%

Scheimpflug, Cristalline Lens and Corneal Cross-Linking

- Objective evaluation of crystalline lens opacity:
  - Complex
  - LOCS III, Age-Related Eye Disease Study
  - Clinical measurement: subjective

(McCarty CA, Dev Ophthalmol 2002)

Oculus Pentacam HR Software (Oculus Optikgeräte, Wetzlar, Germania)
- information from the anterior corneal surface to the posterior crystalline capsule
- objective system measuring densitometry
- full scan to reconstruct the lens

Scheimpflug, Lens and Cross-Linking

Pentacam software evaluates:
- volume
- 3D optical density
- mean optical density

Densitometry Software:
- compares density with an advanced nomogram
- assigns a lens density grade
- quantifies density and area of lens opacification

Measures the lens density in an objective, reproducible and accurate way

Scheimpflug, Lens and Cross-Linking

UV rays: a well-known etiological agent of cataract

The ocular structure most exposed to UV rays during cross-linking, after the corneal endothelium, is the crystalline lens

Ectasia patients are often very young:
- progressive keratoconus
- ectasia following refractive surgery

fabrizio@camesasca.com...
18 eyes of 18 patients with progressive keratoconus, documented CXL performed between April and June 2006. Mean patient age: 34.9 ± 6.5 years (range: 26 to 50).

CXL: well-established and described technique. Preoperatively and 1, 2, 3 years postoperatively.

Materials and Methods

Evaluation:
- Complete ophthalmological examination
- Endothelial cell counts
- Corneal topography
- Aberrometry
- Central pachymetry and/or topography with Scheimpflug system

Scheimpflug system used for objective evaluation of lens transparency. Lens opacities graded with a system ranging from 0 to 3.

Inclusion criteria:
- Progressive keratoconus (series of topographies)
- Age above 18

Exclusion criteria:
- Corneal thickness < 400 μm at thinnest point
- History of herpetic keratitis
- Severe dry eye
- Concurrent corneal infections
- Corneal opacities
- Concomitant autoimmune disease

The Pentacam-based lens opacity evaluation system on provides grades ranging from 0 to 3.

Pentacam Nucleus Staging example

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>Preoperative</th>
<th>1 year</th>
<th>2 years</th>
<th>3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystalline lens opacity (mean)</td>
<td>0.18 ± 0.39 (O-1)</td>
<td>0.21 ± 0.53 (O-2)</td>
<td>0.04 ± 0.20 (O-1)</td>
<td>0.17 ± 0.39 (O-1)</td>
</tr>
</tbody>
</table>

Mean UCVA and BSCVA:
- Preoperative: 20/20 and 20/40
- 3 years after CXL: 20/50 and 20/25 (p < .05)

Mean simulated keratometry reduced (p < .01).

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Scheimpflug, Lens and Cross-Linking
Materials and Methods

Results

Mean UCVA and BSCVA:
- Preoperative: 20/20 and 20/40
- 3 years after CXL: 20/50 and 20/25 (p < .05)

Mean simulated keratometry reduced (p < .01).

Endothelial cell count unchanged (p > .1).

Lentic transparency measured with the Scheimpflug system three years after CXL maintained high (O).

Lens always transparent.

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<table>
<thead>
<tr>
<th>Time Interval</th>
<th>Preoperative</th>
<th>1 year</th>
<th>2 years</th>
<th>3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corneal density (mean ± SD)</td>
<td>0.18 ± 0.39</td>
<td>0.31</td>
<td>0.83</td>
<td>0.39</td>
</tr>
<tr>
<td>Corneal lens opacity grading scale value (range: min to max)</td>
<td>0 - 1</td>
<td>0 - 2</td>
<td>0 - 1</td>
<td>0 - 1</td>
</tr>
<tr>
<td>Average opacity (%) (mean ± SD)</td>
<td>11.51 ± 11.79 (8.50 – 17.2)</td>
<td>16.60 ± 1.79 (13.26 – 20.1)</td>
<td>9.36 ± 3.64 (4.74 – 14.7)</td>
<td>16.81 ± 2.44 (13.7 – 20.2)</td>
</tr>
<tr>
<td>ST Dev (%) (mean ± SD) (range: min to max)</td>
<td>3.14 ± 3.12 (1.3 – 8.2)</td>
<td>1.93 ± 0.60 (0.45 – 2.5)</td>
<td>2.12 ± 1.35 (0.3 – 4.4)</td>
<td>3.10 ± 2.28 (0.6 – 7.8)</td>
</tr>
<tr>
<td>Min % (mean ± SD) (range: min to max)</td>
<td>24.59 ± 3.93 (13.7 – 19.7)</td>
<td>18.43 ± 3.32 (11.4 – 20.3)</td>
<td>18.19 ± 3.72 (8.2 – 32.2)</td>
<td>22.54 ± 3.31 (6.4 – 41.6)</td>
</tr>
</tbody>
</table>

### Scheimpflug, Lens and Cross-Linking

#### Conclusions

Young mean age of the study cohort: completely transparent lens

Lens persistently transparent 36 months after CXL:

the procedure did not induce any lens change measurable with Pentacam and the dedicated densitometry software

Grewal DS, Ophthalmology 2009

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Pentacam dedicated software can measure lens density in an accurate, objective and reproducible way

After CXL, we did not observe any side effect involving the lens or the corneal endothelium at any time interval.

Grewal DS, Ophthalmology 2009
VIII. Anterior and Posterior Corneal Surface

POSTERIOR CORNEAL HIGH-ORDER ABERRATIONS AFTER CORNEAL CROSS LINKING

Scipione Rossi, MD
Director of Ocular Microsurgery Unit
San Carlo Hospital-IDI
Rome, Italy

OBJECTIVE
To evaluate the posterior corneal surface high-order aberrations (HOAs) outcomes 4 years after corneal collagen cross-linking (CXL) in eyes with progressive keratoconus

IN NORMAL EYES:
the posterior corneal surface is a “weak zone”

The cornea does not exhibit uniform biomechanical strength
- The collagen fibrils of the anterior lamellae are smaller (50 µm to 100 µm) and more densely packed and interwoven.
- The posterior lamellae are larger and more loosely packed and do not interweave.
- This lamellar arrangement allows for the cornea to be divided into strong and weak zones, both anterior-posterior and peripheral-central.

IN KERATOCONIC EYES:
the posterior corneal surface is a “critical zone”

1. The posterior corneal surface, its elevation and curvature have been shown to be screening factors for keratoconus
   - For cut-off of 35 µm, sensitivity 93% & specificity 95%.
2. Mean posterior corneal elevation significantly higher compared to mean anterior corneal in keratoconus eyes

POSTERIOR CORNEAL ELEVATION

<table>
<thead>
<tr>
<th>Keratoconus</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td>15</td>
<td>100</td>
</tr>
<tr>
<td>20</td>
<td>100</td>
</tr>
<tr>
<td>25</td>
<td>100</td>
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<tr>
<td>30</td>
<td>100</td>
</tr>
<tr>
<td>35</td>
<td>100</td>
</tr>
<tr>
<td>40</td>
<td>100</td>
</tr>
<tr>
<td>45</td>
<td>100</td>
</tr>
</tbody>
</table>


the posterior corneal surface profile is more irregular than that of the anterior corneal surface in advanced KC eyes.

Elevated High Order Aberrations: COMA-LIKE and SPHERICAL aberrations

leading to impaired visual function.

ANTERIOR AND POSTERIOR CORNEAL WAVEFRONT ABERROMETRY

Exist an aberration compensation effect between the anterior and posterior corneal surface if their irregular surface profiles had the same direction.

METHODS

- 300 eyes with progressive keratoconus were treated with UVA riboflavin CCL from 2007 to 2010
- Clinical and instrumental progression (Refractive, Tomographic, Aberrometric) in the last 6-12 months
- We performed a retrospective study in 40 eyes (follow-up 4 years) to evaluate the HAOs of corneal posterior surface

Group I
- Maximum Posterior Corneal Elevation < 50 µm
- Corneal Thickness between 400 - 520 µm

Group II
- Maximum Posterior Corneal Elevation > 50 µm
- Minimum Corneal Thickness between 380-400

CORNEAL TOMOGRAPHY

1. Anterior and posterior curvature/power maps
2. Enhanced anterior and posterior elevation best fit sphere (BFS)
3. Pachymetric maps

CORNEAL WAVEFRONT ABERRATIONS

1. Anterior/posterior aberrations maps
2. Total corneal aberrations


Dual Scheimpflug Analyzer: PLACIDO + SCHEIMPFLUG TECHNOLOGIES

CORNEAL WAVEFRONT ABERRATIONS

- the wavefront maps of the total cornea using the Zernike Polynomial function
- HOAs for 6 mm pupils were calculated from the difference between the height data and best fit sphere (BFS)
- The reference axes of the measurements were aligned with the primary line of sight
- Trefoil, coma, fourth-order astigmatism, spherical aberration all differ both anteriorly and posteriorly
- For both anterior and posterior surfaces, vertical coma was most important HOAs
Correlation the mean RMS of coma like aberration to the Amsler-Krumeich classification:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>RMS of coma-LIKE (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>• Eccentric steeping • Myopia and astigmatism &lt; 5.00 D • Mean central K readings &lt; 48.00 D</td>
<td>1.50 to 2.50 µm</td>
</tr>
<tr>
<td>II</td>
<td>• Myopia and astigmatism from 5.00 to 8.00 D • Mean central K readings &lt; 53.00 D • Absence of scarring • Minimum corneal thickness &gt;400 µm</td>
<td>&gt; 2.50 to ≥ 3.50 µm</td>
</tr>
<tr>
<td>III</td>
<td>• Myopia and astigmatism from 8.00 to 10.00 D • Mean central K readings &gt;53.00 D • Absence of scarring • Minimum corneal thickness 300 to 400 µm</td>
<td>3.50 to ≤ 4.50 µm</td>
</tr>
<tr>
<td>IV</td>
<td>• Refraction not measurable • Mean central K readings &gt;55.00 D • Central corneal scarring • Minimum corneal thickness 200 µm</td>
<td>&gt; 2.50 µm</td>
</tr>
</tbody>
</table>

**RESULTS AFTER 4 YEARS**

- UVA: 3 mW/cm²
- Exposure time: 30 min
- Depth: 300 mm

**ORDER ABERRATION**

<table>
<thead>
<tr>
<th>ORDER</th>
<th>ABBREVIATION</th>
<th>PRE OPERATIVE MEAN (µm)</th>
<th>POST OPERATIVE MEAN (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean aberration coeficient</td>
<td>1.75 (0.48198)</td>
<td>1.8925 (0.62936)</td>
</tr>
<tr>
<td></td>
<td>3rd Coma</td>
<td>2.3597 (1.18623)</td>
<td>1.0233 (1.925109)</td>
</tr>
<tr>
<td></td>
<td>3rd Trefoil</td>
<td>-0.0548 (0.35627)</td>
<td>-0.0963 (0.51242)</td>
</tr>
<tr>
<td></td>
<td>4th High order astigmatism</td>
<td>-0.0491 (0.48198)</td>
<td>0.1524 (0.77456)</td>
</tr>
<tr>
<td></td>
<td>4th Tetrafoil</td>
<td>0.0294 (0.60129)</td>
<td>-0.0543 (0.52224)</td>
</tr>
<tr>
<td></td>
<td>4th Spherical Aberration</td>
<td>0.3513 (0.73449)</td>
<td>0.6033 (1.08027)</td>
</tr>
<tr>
<td></td>
<td>5th High order coma</td>
<td>0.0488 (0.28599)</td>
<td>-0.0643 (0.38893)</td>
</tr>
<tr>
<td></td>
<td>5th High order trefoil</td>
<td>0.0588 (0.20314)</td>
<td>-0.061 (0.23362)</td>
</tr>
<tr>
<td></td>
<td>5th Pentafoil</td>
<td>0.0121 (0.19826)</td>
<td>-0.0234 (0.40602)</td>
</tr>
</tbody>
</table>

**GROUP I (28 eyes)**

- Average anterior elevation: 12.10, 0.043 µm
- Average posterior elevation: 23.8, 0.072 µm
- Anterior coma: 2.40, 0.027 µm
- Posterior coma: -0.50, 0.015 µm

**GROUP II (12 eyes)**

- Average anterior elevation: 8.98, 0.032 µm
- Average posterior elevation: 28.8, 0.064 µm
- Anterior coma: 2.35, 0.038 µm
- Posterior coma: -0.80, 0.013 µm

**Summary of total HOA s mean before and 4 years after corneal CXL treatment**

Coma and Trefoil aberrations reduction was statistically significant.

**GROUP I:**

- Anterior Elevation: 12.10, 0.043 µm
- Posterior Elevation: 23.8, 0.072 µm
- Anterior coma: 2.40, 0.027 µm
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- Anterior Elevation: 8.98, 0.032 µm
- Posterior Elevation: 28.8, 0.064 µm
- Anterior coma: 2.35, 0.038 µm
- Posterior coma: -0.80, 0.013 µm

**Summary of total HOA s mean before and 4 years after corneal CXL treatment**

Coma and Trefoil aberrations reduction was statistically significant.
**Outcomes:**

- **In the Group I after CXL**
  1. The total corneal HAOS aberrations decreased significantly
  2. The anterior corneal HAOS aberrations decreased
  3. The posterior corneal HAOS aberration increased

- **In the Group II after CXL**
  1. The total corneal HAOS aberrations decreased significantly
  2. The anterior corneal HAOS aberrations decreased
  3. The posterior corneal HAOS aberration decreased

**CONCLUSION**

*What happens after Cross Linking?*

If we treat keratoconic corneas with high thickness (450/500μm):

1. The 300 μm of anterior cornea are cross-linked and the posterior cornea (weak corneas) continue ectatic evolution with no evidence of anterior progression?
2. The cross-linked anterior lamellae produce an increase of post. elevation due to biomechanical effects (transport effect)?
CONCLUSION:

What Happens after Cross Linking?

Does the treatment in low pachymetry cornea (around 400 µm) allow the cross-linking in the posterior corneal stroma?

CONCLUSION

What Happens after Cross Linking regarding HAOs?

• Total Corneal HAOs, especially coma-like aberrations, always decrease significantly

• The posterior surface HOAs are related with posterior elevation and initial pachymetry.

FUTURE PLANNING

• We observe: in our series the age of the first Group was lower than the second one but this data are not significative (a few cases)

• We think that also the age play a role in changing the posterior HAOs aberrations after CXL.

Now our goal is follows the posterior corneal elevation and HOAs in pediatric cases

THANKS FOR YOUR ATTENTION
## Addresses

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