CXL Experts’ Meeting

Epi-on and epi-off applications

Koppen C MD, PhD
Antwerp, Belgium

Zurich, December 2nd 2016
No financial interest

Universiteit Antwerpen
UZA
Transepithelial or epi-on CXL

Addresses the limitations and safety issues of epi-off CXL:

- No wound related complications


Transepithelial or epi-on CXL

Addresses the limitations and safety issues of epi-off CXL:
• No wound related complications
• Less deep effect (demarcation line at ± 100 versus 300 µm)
  – Less toxicity for the stroma and keratocytes (haze)


Transepithelial or epi-on CXL

Addresses the limitations and safety issues of epi-off CXL:

- No wound related complications
- Less deep effect (demarcation line at ± 100 versus 300 µm)
  - Less toxicity for the stroma and keratocytes (haze)
  - Lower dosage at the level of the endothelium
    - thin corneas < 400 µ stroma
- thinning throughout the procedure 87 ± 40 µm 60-min CXL treatment

Transepithelial or epi-on CXL

Addresses the limitations and safety issues of epi-off CXL:

• No wound related complications

• Less deep effect (demarcation line at ± 100 versus 300 μm)
  – Less toxicity for the stroma and keratocytes (haze)
  – Lower dosage at the level of the endothelium
    • thin corneas < 400 μ stroma
    • thinning throughout the procedure 87 ± 40 μm 60-min CXL treatment

• No pain, no anxiety
  – Down patients
  – Very young patients
Transepithelial or epi-on CXL

Addresses the limitations and safety issues of epi-off CXL:

- No wound related complications
- Less deep effect (demarcation line at ± 100 versus 300 µm)
  - Less toxicity for the stroma and keratocytes (haze)
  - Lower dosage at the level of the endothelium
    - thin corneas < 400 µ stroma
    - thinning throughout the procedure 87 ± 40 µm 60-min CXL treatment
- No pain, no anxiety
  - Down patients
  - Very young patients
- Shorter interruption of contact lens wear
Transepithelial or epi-on CXL

But what about efficacy?

1. Riboflavin is a large hydrophylic molecule that cannot penetrate through an intact epithelium

2. Intact epithelium blocks about 20% of UV rays

Wollensak et al have studied the TE CXL treatment in rabbits using the protocol proposed by Boxer Wachler and Pinelli:

- Pretreatment with Proparacaine 0.5% every 5’ for 30’ (BAC 0.005% preserved), followed by standard instillation of riboflavin in dextran 30’ and UVA 365 nm 3mW/cm² 30’

Conclusions of this rabbit experiment:

- Biomechanical effect reduced by about 1/5 compared to standard CXL: increase in rigidity 62% for TE-CXL versus 320% for standard CXL
- Cytotoxic damage restricted to anterior 200 µm stromal depth
Refraction and topographic results of BAC-assisted TE CXL

Prospective study\(^1\) on 53 eyes of 38 patients stage I – III
Statistical analysis for a follow up of 18 months

- **Efficacy? Statistically significant changes?**
  - DCVA improved
  - majority of parameters including K max on EyeSys remained stable
  - K max on Pentacam and I-S value on Placido based topography deteriorated

- **Failures:** 7/53 eyes (13%) versus
  - standard CXL (own results): 2/27 eyes (7%)
  - epi-off CXL in the literature: 7.6%\(^2\)

- **Haze:** none, *complications: none*


TE CXL with Ricrolin TE
(Riboflavin 0.1%, trometamol and EDTA)

**Efficacy?**

- TE CXL appeared to halt progression, with a statistically significant improvement in visual and topographic parameters...

- Functional results after TE CXL showed keratoconus instability, in particular in pediatric patients 18 y old and younger – 50% of pediatric patients were retreated with epi-off CXL after 12 months of follow-up

- This technique does not effectively halt keratoconus progression in children compared to standard CXL

... basic research is lacking


Other methods of TE CXL

Epithelial disruptor

Intrastromal pocket (femtolaser)


**TE CXL: research on pharmacological modification of epithelial permeability**

- Animal experiments by Spoerl et al: TE CXL using riboflavin 0.1% in NaCl 0.44% with BAC 0.01% results in the same biomechanical effect as standard epi-off CXL

Structure of tight junctions is modified -> changes in paracellullar transport lead to increased permeability for riboflavin

- Dextran ↓ ribo transport
- NaCl 0.44% ↑ ribo transport

---

*Kissner et al. Pharmacological modification of the epithelial permeability by benzalkonium chloride in UVA/riboflavin corneal collagen cross-linking.*

*Raiskup et al. Riboflavin osmolar modification for transepithelial corneal cross-linking.*
TE CXL: research on pharmacological modification of epithelial permeability


TE CXL with ribo 0.1% in NaCl 0.44% with BAC 0.01% (preliminary results)

- Prospective study on 20 eyes of 15 patients stage I - III

Change in Kmax after 1 year eyes w/o CL

K max 47.4 -> 53.5 D

Ranking of patients according to age at time of CXL
17 y ---------------------------> 20 y ----------------------------------> 30 y ---------------------> 42 y

TE CXL iontophoresis: principle

Iontophoresis

- physical process in which ions flow in a medium driven by an electric field
TE CXL iontophoresis: stromal uptake

**Iontophoresis**

- **TE iontophoresis imbibition yielded greater and deeper riboflavin saturation with respect to conventional epi-on,** but **did not reach concentrations obtained with standard epi-off.**

![Absorbance vs Wavelength Graph](image-url)

**Photo-spectrometry to investigate trans-epithelial stromal Riboflavin absorption**

School of Optometry, Cardiff - Courtesy David O'Brart

---

**TE CXL iontophoresis: CXL effect**

**Iontophoresis**

- Ex vivo biomechanical studies on rabbit and human cadaveric corneas showed an increase of the biomechanical resistance of human cornea comparable to that obtained with the standard epi-off crosslinking procedure.
- Preliminary clinical results of iontophoresis assisted corneal CXL are promising: keratoconus progression is halted without significant complications.
Epi-on CXL is safer than the standard epi-off procedure. Efficacy, however, remains the weakness:

- Dosage UVA irradiation
- Combination with accelerated CXL
- Epithelial thickness profile
- Oxygen
EVIDENCE-BASED CXL

Epi-on, higher UV power, shorter treatment tantalise, but only epi-off is proven. Howard Larkin reports

Despite many experiments with corneal crosslinking (CXL) technologies designed to preserve the epithelium and shorten the procedure, the traditional method involving epithelium removal and 30 minutes of 3mW/cm² ultraviolet radiation remains the only proven CXL treatment for keratoconus, Frederik Raiskup MD, PhD, FEBO told the XXXII Congress of the ESCRs in London.

Dr Raiskup noted some promising tests of various epi-on, high-power radiation and iontophoresis CXL approaches. But some early studies at long-term clinical sti safety and efficacy ar
TE CXL: enhancement of permeability versus preservation of integrity of the epithelium

- Standardization: exact composition of drops, method of application, duration of application,…

Koppen, unpublished, 2014

Gatzoufias et al, JRS 2016

Instillation of Ribo 0.1% in NaCl 0.44% with BAC 0.01%

Instillation of Ribo 0.25% with BAC 0.01%

- There is a thin line between epi-on and epi-off