CXL Experts’ Meeting

Epi-on and epi-off applications

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Zurich, December 2nd 2016
No financial interest
Transepithelial or epi-on CXL

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  - *Down patients*
  - *Very young patients*
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    • 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

TE CXL: Pharmacological modification of epithelial permeability

- 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

Pinelli R. Corneal collagen crosslinking: is it necessary to remove the epithelium? Journal of the intraocular implant and refractive surgery society, India. 2008;4:28-34
Refractive 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

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Other methods of TE CXL

Epithelial disruptor

Intrastromal pocket (femtolasuer)


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


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.

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.
TE CXL: conclusions

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 safety and efficacy are
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

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