Epithelium on Cross-linking and Iontophoresis

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Epithelium-off Riboflavin CXL

• Wollensak AJO 2003;135:620
• Multiple published case series
• 6-24 mth follow-up, 100s treated eyes
• Including advanced KC*, paediatric cases**, PMD ***
  • Caporossi JCRS 2006;32(5):837-45.
  • Vinciguerra Ophthal 2009;116(3):369-78.
  • Henriquez Cornea 2011;30(3):281-6
  • Asri JCRS. 2011;37(12):2137-43.
  • Hersh JCRS 2011;37(1):149-60.
  • Arora JRS 2012;28(11):759-62 *
  • Vinciguerra Am J Ophth 2012;154(3):520-6. *
  • Ivarsen Cornea. 2013;32(7):903-6. **
  • Spadea JRS 2010;26(5):375-7 ***
  • Hassan Indian J Ophth 2013 10 ***
  • Bayraktar Case Rep Ophthalmol Med. 015:840687 ***

• Stabilization in 90-95%
• Few complications
• Typically significant improvements in
  • Vision/Topographic indices
  • Higher order aberrations
Epithelium off CXL: Randomized Controlled Studies

O’Brart *Br J Ophth* 2011;95:1519
- Bilateral RCT, 18mth f-u, 22 patients
- Treated - Improved CDVA, reduced SimK, astig, RMS, coma, Sph Ab, 2nd astig, pentafoil (p<0.05)
- Untreated Eyes - Worsening of refractive astigmatism p<0.005

- 46 Treated eyes - Reduction in Kmax p<0.001, Improvement in UCVA, CVDA p<0.01
- 48 Control eyes, 3 yr f-u - Increase Kmax p<0.001 cylinder p<0.02, Decrease in UCVA p<0.05

Lang *BMC Ophthalmol.* 2015;15:78
- 29 eyes, 15 treated, avg f-u 3 years
- Treated - Ref power reduced by 0.35 +/- 0.58 D/yr.
- Untreated eyes - Increase of 0.11 +/- 0.61 D/yr - significant difference p<0.02

- Bilateral, RCT 26 eyes, 12 mth f-u
- Treated - K-max reduced by 0.22D, CDVA improved
- Untreated - Kmax increased by 0.41 D, CDVA decreased - (P < 0.02)

Sharma *Int Ophthalmol.* 2015 Feb 24
- RCT with sham treatment control, 43 eyes, treatment (23), sham (20), 6mth f-u
- Improvements in UDVA, Ref Cyl, Kmax (p<0.01)
- Sham group no changes.
Epithelium off CXL: 7-10 year follow up

• Theuring *Ophthalmologe* 2015;112(2):140
  - 30 eyes 20 patients 10yr f-u
  - Kapex -7D (p<0.001), Kmax -4D (p<0.001), Kmin -3D(p<0.001)
  - BCVA -0.13 LogMAR (p<0.005)
  - 2 eyes progressed
  - No long-term loss of transparency

• O’Brart *AJO* 2015 160(6):1154-63
  - 36 eyes 36 pts 7yr fu
  - KC stabilized in 100%
  - Kmax -0.9D (p<0.0001), Kmean -0.74DD (p<0.0001)
  - UCVA/CDVA improved (p<0.001)
    - 4 eyes (11%) lost 1 line of UCVA
    - 22 (61%) gained 1-4 lines of UCVA
    - 3 eyes (8.5%) lost 1 line CDVA
    - 15 (42%) gained 1-4 lines of CDVA
  - SEQ +0.78D (p<0.005) 8 eyes (22%) >=+2.0D
  - RMS, Coma, 2° Astig improved (p<0.005)
  - No sight threatening complications
  - 24% untreated eyes progressed
  - 7 year compared to 5 year
  - Improvements in CDVA (p<0.01 ), trefoil (p<0.05)
Epithelium-off CXL:  
Post-operative Recovery and Complications

But

- Severe post-operative pain +++
  - 24-48 hours
- Blurred vision
  - 2-4 weeks
  - Worse at 1mth, return 3mth
- No contact lens wear
  - 3-4 weeks
- Sight-threatening complications
  - Haze, Scarring
  - Infectious, non-infectious keratitis
  - Persistent corneal oedema
  - Excessive flattening
Epithelium On CXL

• Less pain
• Faster visual recovery
• Less risk of infection
• Reduced risk of:
  • Stromal scarring/corneal melt
    • Reduced epithelial/stromal cytokine interaction
  • Stromal oedema/Endothelial damage
    • Thicker overall corneal thickness
    • Reduced peri-operative dehydration/thinning

• Riboflavin- poor lipid solubility
• Pre-clinical and clinical studies
  • Epithelium removed
  • Facilitates riboflavin stromal absorption
Epithelium On CXL

- Modification of Epithelial permeability
  - Mechanical
    - Partial epithelial disruption
  - Chemical
    - Local anaesthesia, BACS, EDTA, TASS, channel forming peptides
  - Electrical
    - Iontophoresis

- Modification of Riboflavin Solution
  - Without dextran
  - Hypo-osmolar
  - Higher concentration

- Modification of application
  - Increase application time
  - Remove riboflavin from epithelium

- Modification of UV dosage
  - Increase due to epithelial absorption
Epithelium-on CXL: Chemical Enhancement
Comparative Studies: Against

Al Fayez *Cornea*. 2015; 34 Suppl 10:S53
• RCT, 70 pts, 3 yr f-u
• Epi-off: Kmax decreased ave 2.4 D, no progression
• Epi-on: Kmax increased ave 1.1 D, 55% progression

Yuksel J *Ocul Pharm Ther*. 2015;31:296
• 78 eyes epithelial signs and pain scores
• Longer epithelialisation in epi-on (p<0.001)
• Pain scores higher in epi-on day1 (p<0.001)

• Gatziofias, Hafezi, Raiskup, Speorl, O’Brart *JRS*. 2016 Jun 1;32:372
  • Medicross TE (Ribflavin 0.25%, BACS 0.01%)
  • (47.6%) epithelial defect
  • 5 (23.8%) severe punctate keratopathy

Epithelial cell lysis observed with Paracel
Epithelium-on CXL: Chemical Enhancement
Comparative Studies: Against

**Soeters** *AJO 2015;159:821*
- RCT
- Ricolin TE 35 eyes, Epi-off 26 eyes 1yr f-u
- Reduction Kmax epi on, no diff epi-off
  - Significant difference between groups (p<0.05)
- Better improvement in CDVA in epi-on (p<0.05)
- 23% progression epi-on (Kmax >1D)
- 15% epi-off complications (scarring, HSK, infiltrates)

**Kocak** *J Fr Ophtalmol. 2014;37:371*
- Retrospective study, 12+ mth Follow-up
- Greater flattening of cone apex in epi-off eyes (p<0.0005)
- Progression (>1D apical K) in 65% epi-on eyes compared to 11% in epi-on (p<0.0001)
- Epi-off self-limiting corneal oedema
Epithelium-on CXL: Chemical Enhancement
Literature Review Studies: Against

Shalchi *Eye* 2015;29:15
Literature review, 44 epi-on, 5 epi-off studies analyzed

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<th>Transepithelial</th>
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<td>Scar formation</td>
<td>0 – 8.6%</td>
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<td>Infection</td>
<td>0 – 2.9%</td>
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<td>Loss of CDVA</td>
<td>0 – 27%</td>
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CXL: Partial Epithelial Disruption
Comparative studies

Hashemi *J Refract Surg.* 2015;31:110
- Retrospective comparative study
- 80 eyes 65 patients, 12mth f-u
- No diff in improvements in UDVA, SEQ
- Better improvement in CDVA in partial group (p<0.001)
- Less reduction in Kmax, Mean K in partial group (p<0.05)
- Greater reduction in pachymetry in complete group (P<0.01)

- RCT 44 eyes 22 patients
- No diff in haze, refraction, visual acuity
- Total removal improvement of K-max/Q-value (P<0.01)
- Partial removal better improvement of CDVA (P<0.01)
O’Brart et al, 18 month outcomes of CXL using grid-pattern epithelial scratches and Ricrolin TE®

- 28 eyes, 26 KC, 2 post-LASIK
- 18-24mth follow-up
- Pain 24-48 hours, epithelial closure by 1 wk
- Contact lens wear 2-3 weeks
- KC stabilized in 25 eyes (89%)
- UCVA/CDVA improved (p<0.05)
- Apex power reduced 1.3D (p<0.0005)
- High order aberrations improved (p<0.05)
- No eyes lost >1 line CDVA
- But 5 failures >2 years

Alhamad, O’Brart JCRS 2012;38:884.
Stroma begins

Epithelium-on CXL: Limited Riboflavin Absorption
2-photon fluorescence microscopy: ex-vivo rabbit model

Transepithelial Riboflavin Absorption in an Ex Vivo Rabbit Corneal Model
Epithelial absorption of UV
- Kolozsvári IVOS 2002;43:2165-8

UVA absorption of Riboflavin within epithelium
- Will mask UVA stromal absorption
- Impair efficacy of CXL
- Increased UVA energy/exposure time (≥20%)
- Optimum BSS epithelial wash out protocol
Epithelium-on CXL: Iontophoretic Delivery
Clinical Studies

Riboflavin suitable for iontophoresis

• Water soluble
• Negatively charged at physiological pH

• 22 eyes 10 min 1mA
• 12 mths 22 eyes of 19 pts
  • Kmax reduced by 2D (p<0.005)
  • Kmean reduced by 2.35D (p<0.005)

Vinciguerra JRS 2014;30;746
• 20 eyes (20 pts) 12 mth f-u, 5min 1.0mA 0.1% riboflavin
• CDVA improved (p<0.05)
• Stable Keratometry, HoAs, pachymetry, ECC

• 11 pts (15 eyes), 6 mths f-u, 0.1% riboflavin, 5 min 1mA
• Improved visual and topo parameters
• Corneal demarcation line 288µm

Buzzonetti Cornea 2015;34:512
• 14 paediatric eyes (14 pts) 15mth f-u
• CDVA improved (p<0.005)
• Demarcation line 180um
Epithelium-on CXL: Iontophoretic Delivery

• Current protocols
  • Riboflavin 0.1% and 1mA for 5-10min

• Two stage procedure
• Drug deposition - Epidermis/epithelium
• Drug diffusion
  • Concentration gradient
    • Novruzlu Cornea. 2015;348:932
      • 0.2% Riboflavin 1mA 10min rabbit eyes
      • Better absorption than chemical enhancement

• Time dependent
• Chemical enhancement of Iontophoresis
  • Fang J Control Release 1998;54:293
    • Enhancement of iontophoresis with BACS

0.1% 5min 1mA Increased time and concentration
Stromal riboflavin absorption using new and existing delivery protocols for corneal cross-linking
Comparison of different iontophoresis protocols for transepithelial corneal cross-linking using two-photon fluorescence microscopy

_Gore, O’Brart, Allen et al_ IVOS 2015;56(13):7908

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[Graph showing RiboFlavin concentration vs. corneal depth]
Epithelial on CXL: Iontophoresis
Modified Iontophoresis protocol RCT

• Fight for Sight Grant
• Randomized bilateral study
• 46 patients (92 eyes)
• Epi off vs iCXL (modified extended protocol)
• Accelerated CXL 9mw/cm² for 11min
• ISRCT No: 04451470

• 49% epithelial defect in iCXL
  • No BC/L
  • (Cacicol, Amnion)

• 12 months
  • 34 iCXL, 37 epi-off
  • UCVA, CDVA, SEQ, Cyl, K1, K2, Astig
    • No diff between treatments
  • Except reduced pach in Epi-off (p<0.01)
    • Not in iCXL
  • Trend to greater reduction steepest K in iCXL
    • -0.36D vs -0.17D
  • Tend to greater Reduction in Tomographic Astig in iCXL
Epithelial on CXL: Iontophoresis
Modified Iontophoresis protocol RCT

• 18 month follow-up
• 29iCXL, 25 epi-off

• iCXL
  • -0.5D reduction Steepest K (p=0.1)
  • -1.2 reduction in Kmax (p<0.03)
  • Reduction in Topographic astig -0.52D (p<0.04)
  • No eye progressed (Kmax >1.5D) (none >1.0D)
  • Index of Height Decentration improved (p<0.0005)
  • Index of vertical asymmetry reduced (p<0.03)
  • Central pach no diff,
  • Thinnest pach reduced (p<0.05)

• Epi-off
  • -0.4D reduction Steepest K (p<0.02)
  • -1.0D reduction in Kmax (p=0.002)
  • One eye progressed (Kmax increased by 2.0D, mean K only 0.45D)
  • ISV, IVA, IHD, KI improved (p<0.02)
  • Reduced central and thinnest pachymetry (p<0.02)
Epithelial on CXL: Conclusions

• Comercially available protocols
  • Limited efficacy compared to epi-off

• Efficacy limited by
  • Stromal riboflavin absorption
  • Epithelial riboflavin masking UV absorption

• Chemical enhancers
  • Associated with epithelial damage
  • Limited stroma Riboflavin uptake

• Modified iontophoretic protocols
  • Increased stroma absorption
  • Up to 80% epi-off
  • Encouraging results with RCT

• Optimization of epi-on protocols
  • Accurate methodology to assessing CXL efficacy
  • Optimal riboflavin stroma concentration
  • Optimum stromal UVA dosage