

Updates in Corneal Collagen Crosslinking

COPE Category: AS

John D. Gelles OD

Course Description:

Corneal crosslinking is the single most crucial innovation in keratoconus and post cornea refractive ectasia management since the contact lens. The goal of this course is to present a clinically relevant guide to CXL to aid in knowing the expected clinical outcomes, the US FDA clinical trial outcomes, the potential complications, and setting patient expectations. Additionally, we will discuss the impact of crosslinking on the decline in keratoplasties for keratoconus and new use cases for treatment of infectious keratitis and even refractive error.

Course Learning Objectives:

1. Understand the history and current FDA approved method of CXL in the US
2. Understand the purpose of CXL and the expected outcomes
3. Understand how to set patient expectations and timing to CL wear after the procedure

Outline:

1. Topics Covered
 - a. Limited to US FDA approved device, pharma, and labeling
2. Collagen Structure
 - a. Lamellar Architecture
 - i. Meek et al
 1. Natural inter & intramolecular crosslinks
 2. Helix to microfibrils to fibrils to lamella
 3. Orthogonal lamella
 - ii. Abass et al
 1. Anterior interweaving
 2. Posterior stacking
 - b. What's affected in KC
 - i. Morshige et al
 1. Less Bowman's insertions
 - ii. Radner et al
 1. Less lamellar interweaving
 - iii. Smolek et al
 1. Predisposition to inferior cornea weakness
 - iv. Roy et al
 1. Biomechanics > thickness
 - v. Dupps et al
 1. Anterior stromal weakness
 - vi. Scarcelli et al
 1. Focal stromal weakness
 - vii. Zhou et al

1. Cathepsin B
 2. MMP-9
 - viii. Dudakova et al
 1. Lox underexpressed
3. CXL
 - a. CXL origins
 - i. Spoerl et
 1. ex-vivo tissue strain
 - a. Ribo, 365 nm, 45 mins best result
 - ai. Meek et al and Wollensack et al
 1. Collagen molecules at surface of fibrils
 - a. Within/between proteoglycans in individual fibril or adjacent fibrils
 - i. Collagen-proteoglycan matrix
 - bi. Wollensack et al
 1. Prospective study
 - a. Pre-op: Progressive
 - b. Post-op: Regressive
4. Tradition KC Management in the US
 - a. Review
 - b. CXL is a Paradigm shift in KC Management
 - c. Review FDA approval
5. What is Progressive KC
 - a. Gomes et al.
 - b. Subjective and Objective finding indicating progression
 - c. Review Progressive Nature of KC
6. CXL for KC benefits
 - a. Stop progression
 - b. Cost-Benefit
 - i. Lindstrom RL et al
7. Pre-Op
 - a. Considerations and contraindications
 - b. Vital Measurements
 - c. Setting procedural expectations
8. On Label CXL Procedure
 - a. Review procedure
9. Post-Op follow up
 - a. Scheduling
 - b. Expectations and each visit
 - c. P/O medication
 - d. Long term P/O care
10. Post-Op Expectations
 - a. Set visual expectation

11. Review FDA clinical trial data

- a. Hersh PS, Stulting RD, Muller D, Durrie DS, Rajpal RK. United States Multicenter Clinical Trial of Corneal Collagen Crosslinking for Keratoconus Treatment. *Ophthalmology*. 2017;124(9):1259-1270.

12. Expected corneal changes

- a. Kmax
 - i. Flattening by 1.7D
 - ii. Greenstein SA, Fry KL, Hersh PS. Article: Corneal topography indices after corneal collagen crosslinking for keratoconus and corneal ectasia: One-year results. *Journal of Cataract & Refractive Surgery*. 2011;37:1282-1290.
- b. Epi Changes
 - i. Masking of cone
- c. VA
 - i. Improvement by approximately 1 line UCVA and BCSVA
 - ii. Brooks NO, Greenstein S, Fry K, Hersh PS. Article: Patient subjective visual function after corneal collagen crosslinking for keratoconus and corneal ectasia. *Journal of Cataract & Refractive Surgery*. 2012;38:615-619.
- d. Haze
 - i. Transient
 - 1. Back to baseline by month 6
 - ii. Demarcation line
 - 1. Depth of effect
 - iii. Greenstein SA, Fry KL, Bhatt J, Hersh PS. Article: Natural history of corneal haze after collagen crosslinking for keratoconus and corneal ectasia: Scheimpflug and biomicroscopic analysis. *Journal of Cataract & Refractive Surgery*. 2010;36:2105-2114.
- e. Corneal Thickness
 - i. Thinner initially then back to baseline
- f. Endothelial Cell
 - i. No change

13. Review Potential Adverse Events

- a. Infectious Keratitis
- b. Herpetic Keratitis
- c. Corneal Scarring
- d. Endothelial Damage

14. Re-Cap on Post-Op Management

- a. Set correct expectations
 - i. Pain immediate few hours Post Op
 - 1. FB sensation after
 - ii. Visual blur and flux
 - 1. Typically worse at 1 month, returning to pre-op

- 15. Topography
 - a. MUST HAVE
- 16. Contact Lens wear after CXL
 - a. Many misconceptions
 - i. CLEI Retrospective data
 - 1. Average patients are fit or return to CL wear in 4 weeks post-op a. Once the epithelium is smooth and illustrious
 - ai. CLEI Prospective study
 - 1. Fit prior to CXL
 - a. Lens wear at 2 weeks if smooth and illustrious epithelium
 - b. Review if and when parameter changes are necessary
- 17. Paradigm Shift in KC Management in the US with CXL
 - a. Dx Early
 - b. Intervene Early
 - i. CXL
 - 1. Stop progression
 - 2. Prevent advanced disease
 - c. Visually Rehabilitate
 - i. Specialty contact lenses
 - ai. Surgical interventions
 - d. Corneal Transplantation
 - i. Modern transplantation
 - 1. Treatment of last resort
- 18. Current Research
 - a. Desired areas of improvement
 - i. Focal treatment
 - ii. Treatment depth
 - iii. Time
 - iv. Accelerated healing
 - b. Methods
 - i. Ectasia management
 - 1. Epi-On CXL
 - a. FDA clinical trial
 - i. Epi-On, Pulse, O2 supplementation, Accelerated
 - b. Hersh et al
 - 2. Curv
 - a. Topography guided
 - i. Location of thinnest point
 - 1. With Brillouin point of weakest strength
 - 3. Laser assisted CXL
 - a. Focal removal of epi over the cone
 - 4. Future non-photosensitizer technology
 - a. Topical Copper Sulfate

- i. Down regulation of LOX in KC
 - 1. Supplement of LOX
 - a. Phase 2
 - b. Laser-guided Intrastromal CXL
 - i. Femtosecond laser
 - 1. Selected depth within the stroma
 - 2. Modified to not cut tissue
 - a. No epi removal
 - b. Focal treatment
 - ii. Keratitis management
 - 1. PACK CXL
 - a. Hafezi et al
 - i. Corneal infections up to 4 mm
 - 1. One single dose of high-energy UV-light and Riboflavin = same efficacy as medication
- bi. Refractive error correction
 - 1. Low levels of
 - a. Myopia
 - i. Kanellopoulos
 - ii. Lim et al
 - iii. Elling et al
 - iv. Sachdev et al
 - v. Hout et al
 - vi. Fredriksson et al
 - vii. Naslund et al
 - b. Hyperopia
 - i. Stodulka et al
 - c. Astigmatism
 - i. Seven et al