The Future of Cornea And Contact Lens

Christine Sindt, OD, FAAO, FSLS

I have the following financial relationship to disclose:
- Alcon - Consulting Fee
- Allergan - Consulting Fee
- NovaBay - Consulting Fee
- Shire - Consulting Fee
- Valeant - Consulting Fee
- EyePrint Prosthetics - President

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No cameras or recording devices are allowed during the course presentation.

**Keratoconus: management**

- Eyeglasses
- Contact lenses
- Penetrating keratoplasty
- Thermokeratoplasty
- Excimer laser photorefractive keratectomy
- Laser In-Situ Keratomileusis
- Lamellar keratoplasty
- Epikeratophakia
- INTACS
- Collagen Crosslinking

**Procedures which weaken the cornea**

**Procedures that reinforce the cornea**

**Collagen Crosslinking (CXL)**

California Optometric Association
OptoWest 2017
three locations • six hours of CE

**OPTOWEST SAN FRANCISCO**
February 12, 2017

**OPTOWEST SACRAMENTO**
March 19, 2017

**OPTOWEST SAN FRANCISCO**
April 30, 2017
C3-R®
- Verisyse® phakic IOL

“It was incredible, in a matter of 10 minutes I went from 20/250 to 20/20”
- On Brian Williams Nightly News

Steve Holcomb- Gold Medalist
US Olympic Bobsled Team 2010

Natural Corneal Stiffening
- Normal aging increases crosslinking
  - Infant cornea relatively flexible compared to adult
  - May account for slowing of progression in KCN with age
- Cross-linking is enhanced by increased glycation of corneal collagen
  - Hypothesis why we don’t see many diabetics with KCN.

Collagen Crosslinking
- Goal to halt KC progression and reduce need for PK

Things that Crosslink
- Aldehydes
- Chemical Fixatives
- Photosensitizing radiation
  - In vivo studies showed UV radiation and riboflavin to be the most effective and least harmful to the human cornea

CXL Procedure

<table>
<thead>
<tr>
<th>Conventional</th>
<th>Accelerated</th>
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<tbody>
<tr>
<td>Pachymetry &gt; 400µm</td>
<td>Increased illumination</td>
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<tr>
<td>Debride cornea 7 to 8 mm</td>
<td>Biochemically equivalent</td>
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<tr>
<td>0.1% Riboflavin in dextran applied topically</td>
<td>Similar safety profile</td>
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<tr>
<td>1gt every 2 min for 30 min</td>
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Different Collagen Crosslinking Devices

- Avedro – USA
  - Newly FDA approved device
  - Epi off
  - Conventional Protocol
- CXLUSA- USA
- Peshke- Switzerland
- Sooft- Italy
- Vega X-Link

PTK and Crosslinking

- Epithelium removed with Excimer laser
  - Anterior stromal smoothing
  - Not topography guided reshaping
  - Can be performed on thin corneas
- 48% of eyes gained 1 line of CDVA
- Decrease in K's 2-3 D
- Decrease in corneal astigmatism 2D
- No change in ECD


Stromal Expansion with Crosslinking for Ultra-Thin Corneas

- Pachy to determine thickness needed
- 80 – 100 um lenticle inserted into the stroma
- Pachy confirmed
- Crosslinking performed

J Cataract Refract Surg. 2015 May;41(5):918-23

Intrastromal Rings and Collagen Crosslinking

- Single or double ring
- Conventional or Accelerated
  - No significant difference


CXL Procedure

- After procedure
  - Antibiotic drop for 2 weeks
  - Bandage contact lens
    - BCL removed once epi defect healed
  - Steroid for 2-4 weeks


Cornea 2004 23(1):43-49


Eye. 2004 Jan pp 1-5 / Ophthalmologica 218(2) 2004
Post-op Confocal View

- At 1 month:
  - Stromal edema
  - Decrease keratocyte density. Apoptosis
  - Lack of nerve fibers
- At 3-6 month
  - Activated keratocytes
  - Endothelial
    - Unaffected if corneal thickness > 400µm

Results

- Reduction in irregular astigmatism
  - Suggesting improved symmetry
  - Anterior (and possibly posterior) corneal surface
- Reduction in higher order aberrations
  - Particularly coma
- Reduction in Max K
  - At 12 months was 1.45D
- BCVA improved by 0.10 to 0.14 logMAR units
  - Approx 1 line improvement

Potential Risks

- Epi defect healing complications
  - Infectious keratitis
  - Sterile infiltrates
  - BCL complications

Potential Risks

- Over estimation on IOP
  - 2mm Hg in IOP
- Endothelial damage
  - If cornea < 400 um
  - If increase irradiation
  - How do over hydrated cornea respond to
- Stem cell damage
  - ROS toxicity

Failure Rates

- Vision lose of 2 or more lines
  - 2.9%
- Continued progression
  - 7.6%
- Sterile infiltrates
  - 7.6%
- Central stromal scars
  - 2.8%

Failure Rates

- Pre-op max K < 58.00 reduces failure rate to <3%
- Restricting patient age to less than 35 reduces complication rate to 1%
Future Application
- Pellucid Marginal Degeneration
- Post LASIK ectasia
- Prevention of post LASIK ectasia
- Bullous keratopathy
- Microbial keratitis
- Donor tissue modification
- Adjunct to orthokeratology

Anti-fouling surface coatings
- Catechol, PEG, urea groups
- Did not change light transmission
- Biocompatible
- Stable through autoclaving
- Reduces protein absorption
- Effective against *S. Aureus, P aerugenosa, Calibicans, F solani*

The Future Of Contact Lenses
- Silver Impregnated Lenses
  - Galyfilcon A Silicone Hydrogel Lenses Infused With Silver Iodide Delay Or Inhibit In-vitro Surface Colonization By Bacteria And Fungi Associated With Adverse Ocular Events
  - Pseudomonas aeruginosa
  - Fusarium
  - Methods:
    - Unworn and worn silver iodide-infused lenses were challenged in cultures of bacteria and fungi associated with adverse ocular events.
    - Bacterial populations were enumerated after 20 h and fungal populations after 7 days of incubation.
  - Results:
    - Near 2-log fewer bacteria were associated in all instances with the silver iodide-infused lenses compared to control lenses.
    - For non-worn lenses, germination of conidia of Fusarium was delayed for at least 48 hours in the presence of silver iodide-infused lenses.
    - For worn lenses, none of the lens matrices of galyfilcon A lenses infused with silver iodide were invaded by hyphae after 14 days of incubation whereas greater than 40% of the control lenses were observed to be penetrated by Fusarium starting at day 4.
  - Conclusions:
    - Silver-iodide infusion of lenses may reduce the risk of the lens serving as a fomite in the transfer of microorganisms from the contact lens case to the eye.

Contact Lens Safety
- Biomacromolecules 2015, 16(7) 1967-77

Contact Lens- Ocular Surface Disease
- Cornea 2013 Mar;32(3):326-31
Phospholipids
- Reside at interface of aqueous and lipid layer
- Stabilization
- Dysfunction
  - MGD
  - Contact lens adorption

Hyaluronic Acid Lenses
- Daily disposable lenses
- Release of 6 ug/ hour
- Releases up to 48 hours

Phospholipid Lenses
- Phospholipids loaded into a lens, slowly diffuse into the tear film during the day
- Release
  - 0.5 ug @ 2 hours
  - 1ug @ 10 hours

Hyaluronic Acid Lenses
- High Molecular Weight Hydroxypropyl Methylcellulose
- Imprinted
- 1000ug released over 60 days
  - 18ug/ day

Autologous Stem Cell Transplant via Contact Lens
- Cells harvested from superior fornix
- Cultured in autologous serum with silicone hydrogel lens.
- Betadine rinse, removal of corneal and limbal epi/ pannus
- 63% success in patients with LSCD

Contact Lens- Drug Delivery
### Ophthalmic Drug Market

- Driven by:
  - AMD
  - Cataracts
  - Diabetic Retinopathy
  - Glaucoma
  - Dry Eye
  - Inflammation
  - Allergy
  - Infection

### Drug Delivery Goal

- To increase bioavailability from less than 5% to at least 15-20%.

### Topical Drug Delivery

- Topical delivery <5%
- Barriers:
  - Nasolacrimal drainage
  - Epithelial drug transport barriers
  - Clearance by the conjunctival vasculature
- Currently no marketed delivery systems for long-term drug delivery to the anterior segment of the eye.

### Dissolving Contact Lenses

- Nanowaf er lens technology
  - 1/20th the thickness of current contact lenses
  - Polyvinyl alcohol resin
  - Drug laden reservoirs
- Slow release drug dispersal polymer
  - High concentration of drug in the tears
- Animal studies on corneal neovascularization showed 2x the effect compared to drops

### Current Drug Delivery Approaches

- Mucoadhesives
- Viscous polymer vehicles
- Transporter-targeted prodrug design
- Receptor-targeted functionalized nanoparticles
- Iontophoresis
- Punctal plug
- Contact lens delivery systems.

### Contact Lenses & Drug Delivery

- **Entrapment of drug solution in hollow cavity or center of lens**
- **Dispersion of surfactant-drug complexes in contact lens**
- **Dispersion of nanoparticles or liposomes within contact lens hydrogel**
- **Soaking in drug solution for adsorption of drug in preformed contact lens**
- **Molecular imprinting of drug in polymers hydrogel**
- **Surface adsorption of nanoparticles or drugs in contact lens hydrogel**
Soaking Lens in Drug

- HEMA lenses release majority of drug in one day
- Silicone Hydrogel lenses have similar uptake but slower release.
  - **Example:** Ciprofloxacin
    - 200ug/24 hours HEMA
    - 80ug/24 hours SiHy

Molecular Imprinting

- Polymeric content of the lens is molded to recognize the structural features and bonding preferences of the target drug molecule.
- Imprinted lenses exhibit a more prolonged drug release compared to just soaking a lens in a drug.
- Can simultaneously release up to 4 drugs
  - Dexemethesone
  - Flurbiprofen
  - Carbonic anhydrase inhibitors
  - Timolol
  - HPMC
  - Prednisone

Timolol Imprinting

- Timolol embedded onto a HEMA lens
- Single lens with sustained activity
- Can be reused/reloaded
  - Simple soak

Hydrogel Ring for Topical Drug Delivery to the Posterior Segment

- Ofloxocin delivered to the posterior pole using hydrogel ring soaked in the drug

Optom Vis Sci. 2016 Apr;93(4):377-86

Nanoparticles

- Immobilize drug-loaded nanocarriers (liposomes and nanoparticles) to the surface of the lens.
- **Drawback:** rapid detachment
  - 70% release within 5 hours

Nanoparticle treatment of Fungal Keratitis

- hydrogel-based contact lens:
  - quaternized chitosan (HTCC)
  - silver nanoparticles,
  - graphene oxide (GO)
- Electrostatic interactions between GO and HTCC, resulting in strong mechanical properties.
- Voriconazole (Vor), an antifungal drug, can be loaded onto GO
- The contact lenses also exhibited good antimicrobial functions
  - glycidyltrimethylammonium chloride and silver nanoparticles.
- Significant therapeutic effects on a fungus-infected mouse model.
**Ketotifen**

- A micro-emulsion of octyltrimethoxysilane creates a silica-shell on hydrogel contact lens
  - Ketotifen laden
  - Extended drug delivery system
  - More than 10 days
- No change in transmittance or physical properties of the lens

**Vitamin E**

- Extended Ciprofloxin, levofloxacin, chlorhexidine release
  - Increased drug binding
  - Increased release time 3 to 10 times
  - Material dependent
- Timolol-dorzolamide-20%vit E
  - Worn for 4 days
  - IOP reduction sustained for 1 week after removal

**Drug Polymer film coated with a lens**

- Levofloxacin in AC 15X greater at 4 hours compared to drops every 30 minutes.
- Drawbacks:
  - Increased CL thickness
  - Poor O2 permeability

**Cyclosporine A**

- SiHy lenses release Cyclosporine A for 2 weeks
- Coating lens with vitamin E prolongs release to 1 month

**Liposome Loaded CL’s**

- Entrapment of liposomes, nanoparticles, micro-emulsions and surfactant-drug complexes within the contact lens during manufacturing.
  - Swell the matrix of the lens with ethanol
- Vitamin E
  - Strong antioxidant effect
  - Non-irritating
  - 20% concentration
  - Greater concentration reduces O2 transmission

**Scleral Lenses**

- Drug added to the scleral lens
- PF Avastin added to lens has been shown to regress corneal NV and improve vision
Barriers the limit commercialization

- Contact lens critical properties altered
  - water content
  - tensile strength (mechanical properties)
  - ion permeability
  - Transparency
  - oxygen permeability
- Drug Factors
  - drug stability during processing/fabrication (drug integrity test)
  - zero order release kinetics (prevent burst release)
  - drug release during monomer extraction step after fabrication (to remove un-reacted monomers)
  - protein adherence
  - drug release during storage in packaging solution
  - shelf life study
  - cost-benefit analysis

Contact Lenses and Technology

- Smart Contact Lenses
  - Light emitting diode on the surface of a soft contact lens
  - Heads up displays
  - Augmented reality
    - Gaming
  - Video Cameras
  - Super human vision

Nano Lett 2013, 13(6) 2814-21

Monitoring Contact Lens

Thank You

CHRISTINE-SINDT@UIOWA.EDU