Amniotic Membranes in the Optometric Practice Workshop
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Disclosures
- Douglas K. Devries — Consultant or Speakers Bureau for:
  • Allergan
  • Bausch & Lomb
  • Akorn
  • BioTissue
  • BVI
  • OcuSoft
  • Rysing
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  • Allergan
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  • TearLab
  • Science Based Health
  • Shire

Advanced Ocular Surface Disease Treatments
- Androgen drops
- Amniotic Membrane
- Anti-inflammatories
  - Topical
  - Systemic
- Autologous Serum
- Intense pulse light therapy
- MGD therapies
- Punctal occlusion
- Tetracycline

Amniotic Membranes

History of Amniotic Membrane (AM) on the Ocular Surface
- Amniotic membrane (AM) was first used therapeutically by JW Davis for skin transplantation in 1910[1].
- De Roth however is the first person credited with having used fetal membranes in ophthalmic surgery in an attempt to reconstruct the ocular surface in patients with symblepharon[2].

History of AM uses on Ocular Surface
- In 1995 and beyond Dr. Scheffer Tseng and numerous colleagues expanded the clinical applications
What is Human Amniotic Membrane?

- A unique, avascular membrane separating the mother from the fetus: inner lining of placenta
- Provides an incubating environment promoting cellular differentiation
- Provides an immunological barrier to prevent "foreign body" rejection

Amniotic Membrane - Profile

- Unique Grafting Characteristics
  - Provides a matrix for cell migration/proliferation
  - Natural biological barrier
  - Stores at room temperature
  - Mimics the profile of conjunctiva

Indications for Use

<table>
<thead>
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<th>Conjunctival Indications</th>
<th>Corneal Indications</th>
<th>Other Ocular Surface Indications</th>
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<tr>
<td>Pterygium</td>
<td>Corneal Erosion</td>
<td>Chemical Burn</td>
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<tr>
<td>Conjunctivochalasis</td>
<td>HSV/VZV keratitis</td>
<td>Partial Limbal Stem Cell</td>
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<tr>
<td>Pingueculae</td>
<td>Neurotrophic Keratitis</td>
<td>Stevens-Johnson Syndrome</td>
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<tr>
<td>Superior Limbic Keratoconjunctivitis</td>
<td>Persistent Epithelial Defects &amp; Corneal Ulcers</td>
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<tr>
<td>Leaking Blebs</td>
<td>Punctal/Bulbar Keratoconjunctivitis</td>
<td>Scleral Melt or Ischemia</td>
</tr>
<tr>
<td>Removal of Large Tumors</td>
<td>Band Keratopathy</td>
<td>Fornix and Socket Reconstruction</td>
</tr>
<tr>
<td>Removal of Large Scars in Symbiopharon Lysis and Mobilty Restriction</td>
<td>Descemetocele or Perforation</td>
<td>Total Limbal Stem Cell Deficiency</td>
</tr>
</tbody>
</table>

Maternal Birth Tissues Anatomy

What is Human Amniotic Membrane?

- Studies show amniotic membrane enhances the wound healing process:
  - It reduces pain
  - It reduces inflammation
  - It reduces scar formation
  - Contains essential growth factors for cell growth and diversification

Clinical Challenges in Ocular Surface Disease

- DEFECT
- DELAYED HEALING
- DYSTROPHY
- DEGENERATION
- DAMAGE
Ocular Surface Diseases

Inflammation is the Hallmark of All Ocular Surface Diseases

Normal Adult Wound Healing
Our body does not achieve state-of-the-art healing on its own...

PROLONGED INFLAMMATION

SCAR FORMATION

RESIDUAL HAZE

Inflammation’s Effect on Healing
- Inflammation: the first sign of wound healing & is also the hallmark symptom of all ocular surface diseases
- Uncontrolled inflammation leads to:
  - Chronic pain and discomfort/irritation
  - Delayed healing, more tissue damage
  - Vision-threatening complication, e.g., scar/haze
- Effective control of inflammation is an important strategy to promote healing and minimize the risk of scar/haze

Non-Resolved Inflammation

Controlling Inflammation is Key to Preventing Tissue Damage!

Scarless Fetal Wound Healing
Speed & Quality of Healing Count!

HCA-HAP/PTX3, found naturally in amniotic membrane, is the critical biologic component responsible for scarless fetal wound healing.

Current Treatment Paradigm

Passive Therapies to Reduce Inflammation:
- Bandage Contact Lens
  - Pro: Mechanical barrier
  - Con: Potential to induce infection
- Topical Medications—Steroids/NSAIDs
  - Pro: Reduce inflammation
  - Con: Delay healing and increase potential for infection
- Dry Amniotic Membrane

Emerging Treatment Paradigm
Key to minimizing a sight-threatening scar is limiting inflammatory response and promoting healing
Cryopreserved and Dehydrated Amniotic Tissue

CryoTek Cryopreserved Amniotic Membrane Maintains Critical Components Needed for Regenerative Healing

CryoTek Cryopreservation is the ONLY method that retains:

- ECM components that regulate and promote regenerative tissue processes.1,2,3
- HC-HA/PTX-3 complex
  - Stops adult inflammatory immune response4,5
  - Suppresses T-cell activation
  - Inhibits giant cell formation
  - Controls MMP production6
- Growth factors
- Collagens (types I, III, IV, V and VI)
- Fibronectin
- Laminin

*This critical component is degraded or completely absent in dehydrated amniotic membrane


Prevent Further Damage: HC-HA/PTX3 Can Stop the Adult Scarring Process

The only method that retains both:

**The Structural Integrity of the tissue**
- Cells are devitalized but intact
- ECMs components are not degraded or lost
- Structural matrix remains intact
- Tissue maintains high tensile strength

**Biologics needed for Scar-less regeneration at dose dependent levels**
- HC-HA/PTX3 complex
- Growth factors
- Collagens (types I, III, IV, V and VI)
- Fibronectin
- Laminin

PROKERA®

Biologic Corneal Bandage

- PROKERA® utilizes the proprietary CryoTek™ cryopreservation method that maintains the active extracellular matrix (ECM) of the amniotic membrane which uniquely allows for regenerative healing
- PROKERA® is the ONLY FDA-cleared therapeutic device that both reduces inflammation and promotes scar less healing
- PROKERA® can be used for a wide number of ocular surface diseases with severity ranging from mild, moderate to severe
- PROKERA® when used early reduces inflammation and minimizes scarring to prevent sight threatening complications

CRYOTEK® Regenerative Healing

BY PRESERVING THE CATALYST FOR QUALITY HEALING, OUR PRODUCTS ARE FDA-CLEARED FOR:

- ANTI-SCARRING
- ANTI-INFLAMMATION
- ANTI-ANGIOGENESIS
- OPHTHALMIC INDICATIONS
Dehydrated Amniotic Membranes

- BioDOptix (BioD LLC)
- Aril (Seed Biotech)
- Oculomatrix (Skye Biologics)
- AmnioOcular (Liventa BioScience)
- Alpha Patch (Optix LLC)
- AmbioDisk (IOP/Mimedix)

- All store at room temperature
- Shelf Life typically 2-5 years
- Do not need to be rehydrated
- All require the use of BCL

AmbioDisk

Amniotic Membrane Technology

- Purion® Preservations Process
- Dehydrated
- Terminally sterilized
- Retained biostructure
- Over 75,000 surgeries

BioD

Amniotic Membrane Technology

- DryFlex® processing technology
- Dehydrated
- Retains growth factors, cytokines and collagens
- Sizes – 9.0mm / 12.0mm

CASE EXAMPLES

Dry Eye International Task Force: Therapeutic Recommendations

- Patient education
- Environmental modifications
- Control systemic medications
- Preserved tears
- Allergen control
- Nutritional support
- Topical corticosteroids
- Cyclosporine
- Secretagogues
- Tetracyclines
- Punctal plugs (once inflammation is controlled)
- Systemic antiinflammatory therapy
- Acetylcysteine
- Moisture goggles
- Surgery (punctal cautery)

Adapted with permission from O'Brien TP. Refract Eyecare. 2005;9(suppl):7-11.
Common Corneal Pathologies Associated with Dry Eye
- Superficial Punctate Keratitis
- Filamentary Keratitis
- Recurrent Corneal Erosion
- Corneal Ulcers
- Neurotrophic Keratitis
- Exposure Keratitis
- Sjogren’s Syndrome

Stop the Suffering, Offer Something New
- TREAT THE CORNEA
  - Anti-inflammatory, anti-scarring actions
  - Nerve growth factors
  - Hydrated environment that boosts stem cell proliferation
- What this means for your dry eye patients
  - Highly effective with extended periods of relief (average of 6 symptom-reduced/free months)
  - Rapid treatment period: 4-7 days
  - Crystal clear cornea
  - See and feel better
  - Happy eyes, happy patients!

Patient Survey Evaluates the Effectiveness of PROKERA® Slim in Treating Dry Eye

How Long Do the Results Last?
- **Mild cases:** 9-12+ months
- **Moderate cases:** 6-12 months
- **Severe cases:** 3-6 months

Set the patient’s expectations that the procedure may need to be repeated. Remember, 81% said that they would agree to have it again!

What Does the Literature Say?

Case #2
- 07/06/09
- 54 YOMW / Referred from OD for K Ulcer
- Started on levofloxacin 0.5% Q1h OS
- Pain and Redness started 5 days prior
- SCLW / Denies sleeping in lenses
- VA: OD 20/60 OS 20/200
Case #2
• 3+ injection
• 3.5 mm ulcer
• 2+ cells
• Cultures taken
• External photos
• Added tobramycin 0.3% Q2h

Infectious versus Sterile
• Ulcers
  – Rare
  – Painful
  – AC reaction
  – Usually single lesion
  – Discharge
  – Epithelial staining
  – Corneal edema
  – > 2.0mm in size
• Infiltrate
  – Common
  – Mild pain
  – No AC reaction
  – Multiple lesions
  – Minimal discharge
  – Epithelium intact
  – No corneal edema
  – < 2.0mm in size

Case #2 F/U
• 7/7/09 - Cloudy since yesterday
• Labs – No growth
• SLE
  – Conj - 4+ Injection
  – Cornea - 3.5 mm ulcer / Haze / 1+ edema / WBC
  – A/C - Rare cell
• Plan
  – Continue present meds
  – Add subconjunctival injection of gentamycin
  – Add loteprednol 0.5% tid OS

Case #2 F/U
• 7/9/09 – More photophobic
• SLE
  – Conj - 2+ Injection
  – Cornea – 3.0 mm ulcer / 1+ edema / WBC surrounding ulcer
  – A/C – D/Q
• See lab results

Steroids for Corneal Ulcer Trial
• Objective: To determine whether there is a benefit in clinical outcomes with the use of topical corticosteroids as adjunctive therapy in the treatment of bacterial corneal ulcers
• Results: No significant difference was observed
  – 3-month BCVA (P = .82)
  – Infiltrate/scar size (P = .40)
  – Time to re-epithelialization (P = .44)
  – Corneal perforation (P > .99)

What Does the Literature Say?


Chemical Burns

- Emergency!!! - Every minute counts
- Do not waste time on Hx and PE
- Alkali burns more common and worse than acid
  - Alkali
    - Household cleaners, fertilizers, drain cleaners
  - Acid
    - Industrial cleaners, batteries, vegetable preservatives

Hughes Classifications of Ocular Burns

- Grade 1 (Very good prognosis)
  - No corneal opacity nor limbal ischemia.
- Grade 2 (Good prognosis)
  - Corneal haze but iris details are clear. Less than 1/3 cornea limbus ischemia.
- Grade 3 (Guarded prognosis)
  - Sufficient corneal haze to obscure iris details. 1/3 to 1/2 of cornea limbus ischemia.
- Grade 4 (Poor prognosis)
  - Opaque cornea without view of iris or pupil. More than 1/2 of cornea limbus ischemia.

Management of Chemical Burns

- Debride necrotic tissue
- Frequent ATS
- Bandage contact lens
- Quinolone: 1 gtt 4-6x/day [prevents infection]
- Prednisolone phosphate: 1 gtt q 1-2 hr while awake (reduces inflammation)
- Vitamin C: 1-2 gm po qd (reduces corneal thinning/ulceration)
- 10% sodium citrate: 1 gtt q 2 hr while awake (chelates Ca++ and impairs PMN chemotaxis)
- Scopolamine 0.25%: 1 gtt tid [reduces pain/scarring with AC inflammation]
- 10% Mucomyst (n-acetyl-cysteine): 1 gtt 6x/day [mucolytic agent and collagenase inhibitor]
- Oral pain meds
- Diclofenac 100 mg po bid [collagenase inhibitor]
- Glaucoma gtt/oral diamox if IOP elevated
- Significant injury may require admission

What Does the Literature Say?

Pearls - Prevention is KEY!!!

- Know the potential eye safety dangers
- All chemical injuries should be lavaged immediately
- Extent of damage is dependent on concentration and pH of acid or base
- Eliminate hazards before starting work
- Use protective measures

Corneal Abrasions

- Check VA
- Important to know what abraded the cornea
- Self treatment?
- Grade the level of pain/light sensitivity

Fluorescein

- Always instill NaFl for a suspected K abrasion
- Need to use a cobalt blue light to excite the NaFl
- Be careful with the use of topical anesthetics

Abrasions Treatment

- Minor abrasion require only prophylactic antibiotic and ocular lubricants
- Moderate to severe – cycloplegic, oral analgesic, bandage contact lens, antibiotics
  - Clean up margins??
  - Doxycycline??
  - Amnionic membranes??

Are Eye Anesthetics Safe for Home Use?

Salim Rezaie, MD on August 14, 2014
Published in ER Physician’s Monthly

<table>
<thead>
<tr>
<th>Author and Year of Study</th>
<th># of Patients</th>
<th>Topical Anesthetic Used</th>
<th>Type of Study</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen KL et al (1989)</td>
<td>9</td>
<td>0.5% proparacaine</td>
<td>Case Series</td>
<td>Corneal Ulcers</td>
</tr>
<tr>
<td>Miles HW et al (1998)</td>
<td>1</td>
<td>0.5% tropicaine</td>
<td>Case Report</td>
<td>Healthy Corneal Epithelium</td>
</tr>
<tr>
<td>Mathewson KA et al (2003)</td>
<td>4</td>
<td>0.5% proparacaine, 0.5% tropicaine</td>
<td>Case Series</td>
<td>Corneal Ulcers with Corneal Hydrops</td>
</tr>
<tr>
<td>Mathewson KA et al (2003)</td>
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Take Home Message

To date, the only evidence that topical anesthetics in uncomplicated corneal abrasions causing more harm than benefit come from experimental animal studies, case reports, and case series. Other studies showed superior pain control without delayed wound healing. Based on available evidence, it is most likely reasonable to send patients home with dilute (0.5%) topical anesthetics for a period of no more than 24 – 48 hours as long as these patients do not have complications. Larger, prospective studies would lend more weight to this recommendation.
Pears

- Never prescribe topical anesthetics
- Avoid patching CL wearers and pts who sustained injury from vegetative matter or fingernails
- Corneal infiltrate is suggestive of infection
- AC reaction is suggestive of infection
- May lead to RCE

RCE Treatment

- Treat abrasion first
- Loteprednol with taper X 2 mos
- Muro 128 ung X 2 mos
- Freshkote TID X 2 mos
- Doxy BID X 2 mos
- Restasis BID
- Superficial Keratectomy

Post op - Superficial Keratectomy

- Post op just like a PRK case
- Steroid, antibiotic, NSAID for 1 week with BCL

What Does the Literature Say?

  - Debridement followed by placement of self-retained cryopreserved amniotic membrane via ProKera® can be performed in the office for treating RCE. Further studies to validate its efficacy in comparison to other surgeries are warranted.

Self Retaining Amniotic Membrane

- Cost of ProKera Approximately $900 to $1000
- Cost of Bio Optix Approximately $600
- Medicare Allowable approx. $1300-1500

Self Retaining Amniotic Membrane

- CPT 65778 “Placement of amniotic membrane on the ocular surface; without sutures”
  - Bundled with supply
  - V2790 supple code for non CMS
- Not billed with office visit
- Global period: Zero days
- Moderate to advance disease
• "Amnion can be prepared for implantation a number of ways. Heat- or air-dried amniotic membrane loses some of its biologic properties and is not ideal for ocular surface rehabilitation. The tissue can be lyophilized (freeze-dried), which induces minimal change in its properties. Amnion can be preserved in cold glycerol and cryopreserved and stored frozen at -80 degrees. The cryopreservation method allows for greater retention of the membrane’s structural, physiological and biochemical properties responsible for its dramatic healing and easier handling intraoperatively."

Wetlab

• Gloves
• Saline Solution
• Remove Protective Covering
• Retention Ring
• Rinse with Retaining Ring in Place
• Remove ProKera
• Rinse in Gloved Hand
• Determine Right Side Up

Overcoming Objections

<table>
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<th>Objections</th>
<th>Response</th>
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<tr>
<td>Lack of perceived clinical value</td>
<td>Peer reviewed journal articles and case studies</td>
</tr>
<tr>
<td>Perceived inferiority to a competitor/product</td>
<td>Convenience, handling, safety, performance</td>
</tr>
<tr>
<td>Too expensive</td>
<td>Competitively priced with superior handling characteristics, performance</td>
</tr>
<tr>
<td>Initiative with another group</td>
<td>Explore how we can break in, whether by price or other means</td>
</tr>
<tr>
<td>Clinical proof</td>
<td>Case studies, key thought leaders, peer reviewed journal articles</td>
</tr>
<tr>
<td>Packaging</td>
<td>New packaging with excellent feedback from clinicians</td>
</tr>
<tr>
<td>Reimbursement</td>
<td>BioDOptix is reimbursed with the same codes and manner as the competitive tissue</td>
</tr>
<tr>
<td>Patent issues</td>
<td>IOP has no patent that precludes BioDOptix from distribution of BioDOptix tissue</td>
</tr>
</tbody>
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THANK YOU

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