The Evolution of Transplantation Techniques for Corneal Endothelial Disease

Christopher Chow, MD

Michigan Cornea Consultants
Oakland University William Beaumont School of Medicine
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The Corneal Endothelium

- Single cell layer, non-replicating
- Birth = 4200 cells/mm²; Adulthood = 2400-2800 cells
- Passive diffusion of nutrients from aqueous
- Maintenance of corneal hydration and clarity
Key Points on the Timeline of Corneal Transplantation

- Concepts
  - Original concept of corneal transplantation
    - Galen – 130-200 AD
  - Original concept of a keratoprosthesis
    - Pellier de Quengsy – 1789
    - Proposed use of glass to replace opaque cornea
  - Erasmus Darwin (grandfather of Charles) – 1796
    - “Could not a small piece of cornea be cut out by a kind of trephine, about the size of a thick bristle or small crow quill, and would it not heal with a transparent scar?”
Key Points on the Timeline of Corneal Transplantation

- Animal Studies
  - Karl Himley and Franz Riesinger – 1818
    - Animal transplants – rabbits, chickens
    - Coined the term “keratoplasty”
  - Johan Dieffenbach – 1820
    - The idea of cornea transplantation is “one of the most audacious of fantasies... It would be the highest reward of surgery if this operation succeeded”
  - Samuel Bigger – 1837
    - Abducted in Egypt by Bedouins
    - Pet gazelle – within species transplant – “The cornea was taken from another animal of the same species brought in wounded but not quite dead; adhesion took place and 10 days after the operation, the animal gave unequivocal signs of vision, and the upper part of the transplanted cornea remained perfectly transparent.”
Key Points on the Timeline of Corneal Transplantation

- Human studies
  - Richard Kissam – 1838
    - First human cornea transplant - xenograft (pig)
    - “increased light perception” in immediate postop period
    - Failed in 2 weeks
  - 1800s – xenografts vs. allografts
  - 1800s – lamellar vs. penetrating surgeries
Eduard Zirm - 1905

- 45 yo farmer with bilateral alkali burns after trying to clean out a chicken coop with lime
- Donor – 11 yo boy with blind eye from penetrating injury to sclera and intraocular foreign body.
- One cornea provided two 5mm grafts
- 15 weeks in hospital
- OD - failed
- OS – 6/36 distance, J4 near at 1 year.
Key Points on the Timeline of Corneal Transplantation

- **Vladimir Filatov – 1937**
  - Suggested the use of cadaver corneas, developed trephines

- **Richard Paton – 1944**
  - Established the first eye bank in New York

- **Ramon Castroviejo – 1940-50s**
  - Many studies on graft technique
  - Popularized direct sutures and innovative surgical instruments.

- **McCarey and Kaufman – 1970s**
  - Tissue storage media
Other developments
- 1846 - Development of anesthesia - ether
- 1867 - Lister
  - Principles of antiseptic surgery
- 1940s - Medwar and Billingham
  - Advances in immunology
- 1948 – Paufique; and 1951 - Maumenee
  - Understanding concept of graft rejection
- 1940s – Antibiotics
- 1950s – Corticosteroids
- 1960s – Nylon sutures
- 1960s – surgical microscopes
Key Points on the Timeline of Corneal Transplantation

- Limited success in early grafts
  - Elschnig in 1930 reported 170 grafts (over 20 years) with a success rate of 22%
  - At the AAO meeting in 1957, Owens reported on 417 grafts of which 36.5% had remained clear
  - In the 1960’s success rates were about 50-60%

- 1970 = 7000 cornea transplants
- 1980 = 14,400 cornea transplants
- 1999 = 45,000 cornea transplants

Almost exclusively penetrating grafts
Penetrating Keratoplasty at the start of the New Millennium

- Success in the 90% + range for keratoconus, Fuchs’ and PBK
  - Highest success rate of any solid organ transplants
- Rejection rates of 6-20% for many of these conditions
  - Lowest rejection rate of all solid organ transplants
  - Achieved without systemic immunosuppression
Why so much interest in lamellar grafts once again?
Problems Related to Penetrating Keratoplasty

- Slow visual recovery for many patients
- Astigmatism and anisometropia
  - Average post-suture-removal astigmatism is 3-4 D
- Poor re-epithelialization
- Suture-related problems/infections
- Lifelong risk of rejection
- Wound weakness resulting in late wound shifting or risk of rupture with mild trauma
Advantages of Lamellar Procedures

- Compared to penetrating keratoplasty, lamellar procedures are either extraocular or allow one to work through a small peri-limbal incision
  - Better operative control
  - Reduced risk of expulsive hemorrhage
  - Minor reduction in globe structural integrity
  - No surface disruption – sutures, epithelium, astigmatism
- With reduced antigen exposure in EK, preliminary data suggests there may be a reduced incidence of rejection
- Diminished postoperative steroid use
- Expands the availability of donor tissue
  - Quality donor endothelium is not required for stromal scarring (Anterior procedures)
  - Donor tissue with stromal scarring can be used for endothelial keratoplasty (Posterior procedures)
Lamellar Keratoplasty (LK) - Nomenclature

ANTERIOR (ALK)
- Anterior lamellar keratoplasty (ALK)
- Deep anterior lamellar keratoplasty (DALK, FALK)

POSTERIOR (PLK)
- Deep lamellar endothelial keratoplasty (DLEK)
- Descemet's stripping (automated) endothelial keratoplasty (DSEK, DSAEK)
- Descemet's membrane endothelial keratoplasty (DMEK)
Lamellar Keratoplasty (LK) - Nomenclature

ENDOTHELIAL KERATOPLASTY

POSTERIOR (PLK)

- Deep lamellar endothelial keratoplasty (DLEK)
- Descemet's stripping (automated) endothelial keratoplasty (DSEK, DSAEK)
- Descemet's membrane endothelial keratoplasty (DMEK)
The Last 10 Years

Domestic Surgery Use of U.S. Supplied Intermediate-Term Preserved Tissue

EBAA Statistical Report 2014
DLEK

(Deep Lamellar Endothelial Keratoplasty)
Early attempts (1950s-60s) at posterior lamellar keratoplasty failed
  - All attempted to suture the posterior donor graft in place

Gerrit Melles 1998 –
  - Suggested against suture of posterior graft
  - Suggested pushing it into place with an air bubble
  - Posterior lamellar keratoplasty (PLK) or deep lamellar endothelial keratoplasty (DLEK)
Scleral incision, lamellar dissection

Excision of posterior stromal disc

Recipient tissue removed

Donor tissue placed into recipient

No sutures, no corneal surface incisions!
Recipient Lamellar Dissection

Courtesy of Dr. David Heidemann
Excision of Posterior Recipient Disc

Courtesy of Dr. David Heidemann
Artificial Anterior Chamber

Fill well with BSS or viscoelastic
Donor Lamellar Dissection
Trephination of Donor

Courtesy of Dr. David Heidemann
“Over-Folding” of Donor Disc

Courtesy of Dr. David Heidemann
Insertion of Donor Disc

Courtesy of Dr. David Heidemann
“Run the Rim” Under Air

Courtesy of Dr. David Heidemann
Small Incision DLEK

- 76 year old man
- Fuchs dystrophy
- Three months post-op
- \(-0.25 + 0.50 \times 175 = 20/40\)
## PK vs. DLEK (Dr. Mark Terry)

<table>
<thead>
<tr>
<th></th>
<th>Best PK Studies</th>
<th>DLEK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vision, mean</td>
<td>20/40</td>
<td>20/46</td>
</tr>
<tr>
<td>Corneal power, range</td>
<td>32 - 55 D</td>
<td>42 - 45 D</td>
</tr>
<tr>
<td>Astigmatism, mean</td>
<td>3 - 6 D</td>
<td>1.34 D</td>
</tr>
<tr>
<td>Cell count, mean</td>
<td>1,958</td>
<td>2,140</td>
</tr>
</tbody>
</table>
Michigan Cornea Consultants Experience with DLEK

- Heidemann DG, Dunn SP and Chow C, Cornea, 2008
  - 43 patients with Fuchs or PBK
  - 20 patients – DLEK; 23 patients – PK
  - Twelve month follow up
  - DLEK better than PK (p < 0.0001):
    ▪ Refractive, topographic astigmatism
    ▪ Change in spherical equivalent
    ▪ Irregular astigmatism (SRI index)
  - ECC similar in each group
  - Better BCSVA in DLEK at six months
  - Similar BCSVA in each group at one year
  - All grafts clear at one year
MCC Cases

- By the time this study was published, we had not performed DLEK surgery for >18 months!

Why?
From DLEK to DSAEK
Factors limiting widespread adoption of DLEK

- Technical difficulty of procedure
- Long surgical time
- Large 9mm incision
- Apposition of manually dissected donor and recipient stromal surfaces
  - Light scatter and degradation of visual acuity
Subsequent developments

- **2002** – Reduction of 9mm incision to 5mm
  - Folding of donor tissue for placement into anterior chamber
- **2004** – Descemetorhexis (Melles)
  - Stripping and removal of only Descemet’s membrane through a small incision
- **2005** – Descemet’s stripping with endothelial keratoplasty (DSEK) - (Price)
- **2006** – Use of automated motorized microkeratome to prepare donor posterior lamellar graft
  - DSAEK (Gorovoy)
DSAEEK

DLEK

DSAEEK
DSAEK Procedure

- 30-45 minute surgery
- retro/peri-bulbar vs. topical anesthesia
- Working on the “ceiling” instead of the “floor”

- 4 steps
  - Donor lamellar dissection and trephination
  - Removal of recipient Descemet’s membrane
  - Insertion of donor graft
  - Positioning and attachment of donor graft
DSAEK –
1. Donor lamellar dissection and trephination

Fill well with BSS or viscoelastic
DSAEEK –
1. Donor lamellar dissection and trephination
DSAEK –

1. Donor lamellar dissection and trephination

Pre-cut tissue.
2. Removal of recipient Descemet’s membrane
2. Removal of recipient Descemet’s membrane
DSAEK –
3. Insertion of donor graft
DSAEK –
3. Insertion of donor graft
DSAEK –
3. Insertion of donor graft
Insertion techniques
- Taco/fold technique
- Push/pull over Sheets glide
- Inserters
New Insertion Devices
DSAEK -
4. Positioning and attachment of donor graft
DSAEK Video
(From the University of Michigan Kellogg Eye Center)
DSAEK -
Post-op day 1
DSAEK - Complications
DSAEK - Complications
DSAEK - Complications
DSAEEK - Complications
DSAEK - Complications
## DSAEK - Outcomes

<table>
<thead>
<tr>
<th>Type of graft</th>
<th>No. of eyes</th>
<th>Diagnosis</th>
<th>6/12 or better</th>
<th>Postoperative refractive cylinder (D, mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMEK&lt;sup&gt;14&lt;/sup&gt;</td>
<td>60</td>
<td>Fuchs’/BK</td>
<td>88%</td>
<td>0.85 ± 0.70</td>
</tr>
<tr>
<td>DSAEK&lt;sup&gt;25&lt;/sup&gt;</td>
<td>100</td>
<td>Fuchs’/BK</td>
<td>81%</td>
<td>1.2 ± 0.99</td>
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<tr>
<td>DSAEK&lt;sup&gt;12&lt;/sup&gt;</td>
<td>93</td>
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<td>69%</td>
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<tr>
<td>DSAEK&lt;sup&gt;4&lt;/sup&gt;</td>
<td>13</td>
<td>Fuchs’/BK</td>
<td>77%</td>
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<tr>
<td>PK&lt;sup&gt;46&lt;/sup&gt;</td>
<td>71</td>
<td>Fuchs’</td>
<td>54%</td>
<td>4.2 ± 2.9</td>
</tr>
<tr>
<td></td>
<td>96</td>
<td>PBK</td>
<td>31%</td>
<td>4.7 ± 2.6</td>
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<td>PK&lt;sup&gt;47&lt;/sup&gt;</td>
<td>130</td>
<td>Fuchs’</td>
<td>64%</td>
<td>3.9 ± 1.9</td>
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<td>PK&lt;sup&gt;48&lt;/sup&gt;</td>
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<td>Fuchs’</td>
<td>65%</td>
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<tr>
<td></td>
<td>374</td>
<td>PBK</td>
<td>40%</td>
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<tr>
<td>PK&lt;sup&gt;49&lt;/sup&gt;</td>
<td>733</td>
<td>Fuchs’</td>
<td>53%</td>
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Price MO and Price FW, Cornea, 2010
**DSAEK - Outcomes**

- Graft clears over 1-4 weeks
- Ready to update glasses in 3 months
  - Often a hyperopic shift of 0.75-1.5 D
  - Due to addition of stromal tissue and increased thickness at periphery
- Following DSAEK – a greater improvement in visual function than would be suggested by the Snellen acuity alone
  - The happy patient going from 20/40 to 20/40
- Benefits of “ultra thin” DSAEK?
From DSAEK to DMEK
DMEK
(Descemet’s membrane endothelial keratoplasty)

- The progression in corneal surgery has been to replace only the layer or layers causing visual dysfunction.
- 2006 – Melles reported on DMEK in Fuchs’ dystrophy patient.
- DMEK is the most anatomically correct surgery for replacement of the corneal endothelial layer. Replacement with Descemet’s membrane and endothelium only.
Why move to this procedure from DSAEK?

- Better vision
  - DSAEK is excellent but rarely recovers 20/20 vision.
- Other potential advantages
  - Less refractive error, smaller induced refractive shift
  - Quicker visual recovery
  - Lower rejection rate
  - Smaller incision
  - Greater endothelial cell counts
Disadvantages of DMEK

- More difficult to perform
- Higher potential for primary graft failures
- New set of complications for surgeons to master during the learning curve
- Lower success rate
DMEK - Procedure

- Trephine donor with 7.75mm punch
- Strip Descemet’s membrane
- Stain with trypan blue for 60 seconds
- Load donor tissue into Straiko-Jones tube injector
- Inject slowly into anterior chamber with very low pressure
DMEK

- Tissue scroll has endothelium on outside
- Must understand orientation of tissue in anterior chamber
- Look for double scroll with scrolls oriented toward stromal surface
  - Orientation stamp, Moutsouris sign, portable slit lamp, intraoperative OCT
- May need to “puff” fluid into anterior chamber to properly orient tissue
Moutsouris Sign (Melles Group)

DMEK
DMEK

- Once tissue oriented correctly, lower pressure in eye and unroll the tissue
- Use stroking and tapping to center tissue
  - Many techniques described to unroll and position tissue
- Inject either air or 20% SF6 gas to fill anterior chamber
DMEK
DMEK
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Price MO and Price FW, Cornea, 2010
Guerra FP et al., Cornea, 2011
- 15 patients with DSAEK in one eye and DMEK in the other
- 13 preferred the vision in the DMEK eye
- 1 preferred the vision in the DSAEK eye
- 1 expressed no preference
DMEK

- Improved visual outcomes
- Faster visual recovery
- Lower rejection rates
- Less hyperopic shift – +0.24 - +0.74 D
- Steep learning curve
- High re-bubbling rate
  - 10-30%

Probability of Graft Rejection in 2 years
Price MO and Price FW, 2013
DSAEK and DMEK Trends

Figure 2: Domestic DSEK Trends
2011-2014 Domestic DSEK Trend - U.S. Eye Banks

Figure 3: Domestic DMEK Trends
2011-2014 Domestic DMEK Trend - U.S. Eye Banks

EBAA Statistical Report 2014
DMEK

- Which patients are better DMEK candidates?
  - The patient must have good vision potential
  - Normal anterior segment, small pupil
    - No glaucoma tubes
    - No glaucoma filters
    - No ACIOLs
    - No aphakic eyes
    - No previous vitrectomy
DMAEK
(Descemet’s Membrane Automated Endothelial Keratoplasty)
Future Directions

In the Management of Endothelial Dysfunction
Future Directions

- Trend towards transplanting less tissue
  - DMEK compared to DSAEK
- Trend toward faster visual recovery
  - EK compared to PK
- Trend toward simplified surgery
  - DSAEK/DMEK compared to DLEK
- Trend toward even simpler surgery?
- Non-surgical options?
DMEK complications

- Most dreaded by cornea surgeons: Graft dislocation
- What happens if you leave the graft dislocated in the AC?

- It turns out, if you wait long enough (6 months) the corneal may clear!
- DMET – Descemet’s Membrane Endothelial Transfer
DMET
Descemet’s Membrane Endothelial Transfer

D

E

Dirisamer M et al., Cornea, 2012
DMET

Dirisamer M et al., Cornea, 2012
How does it work?

- Raises questions regarding endothelial cell physiology, endothelial dysfunction, endothelial migration, endothelial regeneration
Rho Kinase Inhibitor

- Rho Kinase (ROCK) Inhibitor
  - Serine/threonine kinase
  - Signaling molecule that influences regulation of the cytoskeleton of cells, cell migration, proliferation and apoptosis
  - Can it promote cell cycle progression?
Nakamura N et al., IOVS, 2013

- 8 human subjects – 4 with Fuchs’ dystrophy and central edema, 4 with diffuse corneal edema
- Transcorneal freezing to central 6mm to kill endothelium
- ROCK inhibitor 6 times a day for 1 week.
- Corneal clarity restored in 4 patients with Fuchs’, but not in patients with diffuse edema
Rho Kinase Inhibitor

- Koizumi N et al., Cornea, 2013
  - 52 yo man with Fuchs’ dystrophy
  - VA = 20/63, CT = 703 μm, ECC = 757 cells/mm²
  - Transcorneal freezing and ROCK inhibitor
  - In 2 weeks, VA = 20/20!
  - 6 months later – CT = 568 μm, ECC = 1549 cells/mm²
  - 2 years later – VA = 20/16
Rho Kinase Inhibitor

Before

2 yrs After
VA = 20/16!

Koizumi N et al, Cornea, 2013
Research on culturing patient endothelial cells for reimplantation
Research on culturing donor endothelial cells for transplantation
There is work being done to take stem cells from blood or bone marrow, induce them to become pluripotent and stimulate them to differentiate into corneal endothelial cells
An entirely bioengineered cornea??
Conclusion

- We have come a long way in the last century in our management of corneal endothelial dysfunction.
- In the last 15 years we have seen the dramatic evolution of keratoplasty techniques.
- Eventually we might have the ability to proliferate new endothelial cells.
- We may even have the ability to use eye drops to promote adhesion and proliferation of endothelial cells.
- Likely will use a combination of techniques in the future.
- This will continue to be an exciting area in the next 10 years!
Thank you!!