Retinopathy of Prematurity

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Disclosure Statement
Dale L Phelps, MD

- Financial Relationships: Dr. Phelps receives research support from NICHD. Her spouse is a paid consultant to CARDIODX Inc. on evaluation of diagnostic testing and Kaiser Permanente; he is on the Board of Directors for VirtualScopics, Inc.
  - She has no Conflict of Interest.
- FDA: Dr. Phelps has disclosed that her presentation may involve discussion of the non-FDA approved use of vitamin E, inositol or bevacizumab for ROP.
Objectives

Participants should understand the pathophysiology and time course of ROP to:

- Identify inadvertent oxygen overuse
- Understand barriers to a successful ROP examination program
- Name 3 concerns with the off-label use of bevacizumab to treat severe ROP
Objectives

Pathophysiology

- Seeking out inadvertent oxygen overuse

Detection: Natural course, critical time points
- Measure the rate of ROP examinations and address barriers to its success

Treatments: Established & Novel
- Name 3 concerns with the off-label use of bevacizumab to treat severe ROP
National Eye Institute 2003

http://www.nei.nih.gov/photo
http://www.nei.nih.gov/rop/images/ROP10-31-03.mpeg
Relative Eye Sizes

26 weeks

Adult

Courtesy of R. Foos, personal, and in NeoReviews July 2001, 2:153-179
Looking Inside the Eye

Point of View
Immature Eye
Initial Injury of ROP
Neovascularization

Artist’s Renditions prepared by D Phelps, and portions have been previously used in a review article in NeoReviews July 2001, 2:153-179.
Repair Creates Retinopathy

Photographs courtesy of E. Palmer: CRYO-ROP study and ICROP: 1984
The Posterior Pole View

Normal Fundus

Plus

Photographs courtesy of E. Palmer, W. Good: CRYO-ROP and ET-ROP studies
Regression (Healing)

Courtesy of J. Flynn

From D Phelps Review
NeoReviews 2001; 2:153
Retinal Detachment

Blind from ROP
Leucokoria

Used with permission: Courtesy of Dr. Arnall Patz
National Eye Institute 2003

http://www.nei.nih.gov/photo
http://www.nei.nih.gov/rop/images/ROP10-31-03.mpeg
Animal Models

- Normal Ashton, Arnall Patz originally
- Kitten, puppy, rat, mouse
- Varied oxygen exposure (days)
- Varied age after birth exposure started
- Varied intermittent & with hypoxia

![Graph showing days after birth and oxygen exposure](image)
Feline Retina: OIR Model

Hours in hyperoxia
Target Oximetry and Morbidities

Stated Pulse Oximetry Goals

NICU A
95-99%

NICU B
90-96%

NICU C
70-92%

Tin et al, Arch Dis Child Fetal Neonatal Ed 2001; 84:F106-10
Outcomes: Tin et al

Tin et al, Arch Dis Child Fetal Neonatal Ed 2001; 84:F106-10
Randomized Trial of infants 24\textsuperscript{0/7}-27\textsuperscript{6/7} weeks gestation (n = 1,316)

Masked/blinded oximeter Target was saturation of 88\%-92\%

Actual was 85-89\% vs 90-95\% sat
Outcomes

Saturation Group:

- Severe ROP
- Death before discharge
- 20mo. NDI/death

Lower

- 8.6% vs 17.9%  
  (sROP down 9.3%)

- 19.9% vs 16.2%  
  (Death up 3.7)

Higher

- 27.5% vs 30.2%

What to do?

- 2013 AAP Perinatal Section: 7th Ed. cites data, but only obliquely says
  * <95% O₂ Saturation, especially for preterms, and implies that
    - 85%-89% as a saturation target is too low
  - only Guidelines! Gaps in application
Applying the Information


A textbook description of how to apply the process of studying an issue, planning the approach, doing it, and then studying again.

Severe ROP in infants <1500g BW was reduced from 11% to 5.8% over 5 years
Non-blended, 100% oxygen?

- Deliveries: 73% yes
- Transports (out-of-hospital): 15%
- Transports (in-hospital): 56%
- Nebulizer treatments: 35%

Ellsbury: PAS Abstract 2007
Hidden Oxygen
52 NICUs: QA Project: Policy for <1500g

Routine large increases in O2 (>5%)

- apnea: 58%
- Prior to suctioning: 43%
- Before routine handling: 17%
- Before minor procedures: 15%

Ellsbury: PAS Abstract 2007
Be Alert, Remain Vigilant

Watch the oximeters!
Alarms on?
Seek out Unsuspected
overuse of oxygen
Objectives

**Prevention:** Pathophysiology
- Seek out inadvertent oxygen overuse

**Detection:** Natural course, critical time points
- Measure the rate of ROP examinations and address barriers to its success

**Treatments:** Established & Novel
- Name 3 concerns with the off-label use of bevacizumab to treat severe ROP
Peripheral Ablation

With experience and Laser further Reduced detachments

Modified from Teaching image from Ross Products/Abbott Laboratories
ETROP Outcomes

Percent Poor Retinal Outcomes

56% CRYO Control
15.6 ETROP Control
9.1 ETROP Early

P<0.001
Examining for ROP

- Goal: detect Type 1 ROP in time to treat it before detachment
  - Who to examine?
  - When to start examinations?
  - When to repeat them?
Timing of Threshold ROP

Recommended First Examination Range
31-33 weeks

Youngest, 31.6 weeks

Discharge Home

Postmenstrual Age (weeks)
2006 2013 Guidelines

Who?

- \( \leq \) 30 weeks gestation
- \( \leq \) 1500 grams birth weight
- other premature infants, if medically unstable

When? the later of either

- 31-33 weeks postmenstrual age, or
- 4-6 weeks after birth (caution <24 wk)

Pediatrics: 2013; 131:189-95
Many Opportunities to Slip Up

- Clinical Evidence
- Busy Units
- Complex Systems
Successful ROP Program

- Written Policy/System Developed together with Ophthalmology
  - Who, when, tracking repeats, discharge
- A Designated person is responsible and has established back-up
  - (Training Programs: involve the trainees)
- Periodic QA conducted
Nice Touches

- Standard Information for families
  - Brochures, DVD, Web-based, meetings
- Bedside tracking card of exams
  - Engage staff and family
- Discharge letter – personalized info
  - Status, scheduled appointment, phone number, use the “B” word, Parent signature
QA for ROP Program

List all infants <1500g BW or <30 weeks

Before you start: What are your acceptable rates?

**Level 1 QA:** Determine the % that:
- Died before Examination
- Examination Completed
- Examination Missed, no documented plan
- Discharged before examination with a specific plan (vs without)
QA for ROP Program

- **Level 2** (and advanced)
  - Once examined, was repeat exam recommended and addressed?
  - Was the repeat done, on time?
  - If discharged before repeat, was a visit scheduled for the family -- before discharge. Was its importance explained and documented?
  - *(Advanced : Did they get the exam?)*
Pitfalls for the System

- Lack of ROP Coordinator depth
  - Vacation / ill /changes jobs/etc)
- Lack of medical back up for ROP coordinator
- Emergency transfers, early discharges
- Ophthalmology shortages / outages
- Outpatient (or transfer) follow up
The Future for Reducing Exams

- Preterm infants who grow well are at very low risk for serious ROP
- Formalized in “WIN-ROP” algorithm
- Based on weekly weight gain, infants are identified as not at risk for serious ROP (no ‘alarm’)
- Many publications appearing in various populations, a work in progress
Objectives

**Prevention:** Pathophysiology

- Seek out inadvertent oxygen overuse

**Detection:** Natural course, critical time points

- Measure the rate of ROP examinations and address barriers to its success

**Treatments:** Established & Novel

Name 3 concerns with the off-label use of bevacizumab to treat severe ROP
Prevention of ROP

- Prevent Preterm Birth
- Use Oxygen Wisely
- Non FDA approved, Investigational
  - Vitamin E, d-penicillamine
- Others Under Investigation
  - Inositol
  - IGF-1
Revised Indications for ROP

<table>
<thead>
<tr>
<th>Type 1 ROP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zone II</td>
</tr>
<tr>
<td><em>Plus disease</em> with</td>
</tr>
<tr>
<td>Stage 2 or 3</td>
</tr>
<tr>
<td>Zone I</td>
</tr>
<tr>
<td><em>Plus disease</em> with ROP or</td>
</tr>
<tr>
<td>Stage 3 (no plus)</td>
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# Intervention for ROP

<table>
<thead>
<tr>
<th>Type 1 ROP</th>
<th>Type 2 ROP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral ablation</td>
<td>Wait, watch closely</td>
</tr>
<tr>
<td><strong>Zone II</strong></td>
<td><strong>Zone II</strong></td>
</tr>
<tr>
<td><em>Plus disease</em> with Stage 2 or 3</td>
<td><em>Stage 3, no plus</em></td>
</tr>
<tr>
<td><strong>Zone I</strong></td>
<td><strong>Zone I</strong></td>
</tr>
<tr>
<td><em>Plus disease</em> with ROP or Stage 3 (no plus)</td>
<td><em>Stage 1 or 2, no plus</em></td>
</tr>
</tbody>
</table>
Peripheral Ablation

ETROP Type 1

With experience and Laser, further Reduced detachments

Modified from Teaching image from Ross Products/Abbott Laboratories
Anti-VEGF injection

Modified from Teaching image from Ross Products/Abbott Laboratories
Bevacizumab (anti-VEGF) is not FDA approved for use in eye. Licensed for IV use in cancer. It’s use has been extrapolated from non-FDA approved use in the eye for macular degeneration.

RCT of laser vs bevacizumab for severe ROP (Type 1)
Study Design

- Stage 3 with plus disease in both eyes
- Randomized to both eyes treated with laser or both treated with bevacizumab
- Treatment not masked
- Zone I: planned enrollment 50
- Zone II: planned enrollment 100
Baseline Characteristics

- Very similar across Zones and Rx
  - M GA 24 weeks, M BW 615-689 g
  - 61-71% male
  - 46-67% Hispanic
  - PMA at Rx: mean 33.7 – 35.8 weeks
### Zone I, Stage 3+ ROP

<table>
<thead>
<tr>
<th></th>
<th>Laser</th>
<th>Bevacizumab</th>
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</thead>
<tbody>
<tr>
<td>Enrolled</td>
<td>34</td>
<td>33</td>
</tr>
<tr>
<td>Rx violation</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Died</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Analyzed</td>
<td>33</td>
<td>31</td>
</tr>
<tr>
<td>No Repeat Rx (1 or both eyes)</td>
<td>19 (58%)</td>
<td>29 (94%)</td>
</tr>
</tbody>
</table>

\[ p < 0.003 \]
Zone II, Stage 3+ ROP

<table>
<thead>
<tr>
<th></th>
<th>Laser</th>
<th>Bevacizumab</th>
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</thead>
<tbody>
<tr>
<td>Enrolled</td>
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<td>42</td>
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<tr>
<td>Rx violation</td>
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<td>0</td>
</tr>
<tr>
<td>Died</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Analyzed</td>
<td>40</td>
<td>39</td>
</tr>
<tr>
<td>0 Repeat Rx (1 or both eyes)</td>
<td>35 (88%)</td>
<td>37 (95%)</td>
</tr>
</tbody>
</table>

\[ p < 0.27 \]
Advantages for bevacizumab

- Procedure Much easier
- Fewer intubations for procedure
- Retinal vessels resume growing, although no measurements of visual function can yet be done to see if this has physiologic meaning
- If repeat injection is needed, the infant is older and more stable
- Repeat injections are needed less often than ‘touch up’ laser
Concerns for bevacizumab

- No PK studies done of bevacizumab in infant eyes (and serum)
- Bevacizumab appears in the circulation and serum VEGF levels fall in adults and infants for many weeks after intravitreal Rx.
- Raises concerns of depressed VEGF at an age when important rapid vascular development is happening throughout all organs (unlike the adult).
Concerns for bevacizumab (2)

- Deaths after treatment were 5 bevacizumab vs 2 in the laser group and deaths were pulmonary related. Could alveolar capillary development be impaired? Maybe just in the face of BPD?
- n too small to determine safety
- ROP threatening vision recurs less often, but when it does it can aggressive and late, up to 27 weeks!
ROP Summary

- Is not going away
- Interruption of developing vessels
- Effective intervention, but
- Timing is critical, fraught with pitfalls
- New interventions must be cautiously evaluated
Thank-you

Questions
References

- **For ROP & Neonatal History:** Silverman WA. Retrolental Fibroplasia: A Modern Parable. New York: Grune & Stratton; 1980
- **'Official 'Screening Examinations for ROP:** Pediatrics 2013; 131(1): 189-95 (and on-line in 7th Ed. Guidelines for Perinatal Care, 2013)
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- Wu C for the WINROP Consortium. Importance of early postnatal weight gain for normal retinal angiogenesis in very preterm infants Arch Ophthalmol 2012; 130(8):992-9
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