Title of Program: Preventing and Treating Retinopathy of Prematurity: Evidence from Cochrane Systematic Reviews

Speakers/Moderators: Roger F. Soll, MD, James Hagadorn, MD

Planning Committee: Jeffery D. Horbar, MD, Madge E. Buus-Frank, RN, MS, APRN-BC, FAAN, Roger F. Soll, MD

Date: December 18, 2017

Learning Objectives:

Participants will be presented with evidence from clinical trials and systematic reviews and will be able to evaluate and translate the evidence in the field of neonatology to better serve their practices. Specifically, evidence for strategies regarding the prevention and treatment of retinopathy of prematurity will be presented and critiqued.

DISCLOSURE:

Is there anything to disclose? *No financial interests to disclose*

**COMMERCIAL SUPPORT ORGANIZATIONS (if applicable):**  *No Commercial Support*

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This activity has been planned and implemented by The Robert Larner College of Medicine at The University of Vermont and Cochrane Neonatal is accredited by the American Nurses Credentialing Center (ANCC), the Accreditation Council for Pharmacy Education (ACPE), and the Accreditation Council for Continuing Medical Education (ACCME), to provide continuing education for the healthcare team.

The University of Vermont designates this web seminar for a maximum of 1 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.
Preventing and Treating Retinopathy of Prematurity: Evidence from Cochrane Systematic Reviews

Conference begins at 12 Noon EST
December 18, 2017

Supported by: Vermont Oxford Network

The Basics

∙ Follow the slides on your screen.
∙ Listen to the Audio Broadcast via your computer speakers.
∙ If the computer audio is not working well, click at the bottom of the Participants panel and follow the prompts to call in on the telephone.
∙ Send questions and comments via Chat to “All Panelists”.

Chat window

Send to: All Panelists

Select a participant in the Send to menu first, type chat message, and send...
Cochrane
Preparing, maintaining and promoting the accessibility of systematic reviews of the effects of health care interventions

Cochrane Neonatal
Prepares and disseminates evidence-based reviews of the effects of therapies in the field of neonatal medicine
Editorial Team

Roger F. Soll  
Coordinating Editor

Colleen Ovelman  
Managing Editor

Jennifer Spano  
Trial Search Coordinator
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Yale University

Jeffrey Horbar
University of Vermont

Bill McGuire
Hull York Medical School

Gautham Suresh
Baylor University
Guest Discussant

James Hagadorn, MD
Associate Professor of Pediatrics
University of Connecticut School of Medicine
In Memory

Jerold F. Lucey, MD
Professor Emeritus
University of Vermont College of Medicine

Remembering Dr. Jerry Lucey, teacher, mentor, colleague, and friend.
Support

Cochrane Neonatal acknowledges the generous support from Vermont Oxford Network in producing these seminars.
Disclosure

Roger F. Soll is the Coordinating Editor of Cochrane Neonatal and President of Vermont Oxford Network
Why These Webinars?

To develop an understanding of the evidence supplied by systematic reviews in neonatal perinatal medicine (as well as other large well conducted trials) and discuss how this evidence might influence your practice.
Retinopathy of Prematurity

We will review the evidence from randomized trials and meta-analyses and discuss the different approaches that teams around the world are using regarding the prevention and treatment of retinopathy of prematurity.
Retinopathy of Prematurity is in many ways the story of oxygen use in the preterm newborn....
Oxygen in the Preterm Infant

“In the 1940s, Wilson and colleagues observed that periodic breathing in premature infants was nearly eliminated with the use of 70% oxygen.

Although Wilson cautioned against unrestricted use of oxygen, other investigators and the American Academy of Pediatrics advocated its liberal use....”

Polin NEJM 2013
Retinopathy of Prematurity
(Retrolental Fibroplasia)

First described in 1942:

"Grayish white opaque membrane behind each crystalline lens”

Terry 1942
Retinopathy of Prematurity
Pathogenesis

**Phase 1**: Relative retinal hyperoxia and interruption of normal vascularization
- retinal response to hyperoxia is vasoconstriction
- reduced vascular endothelial growth factor (VEGF)

**Phase 2**: Hypoxia-revascularization
- VEGF is upregulated in response to hypoxia
- Abnormal neovascularization can occur
Stages of Retinopathy of Prematurity
Retinopathy of Prematurity

Scheme of retina of right eye (RE) and left eye (LE) showing zone borders and clock hours used to describe the location and extent of retinopathy of prematurity (adapted the Committee for the Classification of Retinopathy of Prematurity).

From: The International Classification of Retinopathy of Prematurity Revisited
Effect of Restricted Oxygen on Retrolental Fibroplasia

Overview of 3 Randomized Controlled Trials

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Typical Risk Difference</th>
<th>Decreased</th>
<th>Risk</th>
<th>Increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTIVE RLF</td>
<td>-0.30 (-0.39, -0.21)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CICATRICIAL RLF</td>
<td>-0.13 (-0.20, -0.06)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DEATH</td>
<td>0.03 (-0.02, 0.07)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DEATH OR CICATRICIAL RLF</td>
<td>-0.07 (-0.16, 0.03)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Watts 1992
Epidemic of ROP

Number of cases


Oxygen curtailed
Effect of Restricted Oxygen on Mortality

MORTALITY BEFORE (1944-1948) AND AFTER (1954-1958) INTRODUCTION OF A POLICY OF OXYGEN RESTRICTION IN INFANTS BIRTH WEIGHT 1000-1499 GRAMS

AVERY et al. Recent increase in mortality from hyaline membrane disease. J Pediatrics 1960
Retinopathy of Prematurity

VERMONT OXFORD NETWORK ANNUAL REPORTS 2000-2016

Any ROP
ROP > stage 2

% VLBW INFANTS

Oxygen Monitoring and
Retinopathy of Prematurity

Use of Oxygen and Retinopathy of Prematurity

- Blood gases
- Transcutaneous Monitoring
- Policies/guidelines to decrease oxygen exposure
- Recent multicenter trials (NeoProM)
Oxygen Monitoring and Retinopathy of Prematurity

BLOOD GASES
Blood gases

Like watching a football game and checking in on the score every quarter...

First Quarter  Giants 12  Patriots 9
Second Quarter  Giants 18  Patriots 12
Third Quarter  Giants 25  Patriots 15
Fourth Quarter  Giants 31  Patriots 18
Blood gases

So what happened in the First Quarter?

Did the Giants score 4 field goals, or a touchdown, a missed extra point and 2 field goals, or a touchdown and a field goal and a safety?

Have to watch the game more closely to know!
Transcutaneous oxygen monitoring
Continuous TcPO2 Monitoring Compared to Intermittent PaO2 Monitoring

Retinopathy of prematurity
All Study Infants BW 500-1300 grams

RD -0.11 (-0.21, 0.01)

35%

45%

ANY RETINOPATHY OF PREMATUREITY

TcPO2 MONITORING
CONVENTIONAL MANAGEMENT

### Continuous TcPO2 Monitoring Compared to Intermittent PaO2 Monitoring

**BANCALARI AND COWORKERS 1987**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Risk Difference (95% CI)</th>
<th>Decreased</th>
<th>Risk</th>
<th>Increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANY ROP</td>
<td>-0.11 (-0.21, 0.01)</td>
<td></td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>CICATRICIAL ROP</td>
<td>-0.01 (-0.05, 0.03)</td>
<td></td>
<td>1.0</td>
<td>2.0</td>
</tr>
<tr>
<td>DEATH</td>
<td>0.08 (-0.02, 0.18)</td>
<td></td>
<td>1.0</td>
<td>2.0</td>
</tr>
<tr>
<td>DEATH OR ROP</td>
<td>-0.02 (-0.13, 0.09)</td>
<td></td>
<td>1.0</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Oxygen saturation monitoring

A pulse oximeter estimates the amount of oxygen carried in the bloodstream using infrared technology across the skin.
Oxygen dissociation curve

Percent saturation ($sO_2 \%$)

Oxygen partial pressure ($pO_2$, mmHg)
Lower Oxygen Saturation and the Impact on Retinopathy of Prematurity

Tin W et al. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. Arch Dis Child Fetal Neonatal Ed 2001;84:F106-110
Effects of targeting lower versus higher arterial oxygen saturations on death or disability in preterm infants

Askie LM, Darlow BA, Davis PG, Finer N, Stenson B, Vento M, Whyte R.

Effects of targeting lower versus higher arterial oxygen saturations on death or disability in preterm infants

Objectives:

1. What are the effects of targeting lower versus higher oxygen saturation ranges on death or major neonatal and infant morbidities, or both, in extremely preterm infants?

2. Do these effects differ in different types of infants, including those born at a very early gestational age, or in those who are outborn, without antenatal corticosteroid coverage, of male sex, small for gestational age or of multiple birth, or by mode of delivery?
NeOProM: Neonatal Oxygenation Prospective Meta-analysis Collaboration study protocol

Lisa M Askie¹, Peter Brocklehurst², Brian A Darlow³, Neil Finer⁴, Barbara Schmidt⁵,⁶, William Tarnow-Mordi⁷,⁸, for the NeOProM Collaborative Group¹
### Characteristics of randomized trials included in the NeoProM Collaboration

<table>
<thead>
<tr>
<th>Trial acronym</th>
<th>BOOST II-Australia</th>
<th>BOOST II-UK</th>
<th>BOOST-NZ</th>
<th>SUPPORT</th>
<th>COT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Registration number</td>
<td>ACTRN12605000055606</td>
<td>ISRCTN00842661</td>
<td>ACTRN126050000253606</td>
<td>NCT00233324</td>
<td>ISRCTN62491227</td>
</tr>
<tr>
<td>Planned sample size</td>
<td>1200</td>
<td>1200</td>
<td>320</td>
<td>1310</td>
<td>1200</td>
</tr>
<tr>
<td>Countries of recruitment</td>
<td>Australia</td>
<td>United Kingdom</td>
<td>New Zealand</td>
<td>United States</td>
<td>Canada, USA, Argentina, Germany, Israel, Finland</td>
</tr>
<tr>
<td>Participants</td>
<td>Infants &lt; 28 wks gestation inborn or outborn &lt; 24 hrs old</td>
<td>Infants &lt; 28 wks gestation &lt; 12 hrs old (24 hrs if outborn)</td>
<td>Infants &lt; 28 wks gestation inborn or outborn &lt; 24 hrs old</td>
<td>Yes</td>
<td>Infants 24-27 wks gestation &lt; 2 hrs old</td>
</tr>
<tr>
<td>Masked?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Lower oxygen saturation (85%-89%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Intervention</td>
<td>Lower oxygen saturation (85%-89%)</td>
<td>Lower oxygen saturation (85%-89%)</td>
<td>Lower oxygen saturation (85%-89%)</td>
<td>Yes</td>
<td>Lower oxygen saturation (85%-89%)</td>
</tr>
<tr>
<td>Comparator</td>
<td>Higher oxygen saturation (91%-95%)</td>
<td>Higher oxygen saturation (91%-95%)</td>
<td>Higher oxygen saturation (91%-95%)</td>
<td>Yes</td>
<td>Higher oxygen saturation (91%-95%)</td>
</tr>
<tr>
<td>Intervention &amp; comparator duration</td>
<td>Oximeter applied asap after admission to NICU, continued for minimum 2 wks. Thereafter continued until 36 wks corrected age or SpO₂ &gt; 96% in room air for 95% of time over 3 days.</td>
<td>Oximeter applied from randomisation until postmenstrual age (PMA) of 36 wks or until baby is breathing air. All monitoring at any time prior to 36 wks to be done using study oximeter. BPD defined at 36 wks using a physiological test.</td>
<td>Oximeter applied asap after admission to NICU, continued for minimum 2 wks. Thereafter continued until 36 wks corrected age or SpO₂ &gt; 96% in room air for 95% of time over 3 days.</td>
<td>Oximeter applied within 2 hrs following admission to NICU until infant has been in room air for 72 hrs or until 36 wks corrected age, assessed by physiologic oxygen test.</td>
<td>Oximeter applied from day of birth until a minimum 36 wks PMA. If breathing room air without any form of respiratory assistance from 35 wks PMA onward, study oximetry discontinued at a 36 wks PMA. If receiving any form of respiratory assistance and/or oxygen therapy from 35 wks PMA onward study oximetry continues until 40 wks PMA. Study oximetry stopped at any time before 40 wks PMA if baby discharged home (with or without respiratory assistance and/or oxygen).</td>
</tr>
</tbody>
</table>
Effects of targeting lower versus higher arterial oxygen saturations on death or disability in preterm infants

Results:

• Five trials, which together enrolled 4965 infants, were eligible for inclusion.

• The investigators of these five trials had prospectively planned to combine their data as part of the NeOProM (Neonatal Oxygen Prospective Meta-analysis) Collaboration.
Target Ranges of Oxygen Saturation in Extremely Preterm Infants

SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network

SUPPORT TRIAL

Median Oxygen Saturation with Oxygen Supplementation in the Low Target and High Target Groups

OXYGEN SATURATION TARGETS AND OUTCOMES IN EXTREMELY PREMATURE INFANTS

OUTCOME OF INFANTS IN THE SUPPORT TRIAL

RR 0.90 (0.76 to 1.06)
RR 0.52 (0.37 to 0.73) RR 1.27 (1.01 to 1.60)

9% 18% 20% 16% 28% 32%

SUPPORT NEJM 2010
OUTCOME OF INFANTS IN THE SUPPORT TRIAL: DEVELOPMENTAL FOLLOW UP

RR 1.12 (0.94 to 1.32)

RR 0.87 (0.60 to 1.28)

9.5% 10.5%

30.2% 27.5%

SUPPORT TRIAL PAS 2012
Effects of targeting lower versus higher arterial oxygen saturations on death or disability in preterm infants

Effect on Death or Major Disability to 18 to 24 months

Typical RR 1.04 (95% CI 0.98 to 1.10)
Effects of targeting lower versus higher arterial oxygen saturations on death or disability in preterm infants

Effect on Death to 18 to 24 months

Typical RR 1.16 (95% CI 1.03 to 1.31)

Typical RD 0.03 (95% CI 0.01 to 0.05)
Effects of targeting lower versus higher arterial oxygen saturations on death or disability in preterm infants

Effect on Major Disability to 18 to 24 months

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Lower oxygen saturation</th>
<th>Higher oxygen saturation</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events  Total</td>
<td>Events  Total</td>
<td>Weight</td>
</tr>
<tr>
<td>Vaucher 2012</td>
<td>223       473</td>
<td>250       456</td>
<td>506    33.5%</td>
</tr>
<tr>
<td>Schmidt 2013</td>
<td>201       488</td>
<td>195       489</td>
<td>489    26.4%</td>
</tr>
<tr>
<td>BOOST NZ 2014</td>
<td>40        142</td>
<td>49        141</td>
<td>141    6.7%</td>
</tr>
<tr>
<td>BOOST-II UK 2016</td>
<td>123       351</td>
<td>122       370</td>
<td>370    16.1%</td>
</tr>
<tr>
<td>BOOST-II Australia 2016</td>
<td>147       449</td>
<td>130       458</td>
<td>458    17.4%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>734       1903</td>
<td>752       1964</td>
<td>1964   100.0%</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 5.13, df = 4 (P = 0.27); I² = 22%
Test for overall effect Z = 0.25 (P = 0.80)

Typical RR 1.01 (95% CI 0.93 to 1.09)
Effects of targeting lower versus higher arterial oxygen saturations on death or disability in preterm infants

Effect on Severe Retinopathy of Prematurity

Typical RR 0.72 (95% CI 0.61 to 0.85)

Typical RD -0.04 (95% CI -0.06 to -0.02)
Effects of targeting lower versus higher arterial oxygen saturations on death or disability in preterm infants

Effect on Necrotizing Enterocolitis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Lower oxygen saturation</th>
<th>Higher oxygen saturation</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Vaucher 2012</td>
<td>76</td>
<td>641</td>
<td>70</td>
<td>649</td>
</tr>
<tr>
<td>Schmidt 2013</td>
<td>74</td>
<td>602</td>
<td>56</td>
<td>599</td>
</tr>
<tr>
<td>BOOST NZ 2014</td>
<td>15</td>
<td>170</td>
<td>12</td>
<td>170</td>
</tr>
<tr>
<td>BOOST-II UK 2016</td>
<td>71</td>
<td>484</td>
<td>52</td>
<td>480</td>
</tr>
<tr>
<td>BOOST-II Australia 2015</td>
<td>41</td>
<td>567</td>
<td>33</td>
<td>567</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>2464</td>
<td></td>
<td>2465</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Total events 277 223
Heterogeneity: $\chi^2 = 0.98, \text{df} = 4 (P = 0.91); P = 0%$
Test for overall effect $Z = 2.55 (P = 0.01)$

Typical RR 1.24 (95% CI 1.05 to 1.47)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Lower oxygen saturation</th>
<th>Higher oxygen saturation</th>
<th>Risk Difference M-H, Fixed, 95% CI</th>
<th>Risk Difference M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
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<tr>
<td>Vaucher 2012</td>
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<td>484</td>
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<tr>
<td>BOOST-II Australia 2015</td>
<td>41</td>
<td>567</td>
<td>33</td>
<td>567</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>2464</td>
<td></td>
<td>2465</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Total events 277 223
Heterogeneity: $\chi^2 = 1.47, \text{df} = 4 (P = 0.83); P = 0%$
Test for overall effect $Z = 2.56 (P = 0.01)$

Typical RD 0.02 (95% CI 0.01 to 0.04)
Effects of targeting lower versus higher arterial oxygen saturations on death or disability in preterm infants

**Author’s Conclusions:**

In extremely preterm infants, targeting lower (85% to 89%) SpO₂ compared to higher (91% to 95%) SpO₂ had no significant effect on the composite outcome of death or major disability or on major disability alone, including blindness, but increased the average risk of mortality by 28 per 1000 infants treated.

The trade-offs between the benefits and harms of the different oxygen saturation target ranges may need to be assessed within local settings (e.g. alarm limit settings, staffing, baseline outcome risks) when deciding on oxygen saturation targeting policies.
Effects of targeting lower versus higher arterial oxygen saturations on death or disability in preterm infants

<table>
<thead>
<tr>
<th>Outcome of concern</th>
<th>Appropriate choice of saturation range (SpO₂)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite outcome of death or major disability</td>
<td>lower (85% to 89%) or higher (91% to 95%)</td>
</tr>
<tr>
<td>Death</td>
<td>higher (91% to 95%)</td>
</tr>
<tr>
<td>Retinopathy of Prematurity</td>
<td>lower (85% to 89%)</td>
</tr>
<tr>
<td>Necrotizing Enterocolitis</td>
<td>higher (91% to 95%)</td>
</tr>
</tbody>
</table>
Death, Severe ROP and NEC in the Vermont Oxford Network 2005-16

% of VLBW (All centres)

Death, Severe ROP and NEC in the Vermont Oxford Network 2005-16

Courtesy of Ben Stenson, MD
Vermont Oxford Network, unpublished data used by permission
Hitting our targets is easier said than done!
VON Day Oxygen Monitoring Audit
Spot Oxygen Saturation
Infants on Oxygen and Respiratory Support
(N = 697 Infants)

Median spot saturation 94% (1st quartile 91%, 3rd quartile 97%)
What’s missing from this discussion?
Mean proportion of time in specified oxygen saturation range

Sink. Arch Dis Child Fetal Neonatal Ed. 2011
Compliance with alarm limits for pulse oximetry in very preterm infants

Dependent on:

Staff knowledge of unit policies and guidelines
Nurse / patient ratio
Patient acuity
Patient age
Trials have now shown us the appropriate range to maintain oxygen saturation.

Maintaining appropriate oxygen saturation is a complex task that includes oxygen targets, alarm settings and staff response and unit culture.
MORE ON OXYGEN!

SUPPLEMENTAL THERAPEUTIC OXYGEN FOR PRETHRESHOLD ROP

Eligibility Criteria

• Preterm infants screened for ROP
• Prethreshold ROP in at least one eye
• Median pulse oximetry saturation < 94%

The STOP-ROP Multicenter Study Group 2000
SUPPLEMENTAL THERAPEUTIC OXYGEN FOR PRETHRESHOLD ROP

Intervention

• Continuous pulse oximetry monitoring
• Conventional arm: maintain oxygen saturation 89-94%
• Supplemental arm: maintain oxygen saturation 96-99%

The STOP-ROP Multicenter Study Group 2000
SUPPLEMENTAL THERAPEUTIC OXYGEN FOR PRETHRESHOLD ROP

PROGRESSION TO THRESHOLD

- 41% SUPPLEMENTAL OXYGEN
- 48% CONVENTIONAL MANAGEMENT

The STOP-ROP Multicenter Study Group 2000
SUPPLEMENTAL THERAPEUTIC OXYGEN FOR PRETHRESHOLD ROP

SUBGROUP ANALYSIS: INFANTS WITH PLUS DISEASE PROGRESSION TO THRESHOLD

PROGRESSION TO THRESHOLD

<table>
<thead>
<tr>
<th>% CASES</th>
<th>SUPPLEMENTAL OXYGEN</th>
<th>CONVENTIONAL MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>32%</td>
<td>46%</td>
</tr>
</tbody>
</table>

The STOP-ROP Multicenter Study Group 2000
SUPPLEMENTAL THERAPEUTIC OXYGEN FOR PRETHRESHOLD ROP
PNEUMONIA/EXACERBATION OF CHRONIC LUNG DISEASE

The STOP-ROP Multicenter Study Group 2000
Moving on from oxygen,
How else can we prevent or treat ROP?
LIGHT REDUCTION IN PREVENTING RETINOPATHY OF PREMATURITY

Glass and coworkers 1985

investigated effect of exposure to light in two intensive care nurseries

• standard bright nursery environment
• reduced light level environment

Effect of bright light in the Hospital Nursery on Retinopathy of Prematurity 1985
Effect of bright light in the Hospital Nursery on Retinopathy of Prematurity 1985

LIGHT REDUCTION IN PREVENTING RETINOPATHY OF PREMATURITY

RETINOPATHY OF PREMATURITY

Effect of bright light in the Hospital Nursery on Retinopathy of Prematurity 1985
Early light reduction for preventing retinopathy of prematurity in very low birth weight infants

Early light reduction for preventing retinopathy of prematurity in very low birth weight infants

Seiberth 1994: 169 infants of less than 1501 grams birth weight from one nursery were enrolled and then randomized to no patching or patching of both eyes from the day of birth until 35 weeks’ postmenstrual age.

Braz 2006: 226 infants of less than 1600 grams birth weight or < 32 weeks’ gestation were enrolled and randomized. In the experimental group, patching of both eyes began on the day of birth and continued until 35 weeks’ postmenstrual age.

Kennedy 1997: 71 infants weighing 1250 grams or less, or of gestational age 32 weeks or less, were enrolled and randomized at 0 to 6 hours after birth to wearing goggles until 31 weeks’ postmenstrual age.

Reynolds 1998: 409 infants of less than 31 weeks’ gestation and less than 1251 grams birth weight were randomized to wearing goggles or control. The goggles were placed on the infant within 24 hours of birth, reducing light by 97% (100% of ultraviolet) and were continued until the infant was 31 weeks’ postmenstrual age or four weeks chronological age, whichever occurred later.
Early light reduction for preventing retinopathy of prematurity in very low birth weight infants

Effect on Any Retinopathy of Prematurity in infants < 2001 grams

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Treatment Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Braze 2006</td>
<td>44</td>
<td>95</td>
<td>43</td>
<td>93</td>
<td>21.6%</td>
<td>1.00 [0.74, 1.36]</td>
</tr>
<tr>
<td>Kennedy 1997</td>
<td>7</td>
<td>24</td>
<td>8</td>
<td>26</td>
<td>3.8%</td>
<td>0.95 [0.41, 2.22]</td>
</tr>
<tr>
<td>Reynolds 1993</td>
<td>130</td>
<td>188</td>
<td>121</td>
<td>173</td>
<td>62.5%</td>
<td>0.99 [0.85, 1.14]</td>
</tr>
<tr>
<td>Seibepath 1994</td>
<td>26</td>
<td>62</td>
<td>25</td>
<td>65</td>
<td>12.1%</td>
<td>1.09 [0.71, 1.67]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>369</strong></td>
<td><strong>357</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td><strong>1.00 [0.89, 1.13]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 207
Heterogeneity: $\chi^2 = 0.21$, df = 3 ($P = 0.98$); $I^2 = 0$
Test for overall effect $Z = 0.04$ ($P = 0.97$)

Effect on “poor” Retinopathy of Prematurity outcomes in infants < 2001 grams

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Treatment Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reynolds 1993</td>
<td>9</td>
<td>188</td>
<td>9</td>
<td>173</td>
<td>95.0%</td>
<td>0.92 [0.37, 2.28]</td>
</tr>
<tr>
<td>Seibepath 1994</td>
<td>2</td>
<td>62</td>
<td>0</td>
<td>65</td>
<td>5.0%</td>
<td>5.24 [0.26, 106.98]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>250</strong></td>
<td><strong>238</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td><strong>1.13 [0.49, 2.61]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 11
Heterogeneity: $\chi^2 = 1.20$, df = 1 ($P = 0.27$); $I^2 = 16$
Test for overall effect $Z = 0.30$ ($P = 0.77$)

EFECT OF ANTI OXIDANT THERAPY ON RETINOPATHY OF PREMATURITY

OVERVIEW OF RANDOMIZED CONTROLLED TRIALS

<table>
<thead>
<tr>
<th>INTERVENTION (# STUDIES)</th>
<th>Typical Risk Difference (95% CI)</th>
<th>Decreased 0.2</th>
<th>0.5</th>
<th>Risk 1.0</th>
<th>Increased 2.0</th>
<th>4.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>VITAMIN A (3)</td>
<td>-0.14 (-0.27, -0.01)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VITAMIN E (7)</td>
<td>-0.02 (-0.07, 0.02)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUPEROXIDE DISMUTASE (2)</td>
<td>-0.03 (-0.14, 0.07)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D-PENICILLAMINE (3)</td>
<td>-0.04 (-0.12, 0.04)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

COCHRANE NEONATAL REVIEW GROUP
Beta-blockers for prevention and treatment of retinopathy of prematurity in preterm infants

Beta-blockers for prevention and treatment of retinopathy of prematurity in preterm infants

Background: The use of beta-adrenergic blocking agents (beta-blockers), which modulate the vasoproliferative retinal process, may reduce the progression of ROP or even restore established ROP.

Objectives: To determine the effect of beta-blockers on short-term structural outcomes, long-term functional outcomes, and the need for additional treatment, when used either as prophylaxis in preterm infants without ROP, stage 1 ROP (zone I), or stage 2 ROP (zone II) without plus disease or as treatment in preterm infants with at least prethreshold ROP.
Beta-blockers for prevention and treatment of retinopathy of prematurity in preterm infants

Three studies incorporating a total of 366 preterm infants met inclusion criteria of this review (Filippi 2013; Korkmaz 2017; Sanghvi 2017).

These trials were conducted as ROP prevention trials and included preterm infants diagnosed with ≤ stage 2 ROP without plus disease (Filippi 2013; Korkmaz 2017) or preterm neonates in whom ROP was not assessed at enrolment but very unlikely to be present as they were < 8 days old (Sanghvi 2017).

Of the three included trials, two trials were placebo-controlled (Korkmaz 2017; Sanghvi 2017), while the third trial compared beta-blocker administration to no treatment (Filippi 2013).
**Beta-blockers for prevention and treatment of retinopathy of prematurity in preterm infants**

**Effect on use or retinal ablation surgery**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Beta-blocker Events</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2.1 Primary prophylaxis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sanghvi 2017</td>
<td>11</td>
<td>55</td>
<td>16</td>
<td>54</td>
<td>46.5%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>11</td>
<td></td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.15 (P = 0.25)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 1.2.2 Secondary prophylaxis | | | | | |
| Filippi 2013 | 4 | 26 | 10 | 26 | 28.8% | 0.40 [0.14, 1.11] |
| Korkmaz 2017 | 4 | 110 | 8 | 95 | 24.7% | 0.43 [0.13, 1.39] |
| Subtotal (95% CI) | | | | | | 0.41 [0.19, 0.90] |
| Total events | 8 | | 18 | | | |
| Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0% |
| Test for overall effect: Z = 2.23 (P = 0.03) |

| Total (95% CI) | 191 | 175 | 100.0% | 0.54 [0.32, 0.89] |
| Total events | 19 | | 34 | | |
| Heterogeneity: Chi² = 0.90, df = 2 (P = 0.64); I² = 0% |
| Test for overall effect: Z = 2.43 (P = 0.02) |
| Test for subgroup differences: Chi² = 0.87, df = 1 (P = 0.35); I² = 0% |

**Typical RR 0.54 (95% CI 0.32 to 0.89)**
Beta-blockers for prevention and treatment of retinopathy of prematurity in preterm infants

Effect on use or retinal ablation surgery

Typical RD -0.09 (95% CI -0.16 to -0.02)
Beta-blockers for prevention and treatment of retinopathy of prematurity in preterm infants

Effect on progression to stage 3 ROP

Typical RR 0.60 (95% CI 0.37 to 0.96)
Beta-blockers for prevention and treatment of retinopathy of prematurity in preterm infants

Effect on progression to stage 3 ROP

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Favours beta-blockers</th>
<th>Favours control</th>
<th>Risk Difference M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>1.4.1 Primary prophylaxis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sanghvi 2017</td>
<td>9</td>
<td>55</td>
<td>12</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td></td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.78 (P = 0.44)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1.4.2 Secondary prophylaxis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Favours beta-blockers</th>
<th>Favours control</th>
<th>Risk Difference M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Filippi 2013</td>
<td>9</td>
<td>26</td>
<td>18</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td></td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.66 (P = 0.008)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Total (95% CI) |     |      |      |      |       |                                    |
| Events         | 18  | 30    |      |      | 100.0%| -0.15 [-0.28, -0.02]               |
| Heterogeneity: Chi² = 3.76, df = 1 (P = 0.05); I² = 73% |
| Test for overall effect: Z = 2.29 (P = 0.02) |
| Test for subgroup differences: Chi² = 3.66, df = 1 (P = 0.06), I² = 72.7% |

Typical RD -0.15 (95% CI -0.28 to -0.02)
Beta-blockers for prevention and treatment of retinopathy of prematurity in preterm infants

Concern and impression regarding other important clinical outcomes

<table>
<thead>
<tr>
<th>Outcome (# studies)</th>
<th>Typical RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension (3)</td>
<td>7.00 (0.38 to 129.11)</td>
</tr>
<tr>
<td>Bronchopulmonary Dysplasia (2)</td>
<td>1.14 (0.75 to 1.73)</td>
</tr>
<tr>
<td>Necrotizing Enterocolitis (2)</td>
<td>2.45 (0.50 to 12.11)</td>
</tr>
<tr>
<td>Mortality (2)</td>
<td>0.99 (0.30 to 3.29)</td>
</tr>
</tbody>
</table>
Beta-blockers for prevention and treatment of retinopathy of prematurity in preterm infants

**Authors' conclusions:** Limited evidence of low to moderate quality suggests that prophylactic administration of oral beta-blockers might reduce progression towards stage 3 ROP and decrease the need of anti-VEGF agents or laser therapy.

The clinical relevance of those findings is unclear as no data on long-term visual impairment were reported.

Adverse events attributed to oral propranolol at a dose of 2 mg/kg/d raise concerns regarding systemic administration of this drug for prevention of ROP at the given dose.
Background: Inositol is an essential nutrient required by human cells in culture for growth and survival. Inositol promotes maturation of several components of surfactant and may play a critical role in fetal and early neonatal life.

Objectives: To assess the effectiveness and safety of supplementary inositol in preterm infants with or without respiratory distress syndrome (RDS) in reducing adverse neonatal outcomes.

Results: Four published RCTs and one ongoing RCT were identified
Inositol in preterm infants at risk for or having respiratory distress syndrome

Effect on Neonatal Mortality

Typical RR 0.49 (95% CI 0.29 to 0.82)

Typical RD -0.09 (95% CI -0.16 to -0.03)
Inositol in preterm infants at risk for or having respiratory distress syndrome

Effect on Retinopathy of Prematurity Stage $\geq 3$

**Typical RR 0.09 (95% CI 0.01 to 0.67)**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Favours inositol</th>
<th>Control</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Friedman 1995</td>
<td>0</td>
<td>20</td>
<td>3</td>
<td>21</td>
<td>0.15 [0.01, 2.73]</td>
</tr>
<tr>
<td>Hallman 1992</td>
<td>0</td>
<td>114</td>
<td>7</td>
<td>107</td>
<td>0.06 [0.00, 1.08]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>0</strong></td>
<td><strong>134</strong></td>
<td><strong>128</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.09 [0.01, 0.67]</strong></td>
</tr>
</tbody>
</table>

Total events: 0

Heterogeneity: $\chi^2 = 0.18$, df = 1 ($P = 0.67$); $I^2 = 0$

Test for overall effect: $Z = 2.35$ ($P = 0.02$)

**Typical RD -0.08 (95% CI -0.13 to -0.03)**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Favours inositol</th>
<th>Control</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Difference M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Friedman 1995</td>
<td>0</td>
<td>20</td>
<td>3</td>
<td>21</td>
<td>-0.14 [-0.31, 0.02]</td>
</tr>
<tr>
<td>Hallman 1992</td>
<td>0</td>
<td>114</td>
<td>7</td>
<td>107</td>
<td>-0.07 [-0.11, -0.02]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>0</strong></td>
<td><strong>134</strong></td>
<td><strong>128</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>-0.08 [-0.13, -0.03]</strong></td>
</tr>
</tbody>
</table>

Total events: 0

Heterogeneity: $\chi^2 = 0.82$, df = 1 ($P = 0.39$); $I^2 = 0$

Test for overall effect: $Z = 3.03$ ($P = 0.002$)
NICHD Neonatal Research Network Inositol Trial
Concerning preliminary reports

Objective: To test the safety and efficacy of inositol to improve survival without severe ROP, defined as Type 1 ROP, in very preterm infants.

Design/Methods: We conducted a randomized, placebo controlled trial of Inositol (INS) in preterm infants.

18 centers of the NICHD Neonatal Research Network conducted a randomized controlled trial of 5% inositol given daily to infants < 28 weeks’ gestation until 10 weeks chronologic age, 34 weeks’ postmenstrual age, or discharge.

Preliminary results: The Data Safety Monitoring Committee ultimately recommended cessation of the trial for a safety concern, unrelated to the manufacturing issue after enrollment of 638 infants.

The unfavorable outcome of Type 1 ROP or death prior to ROP determination was 21% in the placebo group, and 29% in the INS group, p<0.01.

Late onset sepsis was more common in the INS group (26%, vs 20% in placebo), although the difference was not statistically significant (p=0.06). Other diagnoses including BPD and severe IVH, adverse events, and serious adverse events occurred at similar rates in the two groups.

Conclusion(s): Daily inositol at 80mg/kg/day for up to 10 weeks did not benefit infants < 28 weeks’ gestation, and may be harmful for extremely preterm infants. The biologic mechanism for these findings is unknown.
Treatment of Retinopathy of Prematurity
Peripheral retinal ablation for threshold retinopathy of prematurity in preterm infants

MULTICENTER TRIAL OF CRYOTHERAPY

- Infants weighing less than 1251 grams
- Ophthalmologic examinations to begin at 4-6 weeks of age
- Repeated every two weeks until “prethreshold”
- Repeated weekly until “threshold”

Cryotherapy for Retinopathy of Prematurity Cooperative Group 1988
MULTICENTER TRIAL OF CRYOTHERAPY

“threshold” disease
at least five contiguous or eight cumulative 30
degree sectors of stage 3 ROP in zone 1 or 2 in
the presence of plus disease

Cryotherapy for Retinopathy of Prematurity Cooperative Group 1988
Randomization

• “symmetric”: both eyes meet threshold
  one eye randomly assigned to treatment
• “asymmetric”: one eye met threshold
  randomize worst eye
MULTICENTER TRIAL OF CRYOTHERAPY

Cryotherapy for Retinopathy of Prematurity Cooperative Group 1988
MULTICENTER TRIAL OF CRYOTHERAPY

Unfavorable outcome

• a retinal fold involving the macula
• retinal detachment involving zone 1
• retrolental tissue or “mass”

Cryotherapy for Retinopathy of Prematurity Cooperative Group 1988
MULTICENTER TRIAL OF CRYOTHERAPY

UNFAVORABLE OUTCOME

Cryotherapy for Retinopathy of Prematurity Cooperative Group 1988
COMPLICATIONS OF CRYOTHERAPY

Intraoperative ocular complications

• conjunctival hematoma 10%
• conjunctival hemorrhage 5%

Systemic complications

• bradycardia/arrhythmia 9%
• cyanosis 2%

Cryotherapy for Retinopathy of Prematurity Cooperative Group 1988
LASER PHOTOCOAGULATION VS. CRYOTHERAPY FOR THRESHOLD ROP

VISUAL ACUITY

• Follow up at ten years of age
• Good outcome defined as 20/50 or better
• Odds ratio for “good outcome”: 5.2 (95% CI 1.4, 19.8)

NG and coworkers Ophthalmology 2002: 928-934
EARLY TREATMENT FOR RETINOPATHY OF PREMATURITY TRIAL

UNFAVORABLE OUTCOME

Retinopathy of Prematurity (ROP) Surgery

VERMONT OXFORD NETWORK ANNUAL REPORTS 2000-2016
ANTI VEGF IN THE TREATMENT OF RETINOPATHY OF PREMATURITY
Anti-vascular endothelial growth factor (VEGF) drugs for treatment of retinopathy of prematurity

Figure 2. Enrollment, Randomization, and Follow-up of the 150 Study Infants.
Anti-vascular endothelial growth factor (VEGF) drugs for treatment of retinopathy of prematurity

Structural outcome: partial or complete retinal detachment

Anti-vascular endothelial growth factor (VEGF) drugs for treatment of retinopathy of prematurity

Recurrence of ROP

Data from the Canadian Neonatal Network demonstrated 3.1 times higher odds (95% CI 1.2 to 8.4) in infants (gestation less than 29 weeks) treated with bevacizumab versus laser, after adjusting for key confounders like gestation, gender, maternal education, Score for Neonatal Acute Physiology-II (SNAP-II) score, bronchopulmonary dysplasia, sepsis, and severe brain injury further underscore the importance of evaluating long-term safety outcomes following anti-VEGF therapy.

Anti-vascular endothelial growth factor (VEGF) drugs for treatment of retinopathy of prematurity

“Given the potential risk of systemic absorption and consequent adverse effects like cerebrovascular accidents following intravitreal anti-VEGF therapy, the lack of evidence on safety outcomes is a major concern”.

Scanning the Horizon
Emerging Evidence for Prevention and Treatment of ROP
ClinicalTrials.gov

• “Retinopathy of Prematurity”
• 92 trials with ROP as primary or secondary outcome
  • Registered but not yet enrolling
  • Enrolling
  • Closed to enrollment but actively following
1. Oxygen Saturation Targeting: Effects of Closed-loop Automatic Control of FiO2 in Extremely Preterm Infants

- Open treatment RCT
- Projected Enrollment: 2340, Estimated completion December 2022
- Eligible: Gestational age 23+0/7 - 27+6/7 weeks
- Intervention: closed-loop automatic control of the inspiratory fraction of oxygen vs standard care
- Outcomes: mortality; ROP and other in-hospital morbidities; 24-month outcomes

NCT03168516
2. Growth Factor Biologicals: Bevacizumab, Ranibizumab, IGF-1

- 6 trials
- Intravitreal bevacizumab vs laser for severe ROP (BEAT-ROP trial) – visual acuity follow-up continues through 7 years
- Phase 3 ranibizumab vs laser for severe ROP
- Non-inferiority studies of lower dose bevacizumab intravitreal for treatment of ROP Type 1
- Observational studies of serum VEGF levels
- IGF-1/IGFBP3 Prevention of ROP - follow up
- *New data will address current safety concerns regarding anti-VEGF monoclonal Ab therapy*
RAINBOW Study: Ranibizumab Compared With Laser Therapy for Treatment of ROP

- Phase 3 treatment study, Active/Not enrolling
- Randomized open label, 86 sites
- Enrollment: 220
- Eligible: Birth weight < 1500 grams with severe ROP (Zone I, stage 1+, 2+, 3 or 3+ disease, or Zone II, stage 3+ disease, or Aggressive posterior ROP)
- Intervention: intravitreal ranibizumab 0.2 mg, 0.1 mg, or laser
- Outcome: No active ROP or unfavorable structural outcome 24 weeks after starting investigational treatment; many secondary outcomes

NCT02375971
Phase 1 Trial of Bevacizumab Treatment for Severe ROP

- **Purpose:** to find an effective dose of intravitreal bevacizumab that is lower than currently used, and can be tested in future larger studies.
- **Single-group assignment, 10 sites; Enrollment: 110**
- **Eligible:** Infants with Type 1 ROP
- **Intervention:** intravitreal bevacizumab in de-escalating doses
- **Outcome:** improvement by 4-day exam and no recurrence requiring additional treatment within 4 weeks of injection in 80% of participants at that dose.

NCT02390531
3. Nutritional Supplements

• 5 trials
• DHA vs placebo for ROP prevention
• Correlation of RBC omega-3 PUFAs and subsequent ROP severity
• Arachidonic acid/DHA supplementation vs placebo for ROP prevention
• Vitamin A for ROP prevention
Enteral Administration of Docosahexaenoic Acid to Prevent Retinopathy of Prematurity

• Rationale: DHA comprises 40% of the PUFAs in the brain and 60% in the retina
• Phase 2 prevention study, Mexico
• Projected enrollment: 100
• Eligible: Birth weight < 1500 grams
• Intervention: Docosahexenoic acid vs placebo enterally once daily x 14 days
• Outcome: Incidence and severity of ROP through 42-45 weeks corrected age

NCT02683317
4. Erythropoietin

• 2 trials
• Influence of erythropoietin and early iron supplements on ROP prevalence and severity
• Recombinant erythropoietin for neuroprotection in very preterm infants
5. Propranolol

- Rationale: beta-blockers may reduce retinal expression of VEGF and IGF-1 through blockade of beta-adrenoreceptors
- 4 trials - China, Germany, Italy
- Phase 2 studies to prevent progression of moderate ROP
- Projected enrollment 100-276
- Enteral; topical ophthalmic
Prospective Cohort Study for Propranolol Treatment in Retinopathy of Prematurity

- Phase 2 treatment study, Not yet enrolling
- Randomized masked controlled; China
- Enrollment: 100
- Eligible: Birth weight < 1500 grams with stage 1 or 2 ROP without plus
- Intervention: oral propranolol 0.25 mg/kg/day vs propranolol ophthalmic drops vs placebo (NS)
- Outcome: progression of ROP; safety; 12-month visual and developmental outcomes

NCT03038295
6. Retinal Exams

- 2 trials
- RCT oral paracetamol combined with local anesthetics for pain relief during retinal exam
- Comparison of pain using two eyelid retractors
7. Topical ophthalmic NSAIDs: Kerotolac, ibuprofen

- 2 trials
- Single-center RCT of kerotolac vs placebo for ROP prevention
- RCT Synergy of caffeine + ibuprofen + kerotolac for ROP prevention
8. ROP As A Secondary Outcome

- Many trials
- Thyroxine
- Delivery room resuscitation with room air versus FiO2
- Prevention of BPD
- Smartphone screening for eye diseases
- Probiotics
- Feeding approaches during transfusion
Summary:

- Many trials underway examining ROP as a primary or secondary outcome
- Exciting prospects for new evidence to guide prevention and treatment of ROP
Scanning the Horizon
Emerging Evidence for Prevention and Treatment of ROP
Characteristics of infants with severe retinopathy of prematurity in countries with low, moderate, and high levels of development: implications for screening programs.


OBJECTIVE:

The proportion of blindness as a result of ROP varies greatly among countries depending on their level of development, being influenced by the availability of neonatal care, neonatal outcomes, and whether effective screening and treatment programs are in place.

The objective of this study was to compare characteristics of premature infants who developed severe ROP between 1996 and 2002 in highly developed countries with less developed countries.

METHODS:

This was an observational study. A questionnaire was completed by ophthalmologists in countries with low, moderate, and high development rankings (3 highly developed countries and from 10 less well-developed countries) who screen for ROP in which they supplied birth weights and gestational ages (GAs) of infants who were treated for threshold ROP or identified with more advanced stages of the disease. Birth weights and GAs of infants with severe ROP were measured.

Box plots of birth weights of infants reported with severe ROP from 13 countries with varying levels of development.

Box plots of gestational ages of infants reported with severe ROP from 13 countries with varying levels of development.
CONCLUSIONS:

These findings suggest that larger, more mature infants are developing severe ROP in countries with low/moderate levels of development compared with highly developed countries. ROP screening programs need to use criteria that are appropriate for their local population.

Limited ability to prevent Retinopathy of Prematurity

Effective: Appropriate Oxygen Restriction and Monitoring
Ineffective: Vitamin E, Superoxide dismutase, Light reduction
Jury still out: Vitamin A, Inositol, B blockers

Treatment of pre-threshold ROP

Effective: Retinal ablation surgery
Ineffective: Supplemental oxygen in evolving ROP
Jury still out: Anti VEGF Therapy
Questions/Discussion?
Housekeeping details!

CME credit?

https://neonatal.cochrane.org/december-2017-continuing-medical-education-credit-and-nursing-contact-hour-credit

Next web seminar?

Making the GRADE: Understanding the strength of the evidence

Late winter 2018