Oxygen Management in the Delivery Room and NICU – How Much is Enough?

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Learning Objectives

1. Understand recent research and recommendations regarding the use of oxygen for resuscitation of infants at birth
2. Understand the importance of oxygen in the development and evolution of retinopathy of prematurity
3. Relate this understanding to practical guidelines for the use of oxygen in the NICU

Disclosure

I have no actual or potential conflict of interest in relation to this program

Discovery of Oxygen

The Importance of Timely Publication

- Joseph Priestley
  - Credited with discovering oxygen in 1774 (published in 1775)
- Carl Scheele
  - Claimed to have discovered oxygen in 1772
  - Described his discovery in a letter to Lavoisier in 1774
  - Submitted for scientific publication 1775, published 1777
- Antoine Lavoisier
  - Claimed to have independently discovered oxygen after hearing from both Scheele and Priestley about their discoveries
  - First to correctly explain combustion – named it “oxygen”

Oxygen Use in the Delivery Room

- Until a few years ago, delivery room resuscitation areas did not have oxygen-air blenders
- It was assumed that any infant needing oxygen should receive 100% oxygen
- In the past decade, researchers have begun to reexamine this assumption

Air or Oxygen for Resuscitation of Full-Term Infants at Birth: Review of the Evidence

- Three systematic reviews with meta-analysis
  - Saugstad et al. Biol Neonate 2005; 87:27
  - Tan et al. Cochrane Database Syst Rev 2005
- All show lower mortality with air resuscitation compared with 100% oxygen
- No difference in hypoxic-ischemic encephalopathy
- >25% of air infants required oxygen “rescue”
Meta-analysis by Rabi et al (Resuscitation 2007)

Air or Oxygen for Resuscitation of Full-Term Infants at Birth: Review of the Evidence

- There is insufficient information on long-term neurodevelopmental outcome of survivors
- There is insufficient evidence comparing restoration of circulation in severely depressed infants (animal studies show circulation recovers better in 100% oxygen)
- What about preterm infants?

- There is insufficient evidence comparing restoration of circulation in severely depressed infants

Air or Oxygen for Resuscitation of Preterm Infants at Birth: Review of the Evidence

- Preterm infants resuscitated in room air remain hypoxemic longer than term infants
- All preterm infants resuscitated in air had oxygen saturation <70% at 3 minutes (mean 55%) and so received additional "rescue" oxygen
- Infants <30 weeks GA resuscitated in air had median oxygen saturation 54% at 5 minutes

Recommendations for Oxygen Use During Resuscitation at Birth

- Monitor oxygen saturation continuously with pulse oximeter
- Target saturation based on data from healthy term infants at sea level

<table>
<thead>
<tr>
<th>Age</th>
<th>Oxygen Saturation Target</th>
<th>Oxygen Saturation Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 min</td>
<td>&gt; 60%</td>
<td>4 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 75%</td>
</tr>
<tr>
<td>2 min</td>
<td>&gt; 65%</td>
<td>5 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 80%</td>
</tr>
<tr>
<td>3 min</td>
<td>&gt; 70%</td>
<td>10 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 85%</td>
</tr>
</tbody>
</table>

Recommendations for Oxygen Use During Resuscitation at Birth

- Begin with 50% oxygen
- Adjust oxygen concentration based on oxygen saturation
- If you have no blender, begin with room air
- If you have no oximeter, increase oxygen concentration if central cyanosis persists beyond 5 minutes
- If heart rate <60 after 90 seconds of resuscitation, increase to 100% oxygen

1. Joy R. Arch Dis Child 2010; 95:68
Oxygen Use in the NICU

Oxygen and ROP

- In 1942
  - Wilson et al (Detroit) discovered that oxygen reduced periodic breathing in premature infants
  - Smith et al (Boston) found that some infants without cyanosis had low blood oxygen saturation
- Liberal oxygen use began

Appearance of ROP

- First reported in 1942 by Terry (Boston)
- From 1942 to 1945, Terry collected 117 cases
- Called retrolental fibroplasia (RLF)

The Oxygen Hypothesis

- Proposed by Dr. Kate Campbell (Melbourne) in 1951
- Theory derived from several facts
  - Liberal oxygen use and ROP were both more common in U.S. than U.K. until 1948
  - ROP increased in U.K. after 1948
    - National Health Service started in 1948
    - Incubators required to deliver oxygen became available

Role of Oxygen in ROP

- Pathogenesis of ROP
  - Hyperoxia
  - Downregulation of VEGF
  - Arrest of vascular development and vasoconstriction
  - Retinal tissue hypoxia
  - Upregulation of VEGF
  - Neovascular proliferation

Clinical Trials of Liberal or Restrictive Use of Oxygen

- Lanman et al. *JAMA* 1954
- All showed more frequent ROP with liberal use of oxygen for premature infants
Unintended Consequences of Oxygen Restriction

- Restrictive oxygen use was widely adopted
- Increased mortality among infants with RDS (Avery & Oppenheimer)
- Increased spastic diplegia, especially among centers restricting oxygen most vigorously (McDonald)

<table>
<thead>
<tr>
<th>Oxygen use</th>
<th>Spastic diplegia</th>
<th>ROP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Least</td>
<td>17%</td>
<td>9%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>16%</td>
<td>10%</td>
</tr>
<tr>
<td>Most</td>
<td>6%</td>
<td>22%</td>
</tr>
</tbody>
</table>

McDonald AD. Arch Dis Child 1963; 38:579

Balancing Oxygen Deficiency and Excess – Giving Just the Right Amount

- Since the 1970s, efforts have been made to provide sufficient oxygen to meet the body’s metabolic needs while avoiding the excessive amounts that are toxic to the eye (and other organs)

Impact of Strict Guidelines for Oximeter Alarms and FiO2 Adjustment

New guidelines for oximeter alarm limits and adjusting FiO2 introduced in 1998 at Cedars-Sinai Medical Center

Propective Randomized Trials of O2 Management: Recent and Pending

- Completed
  - Benefits Of Oxygen Saturation Targeting (BOOST) trial
  - SUPPORT (SUPlantant, Positive airway pressure, Pulse Oximetry Randomized Trial)
- In progress
  - BOOST II

Can Oxygen Monitoring Reduce ROP? Retrospective Analysis

Oxygen saturation target range (physician discretion) and ROP in infants < 28 weeks

<table>
<thead>
<tr>
<th>Oxygen Saturation Target</th>
<th>Threshold ROP (%; 95% CI)</th>
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<tbody>
<tr>
<td>70-90%</td>
<td>6 (2-15)</td>
</tr>
<tr>
<td>88-98%</td>
<td>28 (17-40)</td>
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Oxygen Management and the Prevention of ROP
BOOST Trial
- Multicenter, double-blind randomized trial
- 358 infants < 30 weeks gestation who still required O₂ at 32 weeks postmenstrual age
- Randomized between 2 ranges of O₂ sat
  - Standard: 91.94% (oximeter shows 93-96%)
  - High: 95.98% (oximeter shows 93-96%)
- Primary outcome
  - No difference in growth or 12-month neurodevelopmental outcome
- Other outcomes
  - No difference in ROP (any stage)
  - High-saturation group required more oxygen


BOOST II Trial (in progress)
- Multicenter, double-blind randomized trial
- Infants < 28 weeks enrolled in first 24 hours
- Randomized between 2 ranges of O₂ sat
  - Low 85-89% (oximeter shows 88-92%)
  - High 91-95% (oximeter shows 88-92%)
  - True sat displayed when below 85% or above 95%
- Primary outcome: Death or major disability at 2 years corrected age
- Sample size: 1200 infants (30/08/10, n=870)
- BOOST-NZ: Companion trial, same design

SUPPORT
- Multicenter RCT – NICHD Neonatal Research Network
- Infant <28 weeks, enrolled before birth, n=1316
- 2 x 2 factorial design
  - Early CPAP and permissive ventilation vs early surfactant and standard ventilation
  - Low vs high oxygen saturation target range (same as BOOST II)
    - Low 85-89% (oximeter shows 88-92%)
    - High 91-95% (oximeter shows 88-92%)
    - True saturation displayed when below 85% or above 95%


SUPPORT 2 x 2 Factorial Design

<table>
<thead>
<tr>
<th>Low oxygen saturation target range (85-89%)</th>
<th>High oxygen saturation target range (91-95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early CPAP and permissive ventilation n=336</td>
<td>n=327</td>
</tr>
<tr>
<td>Early surfactant and standard ventilation   n=318</td>
<td>n=335</td>
</tr>
</tbody>
</table>

SUPPORT Comparison 1: Early CPAP and permissive ventilation vs early surfactant and standard ventilation
- Primary outcome: Death or BPD – no difference
- Secondary outcomes:
  - Death Not significant
  - BPD Not significant
  - NEC Not significant
  - Severe IVH (gr 3 or 4) Not significant
  - Severe ROP Not significant
  - Postnatal steroids for BPD Lower with CPAP, 7 vs 13%
### SUPPORT Comparison 2: Low vs high oxygen saturation target range

- **Primary outcome:** Death or severe ROP = threshold, surgical treatment, or bevacizumab (Avastin) – *no difference*
- **Secondary outcomes:**
  - Death before discharge: Higher with low SO2, 20 vs 16%
  - Severe ROP: Lower with low SO2, 9 vs 18%
  - BPD: Lower with low SO2, 38 vs 47%
  - Severe IVH (gr 3 or 4): Not significant
  - NEC: Not significant

### SUPPORT: Low vs High Oxygen Saturation Target Range

- **Severe ROP or death before discharge**
  - Low 28%, high 32%
  - Adjusted relative risk 0.90 (0.76-1.06)
- **Severe ROP**
  - Low 9%, high 18%
  - Adjusted relative risk 0.52 (0.37-0.73)
- **Death before discharge**
  - Low 20%, high 16%
  - Adjusted relative risk 1.27 (1.01-1.60)

### Cochrane Review: Restricted versus Liberal Oxygen Exposure

- Four studies published 1952-1973, one in 2003
- Oxygen restriction reduces ROP risk without increasing mortality
- “The question of what is the optimal target range for maintaining blood oxygen levels in preterm/LBW infants was not answered by the data available for inclusion in this review”
- Next update will include SUPPORT and, hopefully, BOOST II

### Other Risk Factors for ROP

- Extremely short gestation
- Hypoxemic episodes
  - Di Fiore et al. *J Pediatr* 2010;157:69
- Poor fetal and neonatal growth
  - ROP is associated with low IGF-1 levels
  - IGF-1 treatment reduces oxygen-induced retinopathy in neonatal mice*
  - Improved nutrition helps prevent ROP in animals and humans


### Role of Nutrition in ROP

- Single-center case-control study
- 77 AGA infants with BW 700-1000 g
- 11 with severe ROP (requiring surgery), 66 controls
- Infants with severe ROP had received
  - Less human milk (other studies have had mixed results)
  - Less vitamin E (vitamin E deficiency has long been known to increase risk of ROP)

### Oxygen Management and the Treatment of ROP

*Porcelli & Weaver. Early Hum Dev 2010; 86:391*
STOP-ROP Trial

- Animal evidence and clinical observation were consistent with the theory that the vasoproliferative phase of ROP is mediated by deficient retinal oxygen delivery
- Multicenter randomized trial
- 649 preterm infants with prethreshold ROP randomized between two O₂ sat ranges
  - Low 89-94%
  - High 96-99%


STOP-ROP Trial

- High saturation group was less likely to progress to threshold, 41 vs 48% (P = 0.032, 1-tailed, but fell short of target 0.025)
- Among infants without plus disease, effect greater, 46 vs 32% (P = 0.004)
- Trend toward more episodes of pulmonary exacerbation with higher sats (P = 0.066)
- Number needed to treat
  - 13.7 to cause 1 pulmonary exacerbation
  - 13.2 to prevent 1 case of threshold ROP

High or Low Target Oxygen Saturation: The Importance of Postmenstrual Age

- Systematic review and meta-analysis examining the association of severe ROP with high or low target oxygen saturation
  - Low SO₂ in the first few weeks of life reduces risk of severe ROP
  - High SO₂ after 32 weeks PMA reduces the risk of progression to severe ROP

Chen et al. Pediatrics 2010;125:e1483

Oxygen Management and ROP
Overall: Treatment & Management

- Oxygen is an important factor in the pathogenesis of ROP
  - Too much oxygen in the early phase is bad
  - Too little oxygen in the later phase is bad
- SUPPORT is the first prospective clinical trial showing that targeting lower oxygen saturation can reduce severe ROP, but at the cost of higher mortality
- More evidence is on the way
  - SUPPORT follow-up at 18-22 months corrected age
  - BOOST II results expected in late 2011

Developed by J. M. Klein

Iowa NICU Oximeter Protocol for Preterm Infants

<table>
<thead>
<tr>
<th>Postmenstrual age</th>
<th>Alarm limits</th>
<th>Target range</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 28 weeks</td>
<td>80-93%</td>
<td>84-89%</td>
</tr>
<tr>
<td>29-31 weeks</td>
<td>80-95%</td>
<td>86-92%</td>
</tr>
<tr>
<td>≥ 32 weeks</td>
<td>85-98%</td>
<td>88-95%</td>
</tr>
</tbody>
</table>

Developed by J. M. Klein
Prevention of ROP

- Oxygen is just one modifiable risk factor, although an important one
- Avoiding fluctuation in oxygen saturation (apnea-hypoxemia spells) is important
- Good nutrition helps
  - Maybe someday there will be a role for growth factors
- Extreme prematurity is still the greatest risk factor for ROP

Treatment of ROP

- Reduce risk of progression by maintaining higher oxygen saturation (\( >90\% \)) after 32 weeks postmenstrual age, especially if ROP is present
- For severe cases
  - Laser photocoagulation
  - Maybe angiogenesis inhibition (bevacizumab, i.e. Avastin)