Title of Program: Oxygen in the Delivery Room: Evidence from Systematic Reviews
Speakers/Moderators: Roger F. Soll, MD, Neil Finer, MD, William Tarnow-Mordi, FRCPCH
Planning Committee: Jeffery D. Horbar, MD, Madge E. Buus-Frank, RN, MS, APRN-BC, FAAN, Roger F. Soll, MD
Date: March 10, 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 use of supplemental oxygen during the resuscitation of term and preterm infants 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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· Chat feature - questions anytime
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· Questioner unmuted during Q&A

Use the raised hand icon to queue up for questions

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

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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.

Oxygen in the Delivery Room: Evidence from Systematic Reviews

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 use of oxygen in the delivery room.
Resuscitation of Newborn Infants with 21% or 100% Oxygen: An Updated Systematic Review and Meta-Analysis

Saugstad O.D., Ramji S., Soll R.E., Vento M.

Methods: Randomized or quasi-randomized studies of depressed newborn infants resuscitated with 21% or 100% O2 with or without masking of treatment were considered for inclusion.

Results: Ten studies fulfilled the inclusion criteria. Of these, 6 studies were identified as being strictly randomized. In total, 1,082 infants were allocated to resuscitation with 21% O2 and 1,051 infants with 100% O2. The risk of neonatal mortality was reduced in the 21% O2 group compared to the 100% O2 group both in the analysis of all studies (typical RR 0.69, 95% CI 0.54, 0.88) and in the analysis of strictly randomized studies (typical RR 0.32, 95% CI 0.12, 0.84). A trend toward a decrease in the risk of hypoxic ischemic encephalopathy stage 2 and 3 was noted with resuscitation in 21% O2 in the analysis of all studies (typical RR 0.88, 95% CI 0.72, 1.08).

Saugstad 2010

Room Air vs. 100% Oxygen for Delivery Room Stabilization of Term Neonates

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>N</th>
<th>Evaluation criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ram (1992)</td>
<td>quasi-random</td>
<td>84</td>
<td>Birth weight &gt; 1,500 grams with apnea, HR &lt; 80 bpm, or both</td>
</tr>
<tr>
<td>Saugstad (1998)</td>
<td>quasi-random</td>
<td>430</td>
<td>Birth weight &gt; 1,500 grams, apnea or gasping, HR &lt; 100 bpm, or both</td>
</tr>
<tr>
<td>Banks (2001)</td>
<td>random</td>
<td>44</td>
<td>Term infants with hypoxia, unresponsive to stimulation, HR &lt; 100 bpm, and pH &lt; 7.05. Birth weight &gt; 1,500 grams</td>
</tr>
<tr>
<td>Wang (2002)</td>
<td>quasi-random</td>
<td>435</td>
<td>Birth weight &gt; 1,500 grams, HR &lt; 130 bpm, apnea, or both, and unresponsive to stimulation</td>
</tr>
<tr>
<td>Bae (2003)</td>
<td>quasi-random</td>
<td>104</td>
<td>Birth weight 1,500 grams or more with apnea or gasping respiration and/or from mothers with a birth weight &gt; 3000 grams, requiring positive pressure ventilation after delivery</td>
</tr>
<tr>
<td>Wechs (2004)</td>
<td>random</td>
<td>39</td>
<td>Severe asphyxiated term neonates. Severe asphyxia was defined as prior to 30 minutes of the delivery &lt; 100* baseline HR, corresponding to SCD, a cord pH of 7.0 or less at birth, and an Apgar score of 5 or less for more than 5 min</td>
</tr>
<tr>
<td>Vento (2006)</td>
<td>random</td>
<td>54</td>
<td>Term infants with HR &lt; 100 bpm, apnea</td>
</tr>
<tr>
<td>Vento (2008)</td>
<td>random</td>
<td>44</td>
<td>Gest &gt; 37 weeks with HR &lt; 100 bpm, apnea</td>
</tr>
<tr>
<td>Vento (2007)</td>
<td>random</td>
<td>56</td>
<td>Term infants with HR &lt; 100 bpm, apnea</td>
</tr>
</tbody>
</table>

Neonatology 2008;94:176–182 (DOI:10.1159/000143197)
Air/Oxygen: Term babies.

In term infants receiving respiratory support at birth with positive pressure ventilation (PPV), it is best to begin with air (21%) as opposed to 100% oxygen.

If, despite effective ventilation, there is no increase in heart rate or oxygenation (guided by oximetry wherever possible) remains unacceptable, use a higher concentration of oxygen to achieve an adequate preductal oxygen saturation.

High concentrations of oxygen are associated with an increased mortality and delay in time of onset of spontaneous breathing, therefore, if increased oxygen concentrations are used they should be weaned as soon as possible.


We lack real evidence that room air resuscitation is safe for term infants....
Evidence for use of oxygen in infants receiving cardiac compressions...

Oxygen Delivery During CPR (Neonatal) - Intervention (NRP 738)

In neonates receiving cardiac compressions (P), does 100% O2 as the ventilation gas (I), compared with lower concentrations of oxygen (C), increase survival rates, improve neurologic outcomes, decrease time to ROSC, or decrease oxidative injury (O)?


Oxygen in the Delivery Room: Evidence in Term Infants


Oxygen Delivery During CPR (Neonatal) - Intervention (NRP 738)

Neonatal resuscitation has historically focused on achieving adequate oxygenation as quickly as possible. Recently, it has been recognized that excessive oxygen administration can be toxic.

Current guidelines recommend starting resuscitation with low inspired oxygen and then increasing inspired oxygen as necessary as guided by pulse oximetry. However, once the resuscitation has reached the need for chest compressions, it has been suggested to increase the Fio2.

Treatment Recommendation

There are no human data to inform this question.

Despite animal evidence showing no advantage to the use of 100% oxygen, by the time resuscitation of a newborn baby has reached the stage of chest compressions, the steps of trying to achieve ROSC using effective ventilation with low-concentration oxygen should have been attempted. Thus, it would seem prudent to try increasing the supplementary oxygen concentration (Good Practice Guidance).

If used, supplementary oxygen should be weaned as soon as the heart rate has recovered (weak recommendation, very-low-quality evidence).

Oxygen Concentration for Resuscitating Premature Newborns - Intervention (NRP 864)

Among preterm newborns (less than 37 weeks of gestation) who receive PPV in the delivery room (P), does the use of high O2 (50% to 100%) as the ventilation gas (I), compared with low concentrations of O2 (21% to 30%) (C), decrease mortality, decrease bronchopulmonary dysplasia, decrease retinopathy, decrease IVH (O)?


Preterm resuscitation with low oxygen causes less oxidative stress, inflammation, and chronic lung disease.


Biomarkers of oxidative stress in the low vs. high oxygen group

Vento. Pediatrics 2009

Association of oxidative stress markers with BPD

Vento. Pediatrics 2009
Systematic review and meta-analysis of optimal initial fraction of oxygen levels in the delivery room at ≤ 32 weeks.

Saugstad OD, Aune D, Agar M, Kapadia V, Fisher N, Verno M.

AIM: The optimal initial fraction of oxygen (FiO2) for resuscitating/stabilizing premature infants is not known. We aimed to study currently available information and provide guidelines regarding the FiO2 levels needed to resuscitate/stabilize premature infants of ≤ 32 weeks' gestation.

METHODS: Our systematic review and meta-analysis studied the effects of low and high FiO2 during the resuscitation/stabilization of 677 newborn babies ≤ 32 weeks' gestation.

RESULTS: Ten randomized studies were identified covering 321 infants receiving low (0.21-0.30) FiO2 levels and 356 receiving high (0.60-1.0) levels. Relative risk for mortality was 0.62 (95% CI: 0.37-1.04, I² = 0%, p(heterogeneity) = 0.88) for low versus high FiO2; for bronchopulmonary dysplasia, it was 1.11 (95% CI: 0.75-1.64, I² = 46%, p(heterogeneity) = 0.06); and for intraventricular hemorrhage, it was 0.90 (95% CI: 0.53-1.53, I² = 9%, p(heterogeneity) = 0.36).

CONCLUSION: These data show that reduced mortality approached significance when a low FiO2 (0.21-0.30) was used for initial stabilization, compared to a high FiO2 (0.60-1.0). There was no significant association for bronchopulmonary dysplasia or intraventricular hemorrhage when comparing low and high FiO2. Based on present data, premature babies ≤ 32 weeks' gestation in need of stabilization in the delivery room should be given an FiO2 of 0.21-0.30.


Lower (0.21 to 0.30) vs. Higher (0.60 to 1.00) Oxygen Concentration for Delivery Room Stabilization of Preterm Neonates ≤ 32 weeks

Effect on Mortality

Typical risk ratio 0.62, 95% CI 0.37 to 1.04


Targeted Oxygen in the Resuscitation of Preterm Infants, a Randomized Clinical Trial

Ju-Lee Oei, Ola D. Saugstad, Kie Law, Ian M. Wright, John P. Smyth, Paul Curson, Yeeping Alex Wong, Roshena McMullan, Elizabeth Cueto, Merrilyth Ward, Parag Mora, Koen De Wael, Jawed Tariq, Bows Ching Soo, Irene G.H. Chok, Chen Lin Tsai, Yee Mun Ooi, A亚太 Ahmad Kamar, Fook Chye Chok, Ahmad Masoud, William Tarnow-Mordi

BACKGROUND AND OBJECTIVES: Lower concentrations of oxygen (O2)(≤ 30%) are recommended for preterm resuscitation to avoid oxidative injury and cerebral ischemia. Effects on long-term outcomes are uncertain. We aimed to determine the effects of using room air (RA) or 100% O2 on the combined risk of death and disability at 2 years in infants <32 weeks’ gestation.

METHODS: A randomized, unmasked study designed to determine major disability and death at 2 years in infants <32 weeks’ gestation after delivery room resuscitation was initiated with either RA or 100% O2 and which were adjusted to target pulse oximetry of 65% to 95% at 5 minutes and 85% to 95% until NICU admission.
Targeted Oxygen in the Resuscitation of Preterm Infants, a Randomized Clinical Trial

RESULTS: Of 6291 eligible patients, 292 were recruited and 287 (mean gestation: 28.9 weeks) were included in the analysis (RA: n = 144; 100% O2: n = 143). Recruitment ceased in June 2014, per the recommendations of the Data and Safety Monitoring Committee owing to loss of equipoise for the use of 100% O2. In non-prespecified analyses, infants < 28 weeks who received RA resuscitation had higher hospital mortality (RA: 10 of 46 [22%]; than those given 100% O2: 3 of 54 [6%]; risk ratio: 3.9 [95% confidence interval: 1.1–13.4; P = .01]. Respiratory failure was the most common cause of death (n = 13).

CONCLUSIONS: Using RA to initiate resuscitation was associated with an increased risk of death in infants < 28 weeks’ gestation. This study was not a prespecified analysis, and it was underpowered to address this post hoc hypothesis reliably. Additional data are needed.


Higher or lower oxygen for delivery room resuscitation of preterm infants below 28 completed weeks gestation: a meta-analysis

Objective: To systematically review outcomes of infants ≤ 28+6 weeks gestation randomized to resuscitation with low (≤ 0.3) vs high (≥ 0.6) fraction of inspired oxygen (FiO2) at delivery.

Design: Systematic review of randomized controlled trials of low (≤ 0.3) vs high (≥ 0.6) FiO2 resuscitation. Information was obtained from databases (Medline/Pub Med, EMBASE, ClinicalTrials.gov, Cochrane) and meeting abstracts between 1990 to 2015. Search index terms: preterm/resuscitation/oxygen. Data for infants ≤ 28+6 weeks gestation were independently extracted and pooled using a random effects model. Analyses were performed with Revman V.5.

Main outcome measures: Death in hospital, bronchopulmonary dysplasia (BPD), retinopathy of prematurity > stage 3 (ROP), intraventricular hemorrhage > grade 2 (IVH), patent ductus arteriosus (PDA) and necrotizing enterocolitis (NEC).

Results: A total of 251 and 253 infants were enrolled in 8 studies (6 masked, 2 unmasked) in the lower and higher oxygen groups, respectively, (mean gestation 26 weeks) between 2005 and 2014. There were no differences in BPD (relative risk, 95% CIs 0.88 (0.68 to 1.14)), IVH (0.81 (0.52 to 1.27)), ROP (0.82 (0.46 to 1.46)), PDA (0.95 (0.80 to 1.14)) and NEC (1.81 (0.85 to 3.78)) and overall mortality (0.99 (0.52 to 1.91)). Mortality was lower in low oxygen arms of masked studies (0.46 (0.23 to 0.92), p=0.03) and higher in low oxygen arms of unmasked studies (1.94 (1.02 to 3.68), p=0.04).

Conclusions: There is no difference in the overall risk of death or other common preterm morbidities after resuscitation is initiated at delivery with lower (≤ 0.30) or higher (≥ 0.60) FiO2 in infants ≤ 28+6 weeks’ gestation. The opposing results for masked and unmasked trials may represent a Type I error, emphasizing the need for larger welldesigned studies.

Oxygen in the Delivery Room: Evidence in Preterm Infants

Meta Analysis

Low vs Higher Oxygen in DR – Mortality

Infants < 28 weeks

Typical risk ratio 0.73, 95% CI 0.44 to 1.22
Lower versus higher oxygen concentrations titrated to target oxygen saturations during resuscitation of preterm infants at birth.
Lui K, Foster JP, Osborn DA, Jones LJ, Davis PG, Oei JL, Ching SK.

Survival and Neurodevelopmental Outcomes of Preterms Resuscitated With Different Oxygen Fractions

RESULTS: A total of 253 infants were recruited and 206 (81.4%) completed follow-up. No differences in perinatal characteristics, oxidative stress, or morbidities during the neonatal period were assessed. Mortality at hospital discharge or when follow-up was completed didn’t show differences between the groups. No differences regarding Bayley-III scale scores (motor, cognitive, and language composites), neurosensorial handicaps, cerebral palsy, or language skills between groups were found.
Survival and Neurodevelopmental Outcomes of Preterm Infants Resuscitated With Different Oxygen Fractions

Overall Rates of Disabilities in Preterm Infants Resuscitated with an Initial FiO2 of 0.3 (Lowox) vs. 0.6 to 0.65 (Hiox) At 24 month corrected age

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lowox Total, %</th>
<th>Highox Total, %</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disability</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No disability</td>
<td>67 (27.5)</td>
<td>68 (21.8)</td>
<td>1.17 (0.69-2.00)</td>
<td>.54</td>
</tr>
<tr>
<td>Mild</td>
<td>14 (5.7)</td>
<td>16 (5.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>6 (2.7)</td>
<td>7 (2.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>2 (0.8)</td>
<td>3 (1.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


In 2006 most NICUs in Canada introduced room air resuscitation for babies at term and changed their practice for preterm babies – previously 100% O2, to either starting in 21% or at some intermediate concentration i.e. 40%.

Reviewed CNN database for babies between 23 and 27 weeks gestation.

Evaluat ed occurrence of death or a severe brain injury (grade 3 or 4 IVH or PVL), for the 2 years up to their change in practice, and for 2 years after following 1 year washout

Clinicians in 25 countries prefer to use lower levels of oxygen to resuscitate preterm infants at birth


AIM: This study determined current international clinical practice and opinions regarding initial fractional inspired oxygen (FiO2) and pulse oximetry (SpO2) targets for delivery room resuscitation of preterm infants of less than 29 weeks of gestation.

METHODS: An online survey was disseminated to neonatal clinicians via established professional clinical networks using a web-based survey program between March 9 and June 30, 2015.

RESULTS: Of the 630 responses from 25 countries, 60% were from neonatologists. The majority (77%) would target SpO2 between the 10th to 50th percentile values for full-term infants. The median starting FiO2 was 0.3, with Japan using the highest (0.4) and the UK using the lowest (0.21). New Zealand targeted the highest SpO2 percentiles (median 50%).

CONCLUSION: Clinicians currently favor lower SpO2 targets for preterm resuscitation, despite acknowledging the lack of evidence for benefit or harm, and 65% would join a clinical trial.


Oxygen Concentration for Resuscitating Premature Newborns - Intervention (NRP 864)

Knowledge Gaps

The most appropriate time-specific oxygen targets for premature newborns need to be defined.

Neurodevelopmental outcomes for preterm newborns resuscitated with low- and high-oxygen concentrations need to be determined.

Knowledge Gaps

- Do preterm infants meet SpO2 targets in:
  1. Randomized controlled trials
  2. Guidelines
- What happens to babies who do not reach SpO2 targets?
- No studies comparing outcomes using different targets!!

Achievement of Target SpO2 during Resuscitation – Oei et al. – EAPS 2017

Hypothesis

- Preterm babies (regardless of starting FiO2) who do not reach SpO2 80% at 5 minutes of age are at an increased risk of death and/or major intraventricular hemorrhage (IVH)

Oei et al. Achievement of Target SpO2

- Individual patient data from 8 randomized controlled studies of lower (≤ 30%) vs. higher (≥ 60%) oxygen for preterm infants resuscitation
- Infants categorized according to 5 min SpO2 readings as:
  - Met goal saturation (80 to 85%)
  - Did not reach (< 80%)
  - Overshot (> 85%)

### Studies

<table>
<thead>
<tr>
<th>Year</th>
<th>Low FiO2</th>
<th>High FiO2</th>
<th>Masked</th>
<th>5 min SpO2 Targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang</td>
<td>2005</td>
<td>21%</td>
<td>100%</td>
<td>No</td>
</tr>
<tr>
<td>21%</td>
<td>100%</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escrig</td>
<td>2005</td>
<td>30%</td>
<td>60%</td>
<td>No</td>
</tr>
<tr>
<td>75</td>
<td>75</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vento</td>
<td>2007</td>
<td>30%</td>
<td>30%</td>
<td>No</td>
</tr>
<tr>
<td>75</td>
<td>75</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kapadia</td>
<td>2010</td>
<td>21%</td>
<td>100%</td>
<td>No</td>
</tr>
<tr>
<td>80-85</td>
<td>80-85</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rook</td>
<td>2008</td>
<td>30%</td>
<td>65%</td>
<td>No</td>
</tr>
<tr>
<td>88-94</td>
<td>88-94</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oei</td>
<td>2009</td>
<td>21%</td>
<td>100%</td>
<td>No</td>
</tr>
<tr>
<td>80-85</td>
<td>80-85</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rabi</td>
<td>2005</td>
<td>21%</td>
<td>100%</td>
<td>Yes</td>
</tr>
<tr>
<td>85-92</td>
<td>85-92</td>
<td></td>
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</tr>
</tbody>
</table>

### Patient Demographics

#### Trial Targets

<table>
<thead>
<tr>
<th><strong>Gestation</strong></th>
<th><strong>Did not meet</strong></th>
<th><strong>Met</strong></th>
<th><strong>Overshot</strong></th>
<th><strong>Total</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 29 weeks</td>
<td>28.0 (2.1)</td>
<td>138 (29%)</td>
<td>94 (29%)</td>
<td>486 (29%)</td>
</tr>
<tr>
<td>Masked study</td>
<td>21%</td>
<td>138 (29%)</td>
<td>94 (29%)</td>
<td>486 (29%)</td>
</tr>
<tr>
<td>30%</td>
<td>138 (29%)</td>
<td>94 (29%)</td>
<td>486 (29%)</td>
<td></td>
</tr>
<tr>
<td>60-65%</td>
<td>486 (29%)</td>
<td>94 (29%)</td>
<td>486 (29%)</td>
<td></td>
</tr>
<tr>
<td>90-100%</td>
<td>486 (29%)</td>
<td>94 (29%)</td>
<td>486 (29%)</td>
<td></td>
</tr>
</tbody>
</table>

*P<0.001
SpO\(_2\) in 1st 10 minutes – All Babies

- 21%
- 30%
- 60-65%
- 90-100%

>29 weeks

- 21%
- 30%
- 60-65%
- 90-100%

< 28 weeks

- 21%
- 30%
- 60-65%
- 90-100%

Outcomes of Babies Who Do Not Reach SpO\(_2\) 80% at 5 minutes

- OR 2.4 (1.3-4.4)
- OR 4.5 (2.1-9.8)

Time To Reach SpO\(_2\) 80% - Death

Time To Reach SpO\(_2\) 80% - IVH
**Does Lower SpO₂ Lead to Adverse Outcomes?**

Babies may not have met target SpO2 because:
1. Very sick
2. Given less oxygen
   - Similar outcomes noted in:
   - Retrospective review of Canadian infants – increased death and neurological morbidity after change in resuscitation policy from 100% oxygen to air/titrated oxygen
   - Torpido study – largest RCT showed that air was associated with OR 3.9 increased death compared to 100% oxygen for preterms < 29 weeks gestation
   - Data collected over long period
   - Each study had different methodologies

**Conclusions**

- Almost 50% of infants < 32 weeks do not reach SpO₂ study targets at 5 minutes of age
- Those who do not reach SpO₂ 80% by 5 minutes are at increased risk of death and IVH especially when compared to those who exceed the target
- Is the current 5 min target too Low??
- Do we need more oxygen initially??
- Larger well designed randomised controlled studies are needed to review current oxygen management strategies and outcomes!!
- These include studies of different target levels!!

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**Guest Discussant**

**William Tarnow-Mordi, BA, MBChB, MRCP (UK), DCH, FRCPCH**

Professor of Neonatal Medicine, Sydney Medical School
Director, Neonatal and Perinatal Trials, NHMRC Clinical Trials Centre

**Directions Forward?**

**Study question: SpO₂ targets or initial FiO₂?**

- Individual consent
- Cluster randomized trials
- Parent’s role in designing research

---

**Randomized trials of different oxygen saturation (SpO₂) targets for preterm infants at delivery**

1. We certainly need RCTs of survival or morbidity in infants assigned to lower vs higher ranges of oxygen saturation from birth to NICU admission
2. But first, we need reliable methods to target relatively narrow ranges of oxygen saturation, e.g. the 25th-50th vs the 75th-90th Dawson centile curves.
3. These methods will ensure minimal overlap between assigned target ranges, thus maximising study power.

**Cochrane Neonatal**

Randomized trials of different oxygen saturation (SpO₂) targets for preterm infants at delivery

Achieving Targeted Pulse Oximetry Values in Preterm Infants in the Delivery Room

Bheru Gandhi, MD, Wade Rich, RRT, and Neil Finer, MD.

The Transitional Oxygen Targeting System (TOTS) shows SpO₂ values against the 10th and 50th Dawson centile as a visual target.

Staff manually adjust FiO₂ guided by the real time TOTS display.

In a before-after cohort study, 20 infants spent 37% of the time within target before TOTS was introduced. 20 infants spent 52% of the time within target after TOTS was introduced (P=0.03).
In this study in 22 lambs, time in the target range (25th–75th Dawson centiles) did not differ significantly between manual (41.4%) or automated (44.3%) FiO\textsubscript{2} control during resuscitation. The authors suggested further trials to improve closed loop equipment.


A novel, rapidly responsive proportional-integral-derivative (PID) algorithm for automated oxygen control in 20 non-intubated infants. Automated control achieved 25% more time within target range than manual control [81% vs 56% manual, P<0.001]. The team plan to develop a rapidly adapting algorithm for automated oxygen control during resuscitation of preterm infants.


In this Cochrane Review of 15 RCTs in 738 infants, delaying clamping by 30 to 120 seconds improved four secondary outcomes (i) need for transfusion, (ii) BP, (iii) all grades of IVH and (iv) NEC. Data were insufficient for reliable conclusions about the primary outcomes: death, grade 3 or 4 IVH, periventricular leukomalacia.

The review was last assessed as up to date on 1 Nov 2011. If updated evidence supports delayed clamping of 30-120 sec, oxygen saturation readings may be delayed. This would make the choice of initial FiO\textsubscript{2} even more important.


The PROMOTION Project includes 2 RCTs in infants ≤ 28 weeks.

1. US TORPIDO2 is an individual patient RCT in ~ 3,000 infants
2. HILo is a crossover cluster RCT in up to 66 NICUs
3. Both, when completed, will be combined in a PROspective Meta analysis Of Trials of Initial Oxygen in preterm Newborns.
4. The PROMOTION Project will have > 80% power to show a 16% reduction in relative risk of death, from 12% to 12.6%.

The PROMOTION Project includes 2 RCTs in infants ≤ 28 weeks.

Study interventions and outcomes are identical in both RCTs.

Expressions of interest are invited in either study.

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US TORPIDO

2nd study of Targeted Oxygen in Respiratory care of Premature Infants at Delivery: effects on Outcome

- Funding:
  An application is being submitted to PCORI, the Patient Centered Outcomes Research Institute, Washington, DC for ~US$1,500 per patient to support local recruitment

- Expressions of interest:
  - To request more information or to lodge an expression of interest in joining the US TORPIDO2 study, contact: torpido2@ctc.usyd.edu.au

HiLo Crossover Cluster RCT of initial FiO2 0.6 vs 0.3 in infants ≤28* weeks

- Randomize NICUs 12 – 18 months 12 weeks changeover (no data capture) 12 – 18 months
  - FI02 0.6 → FI02 0.3
  - FI02 0.6 → FI02 0.3
  - FI02 0.6 → FI02 0.3
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  - FI02 0.3 → FI02 0.6
  - FI02 0.3 → FI02 0.6

HiLo Crossover Cluster RCT of initial FiO2 0.6 vs 0.3 in infants ≤28* weeks

- Funding:
  An application is being submitted to PCORI, the Patient Centered Outcomes Research Institute, Washington, DC for ~US$200 per patient to support local co-ordination

- Expressions of interest:
  - To request more information or to lodge an expression of interest in joining the HiLo Prem-Parent study contact: hilo@ctc.usyd.edu.au

Crossover cluster RCTs of low risk treatments in the delivery room can:

- Meet international criteria for opt out or waiver of consent
- Enrol representative samples, including infants at highest risk
- Reduce the burden of prior consent on parents and staff
- Recruit larger populations faster than individual patient RCTs
- Be conducted simultaneously with individual patient RCTs of other interventions, thus helping prevent “trial bottleneck”
- Halve the number of NICUs needed in a standard cluster RCT

Information for parents

Key points:
- 0.3 and 0.6 FiO2 are routinely used for prematurity resuscitation worldwide.
- Both levels of FiO2 are within standard care.
- There is no known additional risk for babies being in this study.
- Data are anonymous. No baby or family will ever be identified.
- The baby’s clinical need will always take precedence over the study. Babies needing more support will receive it, regardless of allocated group.
- A single Data and Safety Monitoring Committee will oversee both US TORPIDO2 and HiLO
- It will recommend early stopping if a clear result is beyond reasonable doubt in either study.
- Each study has been designed with advice from parents of previous premature infants.
- The committee running the trials have parents as part of the team.
- Parents helped write the leaflets for parents used by hospitals and have contributed to the overall design of the study.
Parents will be on every key committee

- No document will go forward until parents have approved it
- Groups of parents will be engaged in a sub-study, PACER (Parent Attitudes to Comparative Effectiveness Research)
- PACER will address parents’ preferences about approaches to consent, whether parents find study processes acceptable and which secondary outcomes they would like measured.

Questions/Discussion?

Housekeeping details!

CME credit?


Next web seminar?
Prevention of Intraventricular Hemorrhage: Evidence from systematic reviews
June 28th 2017