Safe use of oxygen in preterm infants

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Safe use of O2 in preterm infants – Key Points

• O2 is the commonest drug we give preterm infants – both too much and too little can cause harm

• Three phases of care (delivery / NICU / convalescence) may have different needs

• The optimal approach depends upon the resource setting

• Recent RCTs of O2 saturation targeting involved 5000 <28 wk infants in a high resource setting

• There are challenges in optimising SpO2 target compliance

• Prevention of ROP does not depend solely on O2 management – eg handling, pain control, temperature, sepsis all important
Oxygen is the commonest “drug” we give to preterm babies

We should be as careful with the amount of oxygen we give as with any other drug

MORE is NOT BETTER

*but also many dangers in too little*
Three phases of care for preterm infants

• Transition (labour ward)

• Acute phase of illness (first few weeks)

• Chronic phase of illness (recovery / c.32 weeks on)

In theory, at least, might need different oxygen saturation targets in these different phases
There are two ways of measuring oxygen in the baby

Oxygen tension (pO2) by a “blood gas” – arterial blood
(A capillary blood can give pH and pCO2 but not pO2)
(Transcutaneous oxygen estimates pO2)

Pulse oximeter / saturation monitor measures SaO2
This is non-invasive and continuous but beyond 95% the pO2 may be very high

The partial pressure (pO2) determines how much O2 gets to the tissues
Labour ward stabilisation – “the golden hour”

<37 weeks no resuscitation support

SpO2 75% at 4.2 mins; 90% at 6.5 mins

Figure 1. This figure represents idealized SpO₂ targets during the first 8 min of life for the VLBW infant. The information was adapted from the current literature.

Finer Pediatr Res 2009
Labour ward stabilisation – “the golden hour”

Avoid initial 100% oxygen

• ILCOR 2010 consensus (Circulation 2010;122: S516-S538)
"For preterm infants <32 weeks ..... initiation of resuscitation with 30% or 90% oxygen and titration to oxygen saturation" will be less likely to result in hyperoxaemia or hypoxia.

• ILCOR 2015 consensus (Circulation 2015; October 20: S204-S241)
"For preterm infants <35 weeks ..... Recommend initiation of resuscitation with 21% to 30% oxygen”

"If a blend of oxygen and air is not available......(start) with air"

If move to 100% O2 return to a lower FiO2 as soon as possible
NICU care

• Pre-1990s O2 therapy usually monitored by intermittent arterial sampling or continuous oxygen tension.

• Kinsey (1977) cohort study could not establish relationship between PaO$_2$ and ROP

• The AAP (1976 and 1988) recommended a PaO$_2$ target range of 50 to 80 mm Hg - EXPERT OPINION
NICU care

• In 1990s, oxygen saturation (SpO2) monitoring adopted – simple, non-invasive, fewer complications.

• A SpO$_2$ range of 90 - 95% often used but surveys showed high and low targets varied from 100% to 80%.

  Vijayakumar *J Perinatol* 1997

• 2007 the AAP endorsed 85-95% as “pragmatic”, whilst noting the optimal range unknown. EXPERT OPINION

• Early 2000s trend to use lower and lower sat targets (supported by observational studies) mainly to avoid BPD and ROP

**Primary Research Question:**
For infants <28 weeks gestation
Is a target SpO$_2$ 85-89% vs 91-95% associated with a lower rate of death or major disability at 2 yrs of age?

**Double-blind Randomised Controlled Trials**
Eligible infants <24 hours old
Intervention continued until 36 weeks equivalent (most trials)
The NeOProM Collaboration

*BMC Pediatr* 2011; 11: 6

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, the NeOProM Collaborative Group¹

US (SUPPORT) - 1300 - NICHD 1316 Published 2010/12
Can/Eur/S.Am (COT) - 1200 - CHIR 1200 Published 2013
NZ (BOOST-NZ) - 320 - HRC 340 Published 2013/14
Australia (BOOST-II) - 1200 - NHMRC 1130 Published 2013/16
UK (BOOST UK) - 1200 - MRC 973 Published 2013/16

Commenced 2005/07 By May 2011 – 4959 enrolled

**Primary outcome** estimated at 37% (25% mort; 12% disability) - 5,000 babies would have 80% power to detect 4% absolute difference in primary outcome
Effects of targeting higher versus lower arterial oxygen saturations on death or disability in preterm infants (Protocol)

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

23 July 2014  Completed Review under Cochrane editorial review Oct 2016
Cochrane Review

Death or major disability - (trialist defined)*

Study or Subgroup

- SUPPORT 2012
- COT 2013
- BOOST NZ 2014
- BOOST AUS 2016
- BOOST UK 2016

* SUPPORT BIII <70
Others <85; and
BOOST studies also
used surrogates

N=4751
RR=1.07 (1.00, 1.14)
I²=1%

Favors lower target  Favors higher target

Courtesy Davis PG – presented at PAS 2016
Cochrane Review
Death to 18-24 months

Study or Subgroup
- SUPPORT 2012
- COT 2013
- BOOST NZ 2014
- BOOST AUS 2016
- BOOST UK 2016

Risk Ratio
M-H, Fixed, 95% CI

N=4873
RR=1.16 (1.03, 1.31)
RD=0.03 (0.01, 0.05)
NNT=36
I²=0%

Favours lower target  Favours higher target

Courtesy Davis PG – presented at PAS 2016
Cochrane Review
Treated retinopathy of prematurity (aligned)

SUPPORT 2012
COT 2013
BOOST NZ 2014
BOOST UK 2016
BOOST AUS 2016

Risk Ratio
M-H, Fixed, 95% CI

Study or Subgroup

N=4089
RR=0.72 (0.61, 0.85)
RD=-0.04 (-0.06, -0.02)
NNH=24
I²=69%

All analyses High Grade except Treated ROP – Moderate because of heterogeneity

Courtesy Davis PG – presented at PAS 2016
**SUPPORT / BOOST-II / COT studies**

Rates of severe visual impairment/blindness were low and not different between groups in all five studies

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<th>85-89%</th>
<th>91-95%</th>
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# From retinal or unknown causes – revised oximeters only. When cortical blindness included figures are 3.15 and 3.5%

Vaucher *NEJM* 2012; Schmidt *JAMA* 2013; Darlow *J Pediatr* 2014;
BOOST II Aus and UK *NEJM* 2016
In Summary:

In extremely preterm infants, targeting SpO\textsubscript{2} 85-89\% vs 91-95\% had no significant effect on death or major disability, or major disability alone including blindness,

But

Increased the risk of mort by 28 of NEC by 23
Decreased risk of ROP R\textsubscript{x} by 40 per 1000 treated

**BUT** - <28 weeks, high resource setting, timely retinal examination and treatment available
Interpretation of evidence:

• All analyses/commentaries to date are based on interim data (Manja 2015 inappropriately down-graded evidence on this basis)

• Most suggest target 90-95% (Polin 2013; Bancalari 2013; Saugstad 2013)

• AAP – 90-95% may be safer for some (Cummings 2016)

• My view – 90-94% for <28 weeks in high resource setting (informed by Cochrane and NeOProM meta-analysis of 5000 infants)

• More mature infants in other settings may depend on resources – 88-92% remains reasonable but only EXPERT OPINION
Physiological stability and ROP

• Animal studies indicate that fluctuations in O2 may be a more important trigger of ROP than hyperoxia alone

• Human observational studies also show O2 fluctuations increase severe ROP risk (Saito 1993; Cunningham 1995; York 2004)

• Longer, more variable hypoxemic events associated with increased risk of severe ROP (Di Fiore 2010; 2013)
Physiological stability and ROP

- Need agreed protocols on SpO2 targets and agreed alarm settings – and what to do when alarms sound (eg Chow 2003)

- Pre-NeOProm observational study – better compliance when high alarm 1% above, low 1-2% below target (Hagadorn 2006)

- Nurse training and nurse:infant ratios affect compliance

- Avoid wide fluctuations in FiO2/SpO2 through better temperature control, avoid inappropriate handling, prevent painful episodes, prevent sepsis – hand washing / careful antibiotic use, encourage Kangaroo Care / Supportive care
Summary

• Careful oxygen administration – begins in Labour Ward

• Blenders, oxygen analysers and saturation monitors key equipment items

• Keep babies stable and reduce fluctuations in oxygen

• Have clear agreed protocols for O2 targets and response to alarms

• *My recommendation* after NeOProM family of studies reports
  – target SaO2 90%-94% (at least in VP infants in high resource setting)

• Optimise nurse infant ratios

• Prevention of ROP depends on adoption of evidence based care
Summary – low resource setting

• Use oximeters when can
• More important to use when baby unwell or being handled
• More important to use when baby in >30% oxygen
• Consider nasal cannula oxygen rather than headbox

Preterm babies almost never need 100% oxygen