Oxygen Saturation Targets in Premature Neonates: The Dilemma & The Debate

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September 23rd 2011

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Optimal Oxygen Saturations in the Newborn

- Oxygen is the most common therapy used in the newborn
- High inspired oxygen + Volutrauma = Bronchopulmonary dysplasia in Premature Infants

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Alveolar Stage - Proliferation (Mice: 4-14 days; Humans: 36W-2Yrs)

- Alveolar Simplification after 12 days of Hyperoxia Exposure in Mice
  
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Alveolar Expansion (Mice: 14-28 days; Humans: 2Yrs-Young Adult)
Persistence of alveolar simplification and distended airspaces in the Hyperoxia Group at 15 weeks

Kumar VH et al, Am J Respir Crit Care Med. 2010; 181:A1356

25 2/7 wks
40B g
5 hours old

Chest Radiograph Of Infant With Bronchopulmonary Dysplasia

Exposure To Supplemental Oxygen Increases Oxidative Stress And Downregulates Antioxidant Enzymes In Preterm Lambs


Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) and its interaction with the major anti-oxidant pathways in the lung: SOD (superoxide dismutase); GPx (glutathione peroxidase); CAT (catalase); GR (glutathione reductase); GSH (reduced glutathione); GSSG (oxidized glutathione); ONOOH (peroxynitrous acid); OH. (hydroxyl radical); NO (nitric oxide); NO2 (nitrite and nitrate)

2GSH
GSSG
GPx
GR

OH. + NO2

O2

Epithelial Cells
Endothelial Cells
Fibrosis

ONOOH
H2O

H2O2

Lipid / Protein / DNA Damage

NO

OH

ONOOH
Patients admitted to WCHOB NICU

Percent of infants ≤ 32 weeks with BPD (O2 at 36 weeks)

Average over last 6 years: 50%

Optimal Oxygen Saturations in the Newborn

- Hyperoxaemia = Retinopathy of Prematurity

Retinopathy of Prematurity

Stage 1  Stage 2  Stage 3

1942 – First case of ROP reported
1954 – Blinded 10,000 infants

Optimal Oxygen Saturations in the Newborn

- $\text{SpO}_2 < 90$ –
  - $\uparrow$ Pulmonary Vascular Resistance
  - May increase PDA
  - Impair survival / Neurodevelopment

- $\text{SpO}_2 > 90$ –
  - Severe Retinopathy of Prematurity (ROP)
  - Bronchopulmonary Dysplasia

- Many NICUs are adopting a lower $\text{SpO}_2$ policy

Oxygen & ROP: Some History in order!

Premature infants were restricted to < 40% O₂ in order to prevent ROP
Next 20 years – 150,000 premature infants died of hypoxic respiratory failure
For every infant whose sight was saved, 16 died and many developed spastic diplegia
What Are The Optimal Oxygen Saturations At Birth In Premature Infants?

Infants > 35 wks GA
No supplemental O2
No Assisted Ventilation
N = 115

Infants Delivered By C-section Had Lower Saturations Compared To Vaginal Delivery Infants

Infants > 37 wks GA
No Supplemental O2
No Assisted Ventilation
N = 104

Preductal Spo2 Higher Than Postductal Spo2 In The First 15 Minutes Of Life


Oxygen Saturations in Healthy Infants Immediately After Birth

Table I. Demographic data and times taken to apply sensor, signal processing, and time from birth to display the first data by gestational age

Oxygen Saturations in Healthy Infants Immediately After Birth

Table II. Comparison of Spo2 values at 15 min. after birth in healthy term infants

References Ranges for Oxygen Saturation for infants after birth

TABLE I Infant Characteristics

References Ranges for Oxygen Saturation for infants after birth


Relationship Between Oxygen Saturation And Mode Of Oxygen Delivery Used In Newborn Resuscitation

NRP 2010 Guidelines

- In the absence of studies comparing outcomes of neonatal resuscitation initiated with \( O_2 \) concentrations other than 21% or 100% \( O_2 \) or targeted at various oxyhemoglobin saturations, it is recommended that the goal in babies being resuscitated at birth, whether born at term or preterm, should be an \( \text{SpO}_2 \) value in the interquartile range of preductal saturations measured in healthy term babies following vaginal birth at sea level (Class IIb, LOE B).

Do Premature And Term Infants Need To Maintain Similar Oxygen Saturations At Birth?

Oxygenation During Fetal to Neonatal Transition

- Higher HbF; lower 2,3 DPG; lower P50
- Functioning fraction of 2,3 DPG levels lower compared to term
- Less oxygen unloading capacity initially compared to term (3 months)
- They have a higher level of \( \text{SaO}_2 \) at any given level of \( \text{PaO}_2 \)
Oxygen Saturations At Birth In Preterm Neonates

1 Min saturations – 45 to 48
5 Min – 85 ± 6

Wang CL et al, Pediatrics, 2008; 121: 1083-1089
If by 3 min SpO2 not > 70 - ↑ FiO2 to 50%
All infants in room air groups received oxygen by 3 minutes!

Oxygen Saturations At Birth In Preterm Neonates

Room Air Resuscitation Produces Significantly Lower Oxidative Stress At 24 Hours In Premature Infants < 32 Week Gestation

Clinical Study Of 21%, 40% And 100% Oxygen In Preterm Infants < 32 Weeks Gestation

Clinical Practice Guideline for the Use of Supplemental Oxygen in the Delivery Room

• For infants < 32 wks GA we use 40% O2 & for infants ≥ 32 wks GA we use 21% O2
  – When convenient, place oxygen saturation monitor: < 32 wks GA
  – If the infant requires PPV, place oxygen saturation monitor: ≥ 32 wks GA
  – Continue using 40% or 21% oxygen as long as saturations are steadily increasing. If after 5 minutes of age and saturations are not steadily rising, increase FiO2 by 10% every minute until saturations reach 85-95%. If saturations are >95%, decrease FiO2 by 10% every minute to target of 85-95%
  – SpO2 monitor: at birth
  – ? Practice NRP guidelines

Optimal Oxygen Saturations At Birth

Oximetry in Delivery Room –

• What is normoxia in the first 10 – 20 minutes of life?
• How to interpret and apply SpO2 readings to clinical practice to improve short-term and long-term outcomes in premature neonates
What are the ‘optimal’ Oxygen saturation Targets in Premature Infants admitted to the NICU?

- in the first 8 weeks of life?
- ≤ 32wks Gestational Age?

-Why is it important?

Oxygen and Retinopathy of Prematurity

High Saturations in first 8 weeks of life is Bad!

295 infants / 1990 - 94 / Retrospective

SpO2: 70 - 90 versus 88 - 98
first 8 wks

All Survivors

24 wks 28 wks 40 wks

High Saturation Group - Surgery for ROP 4 times higher; Ventilated longer; likely to be in O2 at 36 wk PMA; likely to have weight < 3rd centile at discharge

ADC. Tin W et al, 2001; 84: F106-F110

High and Low Saturation Targets and Severe ROP: A Meta Analysis

Chen ML, Guo L et al. Pediatrics, 2010; 125:e1483-e1492
High and Low Saturation Targets and Severe ROP: A Meta Analysis

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Support Trial* - Saturation Targets and ROP

1316 infants (2 x 2 factorial design) were randomly assigned to intubation/surfactant vs CPAP within 1 hour of birth. Infants were assigned to one of the two saturation targets: Low saturations versus high saturations.


Oxygen Saturation Targets in Preterm Infants < 32 wks GA

STUDY LOW HIGH
Wright (2006) 83-93 89-95
Wallace (2007) 90-96 98-100
Vanderveen (2006) 85-93 87-97
Tin (2001) 70-94 85-98
Deulofeut (2006) 85-93 92-100
Support (2010) 85-89 91-95

Adjust FiO2 - SpO2 of 88 – 95% - ≤ 32 wks GA (WCHOB)

NeOPrOM: Neonatal Oxygenation Prospective Meta-analysis Collaboration Study Protocol

• Objectives –
  - Does targeting saturation range in extremely preterm infants from birth or soon after, increase or decrease the composite outcome or death or major disability in survivors by 4% or more?

• Hypotheses –
  - Compared with a SpO2 level of 91 – 95%, targeting SpO2 of 85 – 89% within 24 hours of birth is associated with < 4% absolute risk difference from 42% to 46% or from 42% to 38% in mortality and major disability by 2 years corrected age.

Prospective meta-Analysis

Studies usually RCTs are identified, evaluated & determined to be eligible before the results of the included studies are known or published

The methodology can help avoid some of the potential biases inherent in standard, retrospective meta-analyses

NeOPrOM: Neonatal Oxygenation Prospective Meta-analysis Collaboration Study Protocol

• Until longer term survival and morbidity are known, we consider it prudent not to target SPO2 85-89%. This is not a standard of care, and could change when NeOPrOM reports disability-free survival by 2014.


High and Low Saturation Targets and Severe ROP: A Meta Analysis

Chen ML, Guo L et al. Pediatrics, 2010; 125:e1483-e1492

STOP-ROP*

Randomized 649 infants with PT-ROP whose RA saturations were < 94%
89 – 94 versus 96 - 99

Decreased odds of progression from Prethreshold-ROP to Threshold-ROP by 28% (OR = 0.72, 0.58-1.01) - borderline statistical significance
No plus disease: ↓ risk of progression from 46% to 32%; P=0.004
Also at 50 week PMA, more infants in the high saturation group remained hospitalized, on oxygen and on diuretics

*Supplemental Therapeutic Oxygen for Prethreshold ROP. NEJM, 2000; 105:295-310

What Are The Optimal Oxygen Saturations In Infants > 32 Weeks Gestational Age?

Chen ML, Guo L et al. Pediatrics, 2010; 125:e1483-e1492
STOP - ROP

- Pneumonia / CLD exacerbations post randomization – 13% in high saturation Grp vs 8.5% in standard Saturation grp (p = 0.07)

- 3 months corrected gestational age (50 wks PMA)
  - 96-99: 12.7% vs 6.7% p=0.012
  - Oxygen: 46.8% vs 37.3% p=0.02
  - Steroids: 14.2% vs 12.5%
  - Methylxanthines: 14.7% vs 13.5%
  - Diuretics: 35.8% vs 24.4% p=0.02

*Supplemental Therapeutic Oxygen for Prethreshold ROP. NEJM, 2000; 105:295-310

High Saturations At 32 wks PMA Does Not Confer Growth Benefit

Randomized 358 infants at 32 wks PMA
O2 saturations: 91 - 94 versus 95 - 98

- Remained hospitalized: 12.7% vs 6.7% p=0.012
- Oxygen: 46.8% vs 37.3% p=0.02
- Steroids: 14.2% vs 12.5%
- Methylxanthines: 14.7% vs 13.5%
- Diuretics: 35.8% vs 24.4% p=0.02

No significant benefit with respect to growth and development in the higher saturation group
↑O2 requirement at 36 Wk PMA / ↑home based O2 therapy
6 deaths from pulmonary causes in HSG and 1 in SSG (NS)

Askle LM et al. NEJM, 2003; 349:959-967

Saturation Target in WCHOB NICU

- Adjust FiO2 - SpO2 of 88 – 95% - ≤ 32 wks GA
- Adjust FiO2 - SpO2 of 92 – 97% - ≥ 33 wks GA

Clinical Practice Guideline for the Use of Supplemental Oxygen in the Delivery Room

- Infants ≥ 32 weeks gestation
  - Start resuscitation with 21% oxygen.
  - If the infant requires PPV, place oxygen saturation monitor (right hand, pre-ductal). Continue using 21% O2 as long as saturations are steadily increasing. If after 5 minutes of age and saturations are not steadily rising, increase FiO2 by 10% every minute until saturations reach 85-95%. If saturations are >95%, decrease FiO2 by 10% every minute to target of 85-95%.
  - If the baby is bradycardic (HR 60/min) after 90 seconds of resuscitation with a lower concentration of O2, oxygen should be increased to 100% until recovery of a normal heart rate.

Thank You

Are The Oxygen Saturation Guidelines Based On Physiology Or Clinical Evidence in Premature Neonates?

Is it practical to keep SpO2 targets at one minute intervals in the range specified in the DR?
Support Trial* - Saturation Targets and ROP