Oxygen saturations in premature infants at resuscitation. Where is the evidence?

Vasantha HS Kumar*
Department of Pediatrics, University at Buffalo, The State University of New York, Buffalo, NY, USA

Introduction

Premature infants < 32 weeks’ gestation often require resuscitation during fetal to neonatal transition, which includes administration of supplemental oxygen. Hyperoxia is one of the important generators of reactive oxygen species (ROS) and excess ROS is kept in check by antioxidant defense mechanisms. Premature infants have reduced antioxidant defense mechanisms at birth and hence are at risk for toxic effects of oxygen [1]. Supplemental oxygen in premature infants contributes to development of bronchopulmonary dysplasia (BPD) [2], retinopathy of prematurity [3] and brain injury [4]. The awareness of oxygen toxicity in premature infants has led to strategies such as limiting oxygen exposure at birth, use of antioxidants and administering room air at neonatal resuscitation to reduce free radical formation and to optimize long term outcomes.

Numerous studies have defined the percentiles of oxygen saturation as a function of time from birth in uncompromised babies born at term [5,6]. Neonatal resuscitation guidelines in 2010 for the first time recommended the targeted preductal saturations (SpO2) at resuscitation in the first 10 minutes after birth [7]. The SpO2 guidelines were applicable for both term and premature infants, to be achieved by initiating resuscitation with air or blended oxygen and titrating the oxygen concentration to achieve an SpO2 in the target range using pulse oximetry [7]. Oxygen concentration is increased to 100%O2 in a bradycardic (heart rate < 60/min) infant after 90 seconds of resuscitation with a lower concentration of oxygen, until the heart rate recovers to normal. The 2015 NRP guidelines maintained the same saturation targets, recommended against using high O2 concentrations and finally from varying definitions of BPD at 36 weeks (physiologic or clinical) among the groups [10,11]. Despite using diverse target saturations in the first 10 minutes, all the three studies demonstrate the feasibility of administering 30%O2 at resuscitation in premature infants. The oxygen concentration was titrated upwards to meet SpO2 targets in all studies: to 40% [11], 45% or 55%O2 [10] by 5 minutes of birth. The studies indicate that 30%O2 can be used as a starting point to resuscitate a premature infant. The clinical outcomes need to be confirmed, as all these studies used varying target saturations in the first 10 minutes.

Evidence with 21%O2 at resuscitation

Five studies that administered 21%O2 as one of the oxygen resuscitation groups are summarized in Table 1. In the three studies wherein the infants were resuscitated in 100%O2 [12-14], room air failed to maintain the targeted SpO2 and almost all infants required supplemental oxygen. However, resuscitation in 100%O2 resulted in hyperoxic infants with SpO2>95% [13]. Oxygen titration strategy after initial resuscitation with 100%O2 resulted in higher number of infants achieving targeted saturations [13]. The studies imply, that if premature infants were initially resuscitated with 21%O2, then careful attention should be placed to heart rate and SpO2, so that the oxygen can be titrated upwards to achieve saturations as per neonatal resuscitation guidelines.

Studies conducted with 21%O2 as one of the resuscitation group, had the same drawbacks as the studies conducted with 30%O2 resuscitation group. No two resuscitation studies conducted so far (including 21%O2 and 30%O2 resuscitation groups; Table 1,2) had the same drawbacks as the studies conducted with 30%O2. The 2015 NRP guidelines maintained the same saturation targets, recommended against using high O2 concentrations and finally from varying definitions of BPD at 36 weeks (physiologic or clinical) among the groups [10,11]. Despite using diverse target saturations in the first 10 minutes, all the three studies demonstrate the feasibility of administering 30%O2 at resuscitation in premature infants. The oxygen concentration was titrated upwards to meet SpO2 targets in all studies: to 40% [11], 45% or 55%O2 [10] by 5 minutes of birth. The studies indicate that 30%O2 can be used as a starting point to resuscitate a premature infant. The clinical outcomes need to be confirmed, as all these studies used varying target saturations in the first 10 minutes.

Evidence with 30%O2 at resuscitation

The three studies that administered 30%O2 as one of the oxygen resuscitation groups are summarized in Table 1. Escrig et al was the first to demonstrate that 30%O2 can safely be used to resuscitate premature neonates, which can then be adjusted to infant’s needs reducing the oxygen load on the infant [9]. Vento et al. later demonstrated that 30%O2 for resuscitation, leads to less oxidative stress, inflammation, decreasing the incidence of BPD[10]. However, a recent study with 30%O2 did not find differences in oxidative stress markers or BPD among the two resuscitation groups [11] (Table 1). This may be related to differences in target saturations among the groups in the first 10 minutes; changes in oxygen load from differences in the high oxygen resuscitated group (90%O2 [10] versus 65%O2 [11]) at resuscitation and finally from varying definitions of BPD at 36 weeks (physiologic or clinical) among the groups [10,11]. Despite using diverse target saturations in the first 10 minutes, all the three studies demonstrate the feasibility of administering 30%O2 at resuscitation in premature infants. The oxygen concentration was titrated upwards to meet SpO2 targets in all studies: to 40% [11], 45% or 55%O2 [10] by 5 minutes of birth. The studies indicate that 30%O2 can be used as a starting point to resuscitate a premature infant. The clinical outcomes need to be confirmed, as all these studies used varying target saturations in the first 10 minutes.
Table 1. Studies That Administered 30% O₂ as the Initial Gas at Resuscitation in Premature Infants.

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods / Groups</th>
<th>Results / Conclusions</th>
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| Escrig et al. 2008 (≤ 28 wks GA) | 30%O₂ (n=19, lox grp) vs. 90%O₂ (n=29, hox grp)  
Target spo₂ – FiO₂ adjustment based on HR; spo₂ between 85-90 %  
FiO₂ ↑ to 45% in LOX; ↓ to 45%O₂ in HOX for a spo₂ of around 85% at 5-7 minutes in both groups. No difference in morbidity including BPD and ROP. No deaths < 28 days in both groups. |
| Vento et al. 2009 (24 – 28 wks GA) | 30%O₂ (n=37, lox grp) vs. 90%O₂ (n=41, hox grp)  
Target spo₂ – preductal spo₂ of 75% at 5 min and 85% at 10min  
FiO₂ ↑ stepwise to ~55% at 5 min; lower incidence of BPD & less markers of oxidative stress (urine / GSSG/GSH) in the LOX group. |
| Rook et al. 2014 (<32wks GA) | 30%O₂ (n=99, lox grp) vs. 65%O₂ (n=94, hox grp)  
Target spo₂ – FiO₂ ↓ for spo₂ > 94%; FiO₂ ↓ for HR < 100/min before 10 min  
FiO₂ ↑ stepwise to ~40% by 7min in LOX; FiO₂ ↓ to ~40% by 11min in HOX group; No difference in oxidative stress markers or BPD between groups |

Table 2. Studies That Administered 21% O₂ as the Initial Gas at Resuscitation in Premature Infants.

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<tr>
<th>Study</th>
<th>Methods / Groups</th>
<th>Results / Conclusions</th>
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| Wang et al. 2008 (23-32 wks GA) | 21%O₂ (n=18) vs. 100%O₂ (n=23)  
Target SpO₂ – 100%O₂, grp: FiO₂ ↓ for spo₂ < 95% at 5min. 21%O₂ group  
FiO₂ ↑ stepwise to ~40% by 7min in LOX; FiO₂ ↓ to ~40% by 11min in HOX group. |
| Dawson et al. 2009 (<30 weeks GA) | 21%O₂ (n=105) vs. 100%O₂ (n=20)  
Target SpO₂ – 80 to 90%; FiO₂ ↓ by 10% if spo₂ > 90; FiO₂ ↑ for spo₂ <70% at 5min or spo₂ <90% at 5min + HR < 100  
97/105 (92%) in the 21%O₂ group were subsequently treated with supplemental O₂ at 5.05 (4.5-5.5) min. |
| Rabi et al. 2011 (<32 wks GA) | 21%O₂ (Low O₂ strategy; titrate up; n=34); 100%O₂ (High O₂ strategy; n=37)  
Target spo₂ – FiO₂ adjusted 20%O₂ q 15 secs to achieve spo₂ of 85-92%  
Titrating down from 100% O₂ was more effective at maintaining spo₂ in the range of 85 – 92 and these infants spent nearly twice as long in the target range as infants resuscitated in 21%O₂. |
| Kapadia et al. 2013 (24 – 34 wks GA) | 21%O₂ (n=44, lox grp) vs. 100%O₂ (n=44; hox grp)  
Target SpO₂ – 21%O₂, grp: NRP guidelines; 100%O₂, grp: FiO₂ adjusted by 10% to target spo₂ of 85-94  
Low decreased oxygen load by half; had less oxidative stress at one hour of age and reduced incidence of BPD |
| Kumar et al. 2014 (24-32 wks GA) | 21%O₂ (n=6) vs. 40%O₂ (n=7) vs. 100%O₂ (n=5)  
Target spo₂ – First 10 min of birth no change in FiO₂ and spo₂ were blinded; ↑O₂ at 30 min; spo₂< 85% ↑FiO₂ and spo₂> 95% ↓ FiO₂ 10% q 60secs  
Defined the natural evolution of spo₂ in three different O₂ concentrations in the first 10 minutes; 21%O₂ had spo₂ below the NRP-LL in the first 5 min; 40%O₂ mostly within the NRP limits; 100% O₂ leads to higher total O₂ exposure and systemic oxidant stress |

initiating resuscitation of premature infants with high supplementary oxygen concentration (65%O₂ - 100%O₂) [8]. Limiting oxygen exposure at resuscitation by starting low (21%O₂ – 30%O₂) and titrating the oxygen concentration upwards to target the above saturation limits in the first ten minutes after birth, not only decreases the oxygen load but may also decrease the risk for BPD [10].

The 2010 guidelines states that the saturation data are extrapolations from term infants [7]. The lack of induction of anti-oxidant enzyme systems soon after birth [15] along with generation of ROS by hyperoxia, makes it highly likely that the suggested SpO₂ targets in the first 10 minutes after birth are ‘relatively hyperoxic’ for premature infants. The physiology of oxyhemoglobin curves is different in term and premature infants [16-18]. Maintaining similar saturations in both term and preterm infants may lead to higher oxygen delivery, higher oxidant load and downregulation of hypoxia inducible factor (HIF-1) and vascular endothelial growth factor (VEGF) expression in premature infants. HIF-1 expression is tightly linked to O₂ concentration in vivo and hyperoxia or even normoxia in the developing lung rapidly induce HIF degradation and hence VEGF expression [19]. Future studies should address SpO₂ ranges in premature infants, particularly in the first 10 minutes after birth. The question is, what is the natural evolution of SpO₂ in premature infants resuscitated in room air in the first ten minutes after birth and how do they compare to the limits set by NRP?

This was addressed in a small pilot study in infants < 32 weeks GA, randomized to 21%, 40% or 100%O₂ and resuscitated as per 2005 NRP guidelines [20]. Oxygen groups and SpO₂ were unmasked at 10 minutes of age and FiO₂ adjusted to maintain SpO₂ of 85%-95% for the next 20 minutes. The study was stopped at 30% enrollment following publication of the 2010 NRP guidelines. The mean SpO₂ values were 50%, 53% and 69% at 1 min; 77%, 83% and 95% at 5 min and 92%, 92% and 98% at 10 min in 21%O₂, 40%O₂ & 100%O₂ groups respectively (Figure 1) [20]. Resuscitation of premature infants with 100%O₂ resulted in SpO₂ values above the upper limit of the 2010 NRP guidelines (Figure 1 – red line; open diamonds); 40%O₂ resuscitated group had mean SpO₂ values below the NRP lower limit in the first five minutes and within the NRP defined SpO₂ target range from 6 to 10 minutes (Figure 1 – blue line; open circles); 21%O₂ resuscitated group had mean SpO₂ values bordering the NRP lower limit in the first five minutes and within the NRP defined SpO₂ target range from 6 to 10 minutes (Figure 1 – green line; closed squares). Similarly, there were no differences in SpO₂ at 10 and 30 minutes after birth among the groups [20]. Infants in 21%O₂, 40%O₂ and 100%O₂ groups were weaned to 24.8% (+5), 27.9% (+6) and 38% (+20) O₂ respectively at 30 minutes of age (Figure 2) [20]. Despite aggressive weaning, FiO₂ administered was significantly higher in the 100%O₂ group to maintain the target SpO₂ until 30 minutes of age; however, there was no significant difference in FiO₂ between 40%O₂ and 21%O₂ groups during the weaning process (Figure 2). The novelty of this study was in administering a fixed concentration of oxygen and blinding the study gas for the first 10 minutes irrespective of the SpO₂. This pilot study demonstrate that resuscitation with 21%O₂ is feasible and the evolution of SpO₂ in the first 10 minutes following 21%O₂ resuscitation are fairly close to NRP.
Kumar VHS (2016) Oxygen saturations in premature infants at resuscitation. Where is the evidence?

Volume 1(4): 91-94

Pediatr Dimensions, 2016         doi: 10.15761/PD.1000120

... oxygen concentration was constant for the first 10 minutes at 21% O2 [●; green]; 40% O2 [○; blue] and 100% O2 [◆; red] in the three groups. Each time point represents mean ± SD. SpO2 significantly increased over time in the first 10 minutes after birth in all infants (P < 0.0001 mixed model ANOVA). Upper (●▲) and lower (●Δ) SpO2 limits (NRP 2010 guidelines) are superimposed on the SpO2 curves of the three O2 resuscitated groups. SpO2 in the 100% O2 group was above NRP-upper limit; resuscitation with 21% or 40% O2 maintained SpO2 within the NRP range from 5 to 10 minutes of life. (with permission of the authors)

Figure 1. Oxygen saturations (SpO2) in premature infants < 32 weeks GA during the first 10 minutes after birth in the three resuscitated groups. The concentration of oxygen was constant for the first 10 minutes at 21% O2 [●; green]; 40% O2 [○; blue] and 100% O2 [◆; red] in the three groups. Each time point represents mean ± SD. SpO2 significantly increased over time in the first 10 minutes after birth in all infants (P < 0.0001 mixed model ANOVA). Upper (●▲) and lower (●Δ) SpO2 limits (NRP 2010 guidelines) are superimposed on the SpO2 curves of the three O2 resuscitated groups. SpO2 in the 100% O2 group was above NRP-upper limit; resuscitation with 21% or 40% O2 maintained SpO2 within the NRP range from 5 to 10 minutes of life. (with permission of the authors)

Saturation limits. However, low enrollment is a major limitation of the study, leading to lack of clinical significance to study results.

Despite the lack of evidence regarding the appropriate SpO2 ranges at resuscitation in premature infants, particularly in extremely low birth weight infants, studies suggest that using high oxygen concentration at resuscitation is not beneficial [21]. Resuscitation guidelines released last year recommend against using high oxygen concentrations (65%O2 - 100%O2) and to administer 21%O2 – 30%O2 to initiate resuscitation. Administering low oxygen concentrations has not been conclusively proven to improve outcomes. Nonetheless, it decreases the oxygen load exposed in the first 30 minutes after birth contributing to improvement in oxidative stress markers in these infants [10,20].

In a non-asphyxiated premature or term infant administering low concentration of oxygen and titrating it based on saturation limits is prudent at the present time. However, in an asphyxiated infant, whether term or preterm, the oxygen resuscitation guidelines are not clear-cut. It is recommended that oxygen concentration be increased to 100%O2 in a bradycardic / asystolic infant, until heart rate recovers to normal [7]. The key determinant of neonatal resuscitation is more likely to be the heart rate rather than oxygenation. Reperfusion-reoxygenation may lead to additional injury beyond that generated by hypoxia-ischemia alone. Free radicals are produced when myocardium is perfused following ischemia, injuring myocytes & endothelial cells. The release of free radicals, in combination with ischemia deplete intracellular antioxidant activity, rendering myocardium extremely vulnerable to further insult. Weaning and titrating the oxygen concentration to defined saturation targets with pulse oximetry in place is probably the best course at this time. Research into the critical role of heart rate and the myocardial oxygen dynamics at resuscitation, its responses to oxygenation and ultimately on long-term neurodevelopmental outcomes will determine the oxygen concentration after birth.

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