

## Review

### \*Corresponding author

Vasantha H.S. Kumar, MD

Associate Professor of Pediatrics

Department of Pediatrics

The Women & Children's

Hospital of Buffalo

University at Buffalo

The State University of New York

219 Bryant Street, Buffalo

NY 14222-2006, USA

Tel. +1 716 878 7673

Fax: +1 716 878 7945

E-mail: [vkumar3@buffalo.edu](mailto:vkumar3@buffalo.edu)

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# Oxygen and Resuscitation: Saturations, Oxidative Stress and Outcomes in Premature Infants

Vasantha H.S. Kumar, MD\*

Department of Pediatrics, University at Buffalo, The State University of New York, New York, USA

## ABSTRACT

Fetus develops in a relatively hypoxemic environment *in utero*, however they need supplemental oxygen at birth when born prematurely  $\leq 32$  weeks' gestation. Reduced antioxidant defenses from lack of induction of antioxidant enzymes at birth, predispose premature infant susceptible to toxic effects of oxygen such as bronchopulmonary dysplasia and brain injury. Studies have demonstrated that even short exposures to 100% oxygen at birth could have long term implications. Guidelines and nomograms were published in 2010 regarding oxygen concentrations to be administered along with the oxygen saturations (SpO<sub>2</sub>) to be targeted in the first ten minutes after birth in both term and premature infants. We review the impact of differing oxygen concentrations in the first 10 minutes soon after birth on oxygen saturations, the biochemical effects of oxidative stress and on clinical outcomes in premature infants. Initiating resuscitation with an oxygen concentration of 21% O<sub>2</sub> to 30% O<sub>2</sub> as recommended by resuscitation guidelines is a good starting point, despite the lack of evidence of well-defined SpO<sub>2</sub> targets in premature neonates, which necessitate large clinical trials. Starting low oxygen concentration at resuscitation, facilitates lower oxidative stress which is desirable in premature infants with immature anti-oxidant defenses at birth. However, there is insufficient evidence to indicate that resuscitation with lower oxygen concentration ( $\leq 30\%$  O<sub>2</sub>) at birth will decrease BPD or other clinical outcomes in premature neonates.

**KEYWORDS:** Resuscitation; Oxygen; SpO<sub>2</sub>; Premature infants; Bronchopulmonary dysplasia; Oxidative Stress.

## INTRODUCTION

Fetus develops in a hypoxemic environment *in utero* and an abrupt transition to a normoxic extra-uterine environment can generate a physiologic oxidative stress even in term infants.<sup>1,2</sup> Premature infants <32 weeks' gestation, with functional and structural immaturity of the cardio-pulmonary system often require resuscitation at birth, 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 enzyme systems (AOEs). Reduced antioxidant defenses in premature infants at birth, from lack of induction of AOE systems,<sup>3,4</sup> make them particularly susceptible to the toxic effects of oxygen.<sup>5</sup> Supplemental oxygen in premature infants contributes to development of bronchopulmonary dysplasia (BPD),<sup>6</sup> retinopathy of prematurity<sup>7</sup> and brain injury.<sup>8</sup> Optimal management of oxygen during neonatal resuscitation becomes particularly important because of the evidence that insufficient or excessive oxygenation can be harmful to the newborn infant.<sup>9</sup>

It was common to use pure oxygen at resuscitation of premature infants until as recently as 2010, when Neonatal Resuscitation Program (NRP) issued guidelines for oxygen concentrations to be administered at birth and nomograms were made available for oxygen saturation targets in term and premature infants.<sup>9</sup> Studies have defined the percentiles of oxygen saturation (SpO<sub>2</sub>) as a function of time from birth in uncompromised babies born at term.<sup>10,11</sup>

Resuscitation guidelines recommended in 2010 that the goal in babies resuscitated at birth, whether born at term or preterm, should be an oxygen saturation value in the interquartile range of preductal saturations measured in healthy term babies following vaginal birth at sea level.<sup>9</sup>

The guidelines recommend preductal SpO<sub>2</sub> of 60%-65% at 1 min; 65%-70% at 2<sup>nd</sup> min; 70%-75% at 3<sup>rd</sup> min; 75%-80% at 4<sup>th</sup> min and 80%-85% at the end of 5 minutes. The SpO<sub>2</sub> values between 5 and 10 minutes after birth to be 85%-95%.<sup>9</sup> The SpO<sub>2</sub> 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 a SpO<sub>2</sub> in the target range using pulse oximetry.<sup>9</sup> Recently, the guidelines were updated to achieve saturation target range by initiating resuscitation with a low oxygen concentration (21% O<sub>2</sub> to 30% O<sub>2</sub>) and recommended against initiating resuscitation with high supplementary oxygen concentration (65% O<sub>2</sub> to 100% O<sub>2</sub>)<sup>12</sup> in premature infants. However, oxygen concentration can be increased to 100% O<sub>2</sub> in a bradycardic infant (heart rate <60/min) after 90 seconds of resuscitation with a lower concentration of oxygen, until the heart rate recovers to normal.

There is a large body of evidence that blood oxygen levels in uncompromised babies generally do not reach extra

uterine levels until about approximately 10 minutes after birth. We review the evidence in premature infants by focusing into three main areas related to oxygen resuscitation at birth: (A) The effects of oxygen concentration administered at resuscitation on SpO<sub>2</sub> in the first 10 minutes after birth; (B) The biochemical effects of oxygen resuscitation on parameters of oxidative stress; (C) The long-term clinical outcomes of oxygen administered at resuscitation in these infants.

**Oxygen Resuscitation and Oxygen Saturations (SpO<sub>2</sub>)**

As the 2015 resuscitation guidelines recommend to initiate resuscitation in premature infants with a low oxygen concentration (21% to 30% O<sub>2</sub>), all these studies are reviewed. The studies that administered 21% O<sub>2</sub> or 30% O<sub>2</sub> as one of the oxygen resuscitation groups are summarized in Table 1. In the three studies wherein the infants were resuscitated in 21% O<sub>2</sub>,<sup>13-15</sup> room air failed to maintain the targeted SpO<sub>2</sub> and almost all infants required supplemental oxygen. However, resuscitation in 100% O<sub>2</sub> resulted in hyperoxic infants with SpO<sub>2</sub>>95%.<sup>14</sup> Oxygen titration strategy after initial resuscitation with 100% O<sub>2</sub> resulted in higher number of infants achieving targeted saturations.<sup>14</sup> The studies imply that if premature infants were initially resuscitated with 21% O<sub>2</sub>, then careful attention should be placed to heart rate and SpO<sub>2</sub>, so that the oxygen can be titrated upwards to achieve saturations as per neonatal resuscitation guidelines. In a

Study	Methods	Conclusions
<b>21% O<sub>2</sub> Resuscitation</b>		
Wang et al <sup>15</sup> (23-32 weeks GA)	21% O <sub>2</sub> (n=18) vs. 100% O <sub>2</sub> (n=23) Targeted SpO <sub>2</sub> – 100% O <sub>2</sub> grp: FiO <sub>2</sub> ↓ for SpO <sub>2</sub> >95% at 5 min. 21% grp – ↑ FiO <sub>2</sub> for SpO <sub>2</sub> <70% at 3 min or for SpO <sub>2</sub> <85% at 5 min (↑ to 50% × 30 secs; no response ↑ to 75% × 30 secs; no response – ↑100% O <sub>2</sub> )	All infants resuscitated in the RA received O <sub>2</sub> ≤3 min; Resuscitation with RA failed to achieve targeted SpO <sub>2</sub> by 3 min; recommend not to use RA for resuscitation of premature neonates.
Dawson et al <sup>13</sup> (<30 weeks GA)	21% O <sub>2</sub> (n=105) vs. 100% O <sub>2</sub> (n=20) Targeted SpO <sub>2</sub> – 80 to 90%; FiO <sub>2</sub> ↓ by 10% if SpO <sub>2</sub> >90; FiO <sub>2</sub> ↑ for SpO <sub>2</sub> <70% at 5 min or SpO <sub>2</sub> <90% at 5 min + HR<100	97/105(92%) in the 21% O <sub>2</sub> group were subsequently treated with supplemental O <sub>2</sub> at 5.05(4-5.5) min.
Rabi et al <sup>14</sup> (<32 weeks GA)	21% O <sub>2</sub> (Low O <sub>2</sub> strategy; titrate up; n=34); 100% O <sub>2</sub> and then wean (mod. O <sub>2</sub> strategy) (n=34); 100% O <sub>2</sub> (high O <sub>2</sub> strategy; n=37); Targeted SpO <sub>2</sub> – 20% O <sub>2</sub> q 15 secs to achieve SpO <sub>2</sub> of 85-92%	Titrating down from 100% O <sub>2</sub> was more effective at maintaining SpO <sub>2</sub> in the range of 85-92 and these infants spent nearly twice as long in the target range as infants resuscitated in 21% O <sub>2</sub> .
Kapadia et al <sup>16</sup> (24-34 weeks GA)	21% O <sub>2</sub> (n=44; lox grp) vs. 100% O <sub>2</sub> (n=44; hox grp) Targeted SpO <sub>2</sub> -21% O <sub>2</sub> grp: NRP guidelines; 100% O <sub>2</sub> grp: FiO <sub>2</sub> adjusted by 10% to target SpO <sub>2</sub> of 85-94	Lox decreased oxygen load by half; had less oxidative stress at one hour of age and reduced incidence of BPD
Kumar et al <sup>25</sup> (24-32 weeks GA)	21% O <sub>2</sub> (n=6) vs. 40% O <sub>2</sub> (n=7) vs. 100% O <sub>2</sub> (n=5) Targeted SpO <sub>2</sub> – First 10 min of birth no change in FiO <sub>2</sub> and SpO <sub>2</sub> were blinded; 10-30 min: SpO <sub>2</sub> <85% ↑FiO <sub>2</sub> and SpO <sub>2</sub> >95% ↓ FiO <sub>2</sub> 10% q 60 secs	Defined the natural evolution of SpO <sub>2</sub> in 21%, 40% & 100% O <sub>2</sub> in the first 10 min; 21% O <sub>2</sub> had SpO <sub>2</sub> mostly within the NRP limits; 40% O <sub>2</sub> had SpO <sub>2</sub> below the NRP-LL in the first 5 min; 100% O <sub>2</sub> above NRP-UL
<b>30% O<sub>2</sub> Resuscitation</b>		
Escrig et al <sup>17</sup> (≤28 weeks GA)	30% O <sub>2</sub> (n=19; lox grp) vs. 90% O <sub>2</sub> (n=29; hox grp) Targeted SpO <sub>2</sub> – FiO <sub>2</sub> adjustment based on HR; SpO <sub>2</sub> between 85-90	FiO <sub>2</sub> ↑ stepwise to ~45% in LOX; ↓ to 45% O <sub>2</sub> in HOX for a SpO <sub>2</sub> of around 85% at 5-7 min in both groups. No difference in morbidity including BPD and ROP. No deaths <28 days in both groups.
Vento et al <sup>18</sup> (24-28 weeks GA)	30% O <sub>2</sub> (n=37; lox grp) vs. 90% O <sub>2</sub> (n=41; hox grp) Targeted SpO <sub>2</sub> – preductal SpO <sub>2</sub> of 75% at 5 min and 85% at 10 min	FiO <sub>2</sub> ↑ 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 <sup>19</sup> (<32 weeks GA)	30% O <sub>2</sub> (n=99; lox grp) vs. 65% O <sub>2</sub> (n=94; hox grp) Targeted SpO <sub>2</sub> – FiO <sub>2</sub> ↓ for SpO <sub>2</sub> >94%; FiO <sub>2</sub> ↑ for HR<100/min before 10 min	FiO <sub>2</sub> ↑ stepwise to ~40% by 7 min in LOX; FiO <sub>2</sub> ↓ to ~40% by 11 min in HOX group; No difference in oxidative stress markers or BPD between groups

**Table 1:** Studies that administered 21% O<sub>2</sub> to 30% O<sub>2</sub> as the initial gas at resuscitation in premature infants. Saturation targets specific for individual studies are mentioned.

recent study, starting with 21% O<sub>2</sub> at resuscitation and adjusting FiO<sub>2</sub> to achieve preductal SpO<sub>2</sub> set by NRP was not only feasible but also decreased oxygen load and lowered oxidative stress in premature infants.<sup>16</sup>

Escrig et al noted that 30% O<sub>2</sub> can safely be used to resuscitate premature neonates, which can then be adjusted to infant's needs, reducing the oxygen load on the infant.<sup>17</sup> Vento et al later validated that 30% O<sub>2</sub> for resuscitation, may have additional benefits of lowering oxidative stress, and decreasing the risk of BPD.<sup>18</sup> However, a recent study comparing 30% O<sub>2</sub> or 65% O<sub>2</sub> at resuscitation, did not find differences in oxidative stress markers or BPD among the two groups<sup>19</sup> (Table 2). Resuscitation with lower oxygen concentration led to earlier lower FiO<sub>2</sub> mean and hence oxygen load at resuscitation (40% O<sub>2</sub> by 7 min in 30% O<sub>2</sub> group versus 40% O<sub>2</sub> at 11 min in 65% O<sub>2</sub> group).<sup>19</sup> Despite using diverse target saturations in the first 10 minutes, all the three studies demonstrate the feasibility of administering 30% O<sub>2</sub> at resuscitation in premature infants. The oxygen concentration was titrated upwards to meet SpO<sub>2</sub> targets in all studies: To 40%,<sup>19</sup> 45%<sup>17</sup> or 55% O<sub>2</sub><sup>18</sup> by 5 minutes of birth. The studies indicate that 30% O<sub>2</sub> can be used as a starting point to resuscitate a premature infant.

As short-term exposures to high concentration to oxygen can be associated with adverse long-term effects, low oxygen strategy at resuscitation is well-intended and appropriate, however the evidence is not full-proof. Firstly, no two resuscitation studies conducted so far (including 21% O<sub>2</sub> and 30% O<sub>2</sub> resuscitation studies; Table 1) had similar saturation targets in the first 10 minutes after birth, making comparisons among studies difficult. Second, the 2010 NRP guidelines states that the saturation data are extrapolations from term infants.<sup>9</sup> The lack of induction of anti-oxidant enzyme systems soon after birth<sup>20</sup> along with generation of ROS by hyperoxia, makes it highly likely that the suggested SpO<sub>2</sub> 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.<sup>21-23</sup> Maintaining similar saturations in both term and pre-

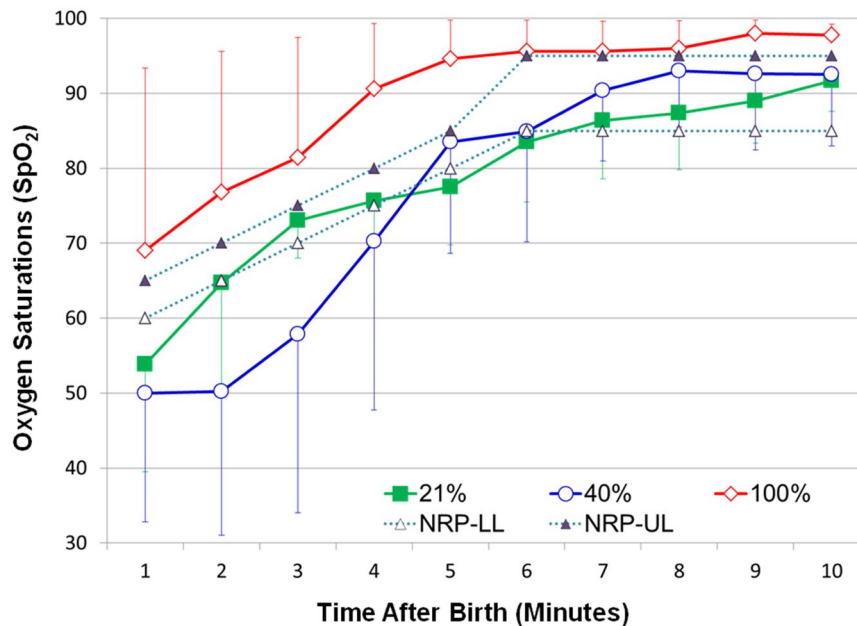
term infants may lead to higher oxygen delivery, higher oxidant load and down regulation of hypoxia inducible factor (HIF-1) and vascular endothelial growth factor (VEGF) expression in premature infants. HIF-1 expression is tightly linked to O<sub>2</sub> concentration *in vivo* and hyperoxia or even normoxia in the developing lung rapidly induce HIF degradation and hence VEGF expression.<sup>24</sup> Predicating SpO<sub>2</sub> in premature infants based on term saturations is difficult, as molecular signaling, growth and its interaction with the developing fetus at transition are different in an extremely preterm infant compared to an infant at term. Studies should address appropriate SpO<sub>2</sub> targets in premature infants, particularly in the first 10 minutes after birth.

The natural evolution of SpO<sub>2</sub> in infants resuscitated in room air may provide some insight into SpO<sub>2</sub> targets in the first ten minutes in premature infants. In a small pilot study infants <32 weeks GA were randomized to 21%, 40% or 100% O<sub>2</sub> and resuscitated as per 2005 NRP guidelines.<sup>25</sup> Oxygen groups and SpO<sub>2</sub> were unmasked at 10 minutes of age and FiO<sub>2</sub> was adjusted to maintain SpO<sub>2</sub> of 85%-95% for the next 20 minutes. The study was stopped at 30% enrollment following publication of the 2010 NRP guidelines, which is a limitation. The mean SpO<sub>2</sub> 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% O<sub>2</sub>, 40% O<sub>2</sub> & 100% O<sub>2</sub> groups respectively (Figure 1).<sup>25</sup> Resuscitation of premature infants with 100% O<sub>2</sub> resulted in SpO<sub>2</sub> values above the upper limit of the 2010 NRP guidelines (Figure 1: Red line, Open diamonds); 40% O<sub>2</sub> resuscitated group had mean SpO<sub>2</sub> values below the NRP lower limit in the first five minutes and within the NRP defined SpO<sub>2</sub> target range from 6 to 10 minutes (Figure 1: Blue line, Open circles); 21% O<sub>2</sub> resuscitated group had mean SpO<sub>2</sub> values bordering the NRP lower limit in the first five minutes and within the NRP defined SpO<sub>2</sub> target range from 6 to 10 minutes (Figure 1: Green line, Closed squares). Similarly, there were no differences in SpO<sub>2</sub> at 10 and 30 minutes after birth among the groups.<sup>25</sup> Infants in 21% O<sub>2</sub>, 40% O<sub>2</sub> and 100% O<sub>2</sub> groups were weaned to 24.8% (±5), 27.9% (±6) and 38% (±20) O<sub>2</sub> respectively at 30 minutes of age.<sup>25</sup> Despite aggressive weaning, FiO<sub>2</sub> administered was significantly higher in

Study	Methods	Conclusions
Vento et al <sup>18</sup> (24-28 weeks GA)	30% O <sub>2</sub> (n=37; lox grp) vs. 90% O <sub>2</sub> (n=41; hox grp) OS Markers – Blood (D0, D1, D3) - GSSG/GSH Urine (D1, D7) – o-tyrosine/ phenylalanine; 8OHdG/2dG; 8-isoprostanes; isofurans	GSSG/GSH: ↑ D1 & D3 in HOX grp o-tyrosine/phenylalanine ↑ on D1, D7; 8OHdG/2dG ↑ on D1, D7; Isofurans ↑ on D1 in HOX grp
Ezaki et al <sup>26</sup> (<35 weeks GA) Mild-Mod Asphyxia	Reduced O <sub>2</sub> grp (to maintain SpO <sub>2</sub> of 90-95; n=23); 100% O <sub>2</sub> grp(n=21); OS Markers - Blood (60 min) - TH; RP	TH ↑ in 100% O <sub>2</sub> grp; RP-NS; RP/TH ↓ in 100% O <sub>2</sub> grp
Kapadia et al <sup>16</sup> (24-34 weeks GA)	21% O <sub>2</sub> (n=44; lox grp) vs. 100% O <sub>2</sub> (n=44; hox grp) OS Markers – Blood (Cord, 1 <sup>st</sup> hour) - TH; BAP	Cord - NS; 1 <sup>st</sup> hour - TH ↓; BAP ↑ in LOX grp
Rook et al <sup>19</sup> (<32 weeks GA)	30% O <sub>2</sub> (n=99; lox grp) vs. 65% O <sub>2</sub> (n=94; hox grp) OS Markers – Blood(D2) – GSH synthesis & concentration Urine (D0, D6) - o-tyrosine/ phenylalanine; 8OHdG/2dG; 3-NT	GSH synthesis & concentration - NS Urine (D0, D6) - o-tyrosine/ phenylalanine; 8OHdG/2dG; 3-NT - NS between groups
Kumar et al <sup>25</sup> (24-32 weeks GA)	21% O <sub>2</sub> (n=6) vs 40% O <sub>2</sub> (n=7) vs. 100% O <sub>2</sub> (n=5) OS Markers – Blood (24 h, 1 wk, 4 wk) – GSH/GSSG Urine (24 h, 1 wk, 4 wk) – 8OHdG; 3-NT	GSH/GSSH ↓ 100% O <sub>2</sub> at 24 h; 3-NT ↑ in 40% O <sub>2</sub> and 100% O <sub>2</sub> over time; 8OHdG ↑ at 4 wks in all groups

GSH: Reduced glutathione; GSSG: oxidized glutathione; 8OHdG: 8-hydroxy-2'-deoxyguanosine; 2-dG: 2'-deoxyguanosine; TH: Total hydro peroxide; RP: Redox potential; BAP: Biologic antioxidant potential; 3-NT: 3-nitro tyrosine; NS: No significance between groups.

Table 2: Studies that measured oxidative stress markers as part of oxygen resuscitation in premature infants.



**Figure 1:** Oxygen saturations (SpO<sub>2</sub>) 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% O<sub>2</sub> [■-; green]; 40% O<sub>2</sub> [○-; blue] and 100% O<sub>2</sub> [◇-; red] in the three groups. Each time point represents mean±SD. SpO<sub>2</sub> significantly increased over time in the first 10 minutes after birth in all infants ( $P<0.0001$  mixed model ANOVA). Upper (---▲---) and lower (---△---) SpO<sub>2</sub> limits (NRP 2010 guidelines) are superimposed on the SpO<sub>2</sub> curves of the three O<sub>2</sub> resuscitated groups. SpO<sub>2</sub> in the 100% O<sub>2</sub> group was above NRP-upper limit; resuscitation with 21% or 40% O<sub>2</sub> maintained SpO<sub>2</sub> within the NRP range from 5 to 10 minutes of life (with permission from the authors.<sup>25</sup>)

the 100% O<sub>2</sub> group to maintain the target SpO<sub>2</sub> until 30 minutes of age; however, there was no significant difference in FiO<sub>2</sub> between 40% O<sub>2</sub> and 21% O<sub>2</sub> groups during the weaning process. 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 SpO<sub>2</sub>. Larger studies are needed to address SpO<sub>2</sub> targets in premature infants to help define the oxygen concentration at resuscitation, however starting at 21% O<sub>2</sub> to 30% O<sub>2</sub> as recommended by NRP is a good starting point.

#### Oxygen Resuscitation and Oxidative Stress in Premature Neonates

Several studies have addressed the role of oxidative stress markers in relation to oxygen resuscitation (Table 2). The studies have used common markers of oxidative stress such as GSH/GSSG ratio, total hydroperoxide and 8-hydroxy-2'-deoxyguanosine (8-OHdG). Most of the studies measured oxidative stress markers within the first week of birth<sup>16,18,19,25,26</sup> and occasionally up to 4 weeks of age.<sup>25</sup> The studies validated that resuscitation with higher oxygen concentration leads to oxidative stress, particularly in the first week after birth. This may be related to production of reactive oxygen species from higher oxygen load at birth in the face of inadequate antioxidant defense mechanisms. Both, GSH/GSSG ratio<sup>25</sup> and oxidative balance ratio,<sup>16</sup> were lower within 24 hours of birth following resuscitation with high oxygen concentration. Both these markers are useful measures of oxidative stress in tissues. Two other studies had bronchopulmonary dysplasia (BPD) as the primary outcome with measurements of oxidative stress markers<sup>18,19</sup> within the first 4 weeks of age. In the study by Vento et al, o-tyrosine to phenylalanine ratio, a marker of protein oxidation and 8-OHdG/2-dG ratio, a

marker of oxidative DNA damage were increased in the high oxygen group compared to low oxygen group on day 7; and this may be related to the oxygen load and generation of ROS from oxygen administered at resuscitation.<sup>18</sup> These markers of protein and DNA oxidation were also correlated with later development of BPD.<sup>18</sup> However, the same oxidative markers were not significantly different among the two oxygen groups in the study by Rook et al<sup>19</sup> (Table 3). Almost contrasting results between the two studies may be related to differences in target saturations in the first 10 minutes; changes in oxygen load from differences in the high oxygen resuscitated group (90% O<sub>2</sub><sup>18</sup> versus 65% O<sub>2</sub><sup>19</sup>) and finally from varying definitions of BPD at 36 weeks (physiologic or clinical) among the resuscitated groups.<sup>18,19</sup> Also oxidative stress could result from factors other than oxygen administered, such as mechanical ventilation in immature newborns. Nonetheless, the studies demonstrate that lower oxygen concentration may help in facilitating lower oxidative stress which is desirable in premature infants with immature anti-oxidant defenses at birth.

#### Oxygen Resuscitation and Clinical Outcomes in Premature Neonates

Immature lungs can be acutely injured by either oxygen or mechanical ventilation resulting in altered alveolar or vascular development of the lung leading to development of bronchopulmonary dysplasia (BPD).<sup>27</sup> Even though, antenatal steroids, gentle ventilation techniques and surfactant administration have decreased the incidence and severity of BPD in more mature infants, it is still a major problem in extremely low birth weight infants. Free radicals are elevated in plasma within 24 to 48 hours after birth,<sup>28</sup> and in bronchoalveolar lavage (BAL) within



Study	Methods	Conclusions
Vento et al <sup>18</sup> (24-28 weeks GA)	30% O <sub>2</sub> (n=37; lox grp) vs. 90% O <sub>2</sub> (n=41; hox grp) Outcome – death <28 days + incidence of BPD (O <sub>2</sub> at 36 wks PMA)	Infants in LOX group received fewer days of O <sub>2</sub> , MV, CPAP and developed less BPD
Kapadia et al <sup>16</sup> (24-34 weeks GA)	21% O <sub>2</sub> (n=44; lox grp) vs. 100% O <sub>2</sub> (n=44; hox grp) Primary outcome – Oxidative balance ratio; Secondary – incidence of BPD (O <sub>2</sub> at 36 wks PMA)	Infants in LOX group received fewer days of O <sub>2</sub> , MV & developed less BPD
Rook et al <sup>19</sup> (<32 weeks GA)	30% O <sub>2</sub> (n=99; lox grp) vs. 65% O <sub>2</sub> (n=94; hox grp) Outcome – BPD at 36 wks PMA (Walsh et all criteria)	BPD - not significantly different between the high & low O <sub>2</sub> groups
Oei et al <sup>30</sup> (<28+6 weeks GA) Meta-analysis of 8 studies	Low O <sub>2</sub> : ≤30% O <sub>2</sub> grp(n=251); high O <sub>2</sub> : ≥60% O <sub>2</sub> grp (n=253) Outcome – short-term morbidities and mortality	Mortality – ns [34/251-low O <sub>2</sub> vs. 32/258-high O <sub>2</sub> ]; BPD – ns [81/217-low O <sub>2</sub> vs. 93/226-high O <sub>2</sub> ]; IVH Gr3/4 – ns; ROP≥St3 – ns; NEC – ns; PDA – ns

LOX: Low oxygen group; HOX: High oxygen group; BPD: Bronchopulmonary dysplasia; PMA: Post menstrual age; MV: Mechanical ventilation; CPAP: Continuous positive airway pressure; IVH: Intraventricular hemorrhage; ROP: Retinopathy of prematurity; NEC: Necrotizing enterocolitis; PDA: Patent ductus arteriosus; ns: not significant between groups.

**Table 3:** Oxygen resuscitation studies and clinical outcomes in premature infants.

a week,<sup>29</sup> in premature infants who subsequently develop BPD. Whether the oxygen load as determined by the concentration of oxygen delivered at resuscitation predisposes to BPD is not clear. Resuscitation studies have addressed this issue with BPD as the primary outcome measure (Table 3). There are conflicting results on the effects of oxygen concentration at resuscitation and BPD. Two studies have reported beneficial effects of resuscitation with low oxygen concentration (21% O<sub>2</sub> - 30% O<sub>2</sub>) on decreasing the incidence of BPD.<sup>16,18</sup> However, oxygen concentration at resuscitation (30% O<sub>2</sub> vs. 65% O<sub>2</sub>) had no effect on the incidence of BPD in a relatively larger study.<sup>19</sup> Interestingly, the same study did not find significant difference in oxidative stress markers among the groups. More recently, a meta-analysis of eight randomized studies of low (≤30% O<sub>2</sub>) vs. high oxygen (≥65% O<sub>2</sub>) resuscitation, found no difference in major clinical outcomes including death or BPD in infants ≤28 weeks gestation.<sup>30</sup> The results of all these studies come with limitations. Meta-analysis included studies done over a relatively long period of time, during which time the clinical practices have evolved regarding management of BPD. Secondly, individual studies had relatively different SpO<sub>2</sub> targets in the first 10 minutes of birth; leading to an inhomogeneous starting point and a variation in FiO<sub>2</sub> adjustment to suit SpO<sub>2</sub> targets specific for each study. This could result in changes in oxygen load in the first 10 minutes impacting markers of oxidative stress and BPD. In a Canadian retrospective cohort study of 17 NICUs, a higher risk of severe neurologic injury or death among preterm infants of ≤27 weeks' gestation was observed following a change in practice to initiate resuscitation with room air or an intermediate oxygen concentration (21% O<sub>2</sub> - 40% O<sub>2</sub>)<sup>31</sup> in these infants. At this time, there is insufficient evidence to indicate that resuscitation with lower oxygen concentration (≤30% O<sub>2</sub>) at birth will decrease BPD or other clinical outcomes such as severe intraventricular hemorrhage, retinopathy of prematurity (Stage ≥3), necrotizing enterocolitis or patent ductus arteriosus.

## CONCLUSIONS

Optimal management of oxygen resuscitation is important as suboptimal or excessive oxygenation can be harmful to the newborn infant. Aggressive use of pulse oximetry in the delivery room to measure SpO<sub>2</sub> and titrating the fraction of inspired oxygen to desired SpO<sub>2</sub> target range is feasible and practical.

Current SpO<sub>2</sub> guidelines in premature infants are based mostly on studies from term infants. However, the current recommendations of administering lower O<sub>2</sub> concentration of 21% O<sub>2</sub> - 30% O<sub>2</sub> to initiate resuscitation and against using high oxygen concentrations (65% O<sub>2</sub> to 100% O<sub>2</sub>) are based on resuscitation studies in premature infants. Administering low oxygen concentrations at resuscitation has not been conclusively proven to improve outcomes. Nonetheless, it decreases the oxygen load in the first 30 minutes after birth contributing to improvement in oxidative stress markers in these infants.<sup>18,25</sup> The effects of oxidative stress in early life and its effects later in adults on cellular function is still not known. It has been noted that resuscitation with 100% O<sub>2</sub> immediately after birth has been associated with an increased risk of childhood cancer<sup>32,33</sup> and the risk was more pronounced when the resuscitation lasted for 3 minutes or longer.<sup>33</sup> Although this association was independent of asphyxial injury,<sup>32</sup> oxygen exposure may be a proxy for a poor transition to extra uterine environment. Oxygen is a drug and has to be used judiciously. Studies have to be done to define SpO<sub>2</sub> targets in premature infants and to determine the impact of low versus high oxygen resuscitation on clinical outcomes with long-term follow-up of these infants. It is important to adhere to the SpO<sub>2</sub> nomogram and oxygen concentration to be administered at birth, as per resuscitation guidelines until new information becomes available. Titrating the oxygen concentration to defined saturation targets with pulse oximetry is 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 may help to clarify the oxygen concentration during resuscitation in premature infants.

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