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Review

Do We Know the Optimal Oxygen Concentration for Resuscitating a Premature Newborn?

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ABSTRACT

Fetus develops in a relatively hypoxemic environment *in utero*; however, extremely premature infants need supplemental oxygen soon after birth at resuscitation. Reduced antioxidant defenses predisposes the premature infant to toxic effects of oxygen such as bronchopulmonary dysplasia (BPD) and brain injury. Guidelines were published in 2010 regarding oxygen concentrations to be administered along with the targeted oxygen saturations (SpO_2) in the first ten minutes after birth in both term and premature infants. Since 2010, there is a widespread tendency to use lower fraction of inspired oxygen (≤0.3) at birth. Recent studies and meta-analysis do not provide sufficient evidence to indicate that initiating resuscitation with lower oxygen concentration (≤30% O_2) at birth decrease BPD or other clinical outcomes in premature neonates. On the other hand, it is of concern that, it may increase mortality particularly in infants <28 weeks gestational age with no demonstrable benefit on clinical outcomes. Did the pendulum swing too quickly from 100% O_2 to 21% O_2 for resuscitation of these infants? Should we initiate resuscitation of all premature infants with >21% O_2, meaning a change in neonatal resuscitation guidelines or conduct a rigorous multicenter trial to address this dilemma.

Keywords
Resuscitation; Oxygen; SpO_2; Premature infants.

Abbreviations
NRP: Neonatal Resuscitation Program; GA: Gestational Age; HR: Heart Rate; NICUs: Neonatal Intensive Care Units; AOR: Adjusted Odds Ratio; ROP: Retinopathy of Prematurity; BPD: Bronchopulmonary Dysplasia; HMD: Hyaline Membrane Disease; VEGF: Vascular Eendothelial Growth Factor; HIF: Hypoxia Inducible Factor; DSMB: Data Safety Monitoring Board.

INTRODUCTION

Optimal management of oxygen during neonatal resuscitation has become particularly important, as insufficient or excessive oxygenation can be harmful to the newborn infant.[1] In 2010, neonatal resuscitation program (NRP) issued guidelines for oxygen concentrations administered at birth based on nomograms for oxygen saturation targets in term and premature infants.[1] Studies have defined the percentiles of oxygen saturation (SpO_2) as a function of time from birth in uncompromised babies born at term.[2,3] The guidelines recommend 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.[1] Furthermore, the guidelines recommend preductal SpO_2 of 60-65% at 1 min; 65-70% at 2nd min; 70-75% at 3rd min; 75-80% at 4th min and 80-85% at the end of 5 minutes. Recommended SpO_2 target from five to ten minutes after birth was 85-95%.[1] The SpO_2 guidelines were applicable for *both term and premature infants*, by initiating resuscitation with air or blended oxygen and titrating the oxygen concentration to obtain a SpO_2 in the target range by pulse oximetry.[1] Recently, the guidelines were updated to achieve saturation target range by initiating resuscitation with a low oxygen concentration (21% O_2-30% O_2) in premature infants and recommended against

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initiating resuscitation with high supplementary oxygen concentration (65% O_2-100% O_2)[4] in these infants. However, the concentration increased to 100% O_2 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 (HR>100/min). The recommendation to use lower concentration of oxygen at resuscitation of preterm neonates is based on various studies in both term[5] and preterm neonates.[6-10]

A recent meta-analysis reviewed outcomes for infants <29 weeks gestation randomized to resuscitation with low (≤0.3) *versus* high (≥0.6) fraction of inspired oxygen at delivery.[11] The meta-analysis included infants enrolled in eight studies conducted from 2005 to 2014 (six masked and two unmasked); with 251 infants enrolled in the low oxygen and 253 infants enrolled in the high oxygen groups. There was no differences in outcome measures such as, bronchopulmonary dysplasia (BPD), intraventricular hemorrhage, retinopathy of prematurity (ROP), patent ductus arteriosus, necrotizing enterocolitis and overall mortality[11] between the two groups. However, mortality was lower in the low oxygen arm in the masked studies and higher in the low oxygen arm in unmasked studies.[11] Opposite effects on mortality from masking or unmasking, suggest an element of bias built into these studies.

The largest study to date to assess both short-term and long-term outcomes of 21% (room air) *versus* 100% oxygen at resuscitation in premature neonates was stopped due to the loss of equipoise for the use of 100% oxygen.[12] This particular study recruited 292 infants over six years and the recruitment was stopped by Data Safety Monitoring Board (DSMB), as infants <28 weeks gestational age (GA) who received room air resuscitation had higher hospital mortality (RA resuscitation: 10/46 (22%) *versus* 100% O_2: 3/54 (6%); CI: 1.1-13.4).[12] In the same study, deaths was not different between the groups for all infants <32 weeks GA. Small sample size and inability to power the study to analyze infants <28 weeks GA limits the conclusions of the study. Nonetheless, this study brings to focus that resuscitation with lower concentration of oxygen may lead to higher mortality compared to using 100% O_2 in premature infants.

Almost half of the premature infants enrolled in oxygen resuscitation studies did not reach a SpO_2 of 80% at 5 minutes and this was associated with increased risk of intraventricular hemorrhage and bradycardia (HR<100/min) at five minutes of age.[13] Both of the above factors were associated with lower gestational age, suggesting these infants are sick soon after birth with immature lungs, a proxy for lower SpO_2. The morbidity and mortality data of the three studies described above is summarized in Table 1.

In a retrospective analysis from Canadian neonatal intensive care units (NICUs), similar conclusions relating to oxygen concentration at resuscitation in premature neonates were noted.[14] The study compared neonatal outcomes in infants born at ≤27 weeks GA who received <100% O_2 (typically 21-40% O_2) during delivery room resuscitation to infants that received 100% O_2 at resuscitation (historical controls prior to 2006). The study found that the adjusted odds ratio (AOR) for primary outcome of severe neurologic injury or death was higher in the titratable oxygen group compared to 100% O_2 group (AOR 1.36; CI: 1.11-1.36).[14] A similar increase was also noted in infants resuscitated with 21% O_2 and titrated upwards compared to 100% O_2 group (AOR 1.33; CI: 1.04-1.69). Despite the infants being of higher birth weight and lower score for neonatal acute physiology (SNAP) scores, resuscitation with less than 100% oxygen led to worse primary outcome.[14] A change in practice to use room air or intermediate concentration of oxygen at resuscitation was associated with a higher risk of severe neurologic injury or death among preterm infants ≤27 weeks GA.

Table 1. Morbidity and Mortality Data Based on the Concentration of FiO_2 used at Resuscitation in Premature Infants

Study	Methods	Mortality	Morbidity
Oei JL et al[11]	All deaths – 34/257 (≤0.3) *vs.* 32/258 (≥0.6)	NS – Mortality not different between groups	No difference in BPD, IVH, PDA, NEC, ROP
All studies with ≤0.3 or ≥0.6 FiO_2 at resuscitation	Death (Masked studies - 3) – 10/98 (≤0.3) *vs.* 18/83 (≥0.6)	p=0.03; death higher in ≥0.6 FiO_2 group	
(Meta-analysis of 8 studies)	Death (Unmasked studies – 5)– 24/153 (≤0.3) *vs.* 14/175 (≥0.6)	p=0.03; death higher in ≤0.3 FiO_2 group	
Oei JL et al[12]	All deaths – 14/144 (0.21) *vs.* 6/143 (1.0)	NS	No difference in BPD, IVH, PDA, NEC, ROP
RCT – 21% O_2 *vs.* 100% O_2 at resuscitation	Deaths <28 wks GA – 10/46 (0.21) *vs.* 4/54 (1.0)	p=0.04; higher death in 0.21 FiO_2	
	Deaths: 28-31 wks GA – 4/98 (0.21) *vs.* 2/89 (1.0)	NS	
Oei JL et al[13]	768 infants of lower (≤0.3) or higher (≥0.6) FiO_2 for resuscitation.	Lower GA, lower birth weight and 5 min HR<100 significantly associated with death	SpO_2<80 associated with ↑ IVH
Relationship between SpO_2 at 5 min, death and IVH	Infants with SpO_2<80 at 5 min: More premature Lower birth weight More likely to receive ≤0.3 FiO_2		
(Meta-analysis of 8 studies)			

NS: No significance, FiO_2: Fraction of inspired oxygen; BPD: Bronchopulmonary dysplasia, IVH: Intraventricular hemorrhage, PDA: Patent Ductus Arteriosus, ROP: Retinopathy of prematurity, NEC: Necrotizing enterocolitis, RCT: Randomized Controlled Trial.

The above studies have highlighted the significant concern of both increased mortality and absence of benefit for other outcome measures especially in extremely low birth weight infants or in infant's ≤28 weeks GA. The only study to demonstrate decreasing incidence of BPD, with BPD being the primary outcome was performed prior to 2010 guidelines.[9] The practice of using 100% O_2 at resuscitation was changed to titratable oxygen based on preductal saturation targets in 2010[1] and since then, the trend has been to use lower concentration of oxygen in the resuscitation of the preterm neonate. With the concerns of increased in-hospital mortality in the room air resuscitated group, it begs to question the practice of initiating resuscitation with room air in premature infants. The association of severe neurological injury and/or mortality with titratable oxygen confuses the issue further. However, neonatal resuscitation guidelines recommends not to initiate resuscitation with ≥65% O_2, as exposing the preterm neonate to additional oxygen is not of proven benefit and in fact may cause harm from oxidative stress.[4] At this time, the right concentration of oxygen to resuscitate a preterm newborn is not established. Too much oxygen (100% O_2) causes harm, so does room air (21% O_2) resuscitation in premature newborns.

Studies on oxygen saturation targets after birth may offer clues to oxygen concentrations at birth in premature newborns. Oxygen administration in premature infants may be the result of initial disease severity, making it difficult to isolate the independent causative effect of inspired oxygen concentration on hyaline membrane disease (HMD) and BPD. Multiple studies have demonstrated that exposure to hyperoxia during critical periods of lung development, impairs alveolar development with inhibition of secondary crest formation.[15-17] Despite the recently conducted randomized trials comparing high (SpO_2: 91-95%) *versus* low (SpO_2: 85-89%) oxygen saturation targets, optimal oxygen saturation range in premature infants has remained elusive. Among the three oxygen saturation trials, infants randomized to the higher SpO_2 group (91-95%) had a significantly higher incidence of severe ROP and infants randomized to the lower SpO_2 group (85-89%) had higher mortality at NICU discharge.[18-20] Canadian oxygenation trial did not demonstrate any difference in mortality between the low and the high SpO_2 groups.[21] The morbidity and mortality outcomes for the oxygen saturation trials in premature infants are summarized in Table 2. Post-hoc study of the SUPPORT trial[19] found evidence of an interaction between small for gestational age and lower oxygen saturation targets (SpO_2: 85-89%) with increased mortality in these infants.[22] Oxygen use and optimal saturation targets in premature infants is as much an enigma as oxygen use and optimal saturation targets at resuscitation of these infants.

The saturation targets in premature infants in the first ten minutes of life are extrapolation from birth nomograms in term infants. The physiology of oxyhemoglobin curve in preterm newborns likely differ compared to term infants.[23-25] Maintaining similar saturations in both term and preterm infants may lead to higher oxygen delivery, higher oxidant load and downregulation of

Table 2. Morbidity and Mortality Data for the Three Saturation Trials

Study	Methods	Morbidity	ND Outcome / Mortality
SUPPORT Trial[19]	SpO_2: 85-89 (n=654) (LOSG) SpO_2: 91-95 (n=662 (HOSG)	**ROP** - Significantly **lower in LOSG** – 41/475 (8.6% *vs* 91/509 (17.9%) **BPD** - Significantly **higher in HOSG** – 203/540 (37.6% *vs* 265/568 (46.7%) NS – IVH, NEC, PDA	**Death before discharge** - Significantly **higher in LOSG** – 130/654 (19.9% *vs.* 107/662 (16.2%)
SUPPORT Trial[27]	SpO_2: 85-89 (n=654) (LOSG) SpO_2: 91-95 (n=662 (HOSG) ND Outcome Study		**Death / NDI** – NS (185/612 (30.2%) *vs.* 171/622 (27.5%) **Death – higher in LOSG** (140/633 (22.1%) *vs.* 118/648 (18.2%) **NDI** – NS (45/472 (9.5%) *vs.* 53/504 (10.5%)
COT Trial[21]	SpO_2: 85-89 (n=578) (LOSG) SpO_2: 91-95 (n=569 (HOSG) ND Outcome Study		**Composite Death / Disability** – NS (298/578 (51.6%) *vs.* 283/569 (49.7%) **Death before 18 months** – NS (97/585 (16.6%) *vs.* 88/577 (15.3%) **Any disability** - NS
BOOST Trial[20]	SpO_2: 85-89 (n=654) (LOSG) SpO_2: 91-95 (n=662 (HOSG)	**ROP** (pooled data) - Significantly **lower in LOSG** – 110/1035 (10.6% *vs* 141/1044 (13.5%) **NEC** (pooled data) - Significantly **higher in LOSG** – 127/1221 (10.4% *vs* 97/1217 (8%) NS – IVH, PDA, BPD	**Death before discharge** (revised algorithm) - Significantly **higher in LOSG** – 137/592 (23.1%) *vs.* 94/590 (15.9%)

LOSG: Lower oxygen saturation group; HOSG: Higher Oxygen Saturation Group; NDI: Neurodevelopmental impairment; NS: No Significance; BPD: Bronchopulmonary dysplasia; IVH: Intraventricular hemorrhage; PDA: Patent Ductus Arteriosus; ROP: Retinopathy of prematurity; NEC: Necrotizing enterocolitis.

hypoxia inducible factor (HIF-1) and vascular endothelial growth factor (VEGF) expression in premature infants. As molecular signaling and growth at transition are distinct in extremely preterm infants, so are oxygenation needs and SpO_2 in preterm infants. There is great variation in the initiating oxygen concentration at birth (21% O_2 to 30% O_2). Titrating oxygen soon after birth is dependent on reliable pulse oximetry tracing. Once the tracing is noted, how the provider responds to titrate oxygen is an extremely variable component, with no two providers responding the same way in a given situation. Postnatal saturations and events are variables over the infant's course in the NICU that can influence both short-term and long-term outcomes. A small for gestational age infant resuscitated in 21% O_2 with relatively low postnatal saturations is more likely to experience mortality. Physiological, clinical and practical variables pose hurdles in standardization of oxygen concentration at resuscitation. In addition, transitioning the extremely premature infant to a similar oxygen environment as the term infant in the face of physiological and biological immaturity is a great challenge.

The current NRP guidelines states 'preterm infants <35 weeks GA should be initiated with 21-30% O_2 and the oxygen concentration to be titrated to achieve preductal oxygen saturations approximating the interquartile range measured in healthy term infants'.[4] Did the pendulum swing from 100% O_2 to 21% O_2 too quickly, without adequately addressing the unique physiological needs of the developing fetus? None of the studies has addressed clinical or neuro-developmental outcomes based on NRP recommended guidelines in rigorous trials. No two studies conducted prior to 2010 (21% O_2 or 30% O_2 resuscitation), on which the NRP recommendations were based, had similar oxygen saturation nor FiO_2 weaning protocols at resuscitation. The only study to demonstrate benefits from initiating resuscitation with 30% O_2 on the incidence of BPD was conducted prior to 2010[9]; the oxygen concentration was weaned to achieve SpO_2 targets of 75% at 5 minutes and 85% at 10 minutes[9], different from NRP guidelines. European consensus guidelines for the management of respiratory distress syndrome recommends that initial concentration of 30% O_2 for infants <28 weeks GA and 21-30% $O_2$for 28-31 week GA infants; FiO_2 titrated guided by pulse oximetry from birth.[26] However, NRP recommends 21-30% O_2 for premature infants across all gestational ages.[1] Is it time to change NRP guidelines to resuscitate preterm infants with oxygen >21% O_2, preferably 30% O_2 to 40% O_2 and titrate it up or down to maintain NRP recommended preductal SpO_2 targets. At this time, there is insufficient evidence to indicate that resuscitation with lower oxygen concentration (≤30% O_2) 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. Alternatively, is it time to evaluate the knowledge gap by large-scale multicenter trials to assess both short-term and long-term clinical and neuro-developmental outcomes. Should we wait for data from more centers post guidelines on clinical outcomes and mortality? With any of these approaches, the answer will not come easy for physicians caring for premature neonates. Fetus has developed a unique physiology over time to meet the developmental needs *in utero*; mimicking similar environment *ex utero* is probably not the answer from the above studies. Titrating the oxygen concentration to defined saturation targets with pulse oximetry is the most favorable option for now until studies find evidence otherwise.

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