

Current Concepts of Oxygen Management in Retinopathy of Prematurity

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Retinopathy of prematurity (ROP) is a potentially blinding disorder in premature infants. The underlying pathophysiology is incompletely understood, limiting the prevention and treatment of this devastating condition. Current therapies are directed toward management of aberrant neovascularization thought to result from retinal ischemia in the developing preterm retina. The molecular mediators important for development of retinal ischemia and subsequent neovascular pathology are not fully understood. However, oxygen has been shown to be a key mediator of disease and the oxygen environment for preterm infants has been extensively studied. Despite this, the optimal oxygen environment for preterm infants remains unclear and recent works seeking to clarify this relationship demonstrate somewhat disparate findings. These data further substantiate that ROP is a complex disease with multifactorial etiology including genetic and environmental factors. Therefore, while environmental factors such as oxygen are important to our understanding of the disease process and care of preterm infants, identification of the molecular mediators downstream of oxygen which are necessary for development of ROP pathology will be critical to improve prevention, diagnosis and treatment strategies.

Keywords: Retinopathy of Prematurity (ROP); Angiogenesis; Neovascularization; Oxygen

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INTRODUCTION

Retinopathy of prematurity (ROP) was first described by Terry in 1942 and is now recognized as a leading cause of childhood blindness in the US and worldwide.¹⁻³ Despite our understanding of the pathogenesis of ROP and subsequent improvements in its management, the incidence of ROP has remained constant and some sources indicate that it has increased.⁴ For example, the overall incidence of ROP was not significantly different between the CRYO-ROP and ETROP study populations, but the incidence of prethreshold ROP increased

from 27% in the CRYO-ROP study to 37% in the ETROP study. Infants in the ETROP who developed prethreshold ROP had lower birth weight and younger gestational age than those in CRYO-ROP.⁴⁻⁶ These observations suggest that technologic and neonatal care advances have enabled the survival of extremely low birth weight infants which may be the reason why the incidence of ROP remains high.

One important factor in ROP which has changed over time is the concentration of oxygen used. In some countries other than the US, UK, Canada, Australia and those with resources to regulate oxygen and technology to

save preterm infants, 100% oxygen is still being used in neonatal nurseries. Many countries that experienced the "ROP epidemic" prior to improved technology to monitor and regulate oxygenation, now avoid high oxygen delivery at birth.⁷ In developing countries, technology to regulate oxygen can be available but resources to implement its regulation may not.⁸ Thus, the incidence of ROP and blindness from it may vary depending on the technology employed to save and care for preterm infants and regulate oxygen delivery. In the US, blindness is reported in approximately 10% of preterm infants even with standard of care treatment; however, the incidence of blindness from ROP can be 20% or higher in developing countries.^{8,9} In addition to the number of infants who are blinded from ROP, many infants with severe ROP have unfavorable visual and structural outcomes despite standard of care therapy.¹⁰ Therefore, ROP is an important cause of childhood blindness and visual morbidity, and the level of oxygen concentration continues to be a question. Recent studies have sought to clarify the role of oxygen in ROP but from these studies, it is apparent that questions still remain. In this report, we review some of the clinical studies on oxygen use in ROP.

HISTORICAL ROLE OF OXYGEN IN THE PATHOGENESIS OF ROP

Seminal studies conducted by Michelson, Ashton et al, and Patz et al revealed damaging effects of high oxygen levels on newly developed retinal vessels in animals that normally undergo postnatal retinal vascular development.¹¹⁻¹³ These studies demonstrated that day-old kittens exposed to continuously delivered 70-80% oxygen experienced constriction of newly formed retinal capillaries, termed "vasoobliteration".¹⁴ Upon returning to room air, the kittens developed "vasoproliferation" into the vitreous rather than within the hypoxic retina.

Clinical evidence of postnatal oxygen exposure and ROP was reported in observational studies by Kinsey and Campbell in 1949 and 1951, respectively. Their work described an association between ROP and high oxygen

concentrations.^{15,16} Subsequent controlled clinical studies demonstrated more definitively that elevated concentrations of oxygen could result in ROP in human infants and further, that oxygen restriction could lead to increased mortality.¹⁷⁻¹⁹

Concurrent investigation by Szweczyk demonstrated that human infants brought from high oxygen levels to room air developed dilated vessels, but that normal vessel caliber could be restored with increased oxygenation.²⁰ This is now believed to be hypoxia-induced vascular dilatation as seen in plus disease. These findings of an association between oxygenation and ROP were summarized by Patz and colleagues.¹⁸ This work supported the original hypothesis by Ashton: high oxygen attenuated newly formed capillaries in the retina and caused avascular retina that became hypoxic once preterm infants were removed from supplemental oxygen into room air.¹³ Even at this early stage of understanding, researchers proposed that a soluble factor or factors, released by the hypoxic retina, promoted intravitreal blood vessel growth.¹¹ Now, it is recognized that many factors play a role in vasoproliferation in ROP, most notably vascular endothelial growth factor (VEGF). However, VEGF and other factors are also essential to the development and neuroprotection of the retina and the preterm infant. In addition, current-day ROP has a different appearance from that believed to occur in the 1950's in the US. Now, a delay in physiologic retinal vascular development is more prominent than vasoattenuation from high oxygen and is followed by vasoproliferation at the junction of vascularized and avascular retina.²¹ Therefore, the appearance of ROP can vary based on preterm infant factors, and resources and technology to save preterm infants. Moreover, molecular mechanisms and factors that appear to have pathologic effects on vasoproliferation also have physiologic benefits to the retina and the developing preterm infant, complicating the management of ROP.

At the time of the studies by Ashton, Michaelson and Patz, high oxygen levels at birth were believed to cause vasoattenuation. Subsequent studies have shown that the duration

of supplemental oxygenation was the variable most strongly associated with development of ROP in preterm infants weighing less than 1,200 grams.²² As survival of even smaller preterm infants occurred, some studies raised the question if any amount of high oxygen, even the transient 100% concentration used during initial resuscitation at birth, is sufficient to increase the risk of severe ROP.²³ Finally, an assessment of ROP risk in relationship to arterial oxygen demonstrated that arterial oxygen levels (PaO₂) in the highest quartile for gestational age, on at least 2 of the first 3 postnatal days, was associated with doubling of the risk of ROP in zone I and of prethreshold/threshold disease as well as a 70% increased risk of plus disease.²⁴

STUDIES ON THE USE OF SUPPLEMENTAL OXYGEN TO REDUCE THE RISK OF SEVERE ROP

Following the thrust to reduce high oxygen levels at birth, it became apparent that insufficient oxygen is detrimental to preterm infant survival.²⁵ Additional studies in animal models raised the hypothesis that oxygen supplementation later in the course of ROP would reduce severe ROP ("threshold ROP") by reducing hypoxia induced release of angiogenic factors believed to be responsible for the vasoproliferation seen in stage 3, severe ROP.²⁶ The Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP) was designed to address this question. STOP-ROP, a randomized clinical trial, tested whether supplemental oxygen leading to higher oxygen saturation values (96%–99% S_pO₂) as compared to 89–94% S_pO₂ could decrease progression to threshold ROP. Infants with mean postmenstrual age (PMA) of 35.4 (range 30–48) weeks who had developed pre-threshold ROP were enrolled and assigned to a conventional oxygen group targeting 89–94% S_pO₂ or supplemental oxygen group with target saturations of 96–99%.²⁶ Supplemental oxygen for 96% to 99% S_pO₂ did not significantly reduce the number of infants requiring peripheral ablative surgery for threshold ROP, and at the same time did not increase the number of infants with pre-

threshold ROP progressing to threshold ROP requiring treatment.²⁶ Significantly fewer infants in the subgroup without plus disease treated with 96–99% S_pO₂ progressed to threshold ROP requiring treatment (46% versus 32%).²⁶

CURRENT ROLE OF OXYGEN THERAPY IN ROP

Noninvasive transcutaneous continuous monitoring of oxygen tension was introduced in the 1980's making it easier to study the relationship between postnatal oxygen saturations and ROP. Early studies demonstrated that ROP occurred less often if transcutaneous PO₂ was ≥ 80 mmHg during the second to fourth weeks of life in premature infants born at birth weights of 500–1300 grams.²⁷ Currently, pulse oximetry is used and demonstrates continuous and reliable oxygen monitoring.²⁸ Castillo and colleagues compared arterial oxygen and pulse oxygen saturation values for 122 preterm infants of average gestational age of 29.2±5.2 weeks and birth weight of 1,338±871.5 grams in a multi-centered prospective study.²⁹ Their data demonstrated that infants given supplemental oxygen with pulse oximetry values between 85–93% had an average arterial oxygen level of 56±14.7 mmHg within a range of 40–80 mmHg, 86% of the time.²⁹ However, preterm infants with pulse oximetry measurements >93% correlated with mean arterial oxygen measurements of 107.3±59.3 mmHg, had arterial oxygen >80 mmHg 60% of the time.²⁹

A number of investigations also studied the role of oxygen fluctuations in ROP. Several studies targeted oxygen saturation to 85–93% SpO₂ and used NICU protocols to avoid overall hyperoxia as well as repeated episodes of hypoxia-hyperoxia in very low birth weight infants. From these studies, it appeared that very low birth weight infants who experienced fluctuating PaO₂ were at higher risk of threshold ROP.^{30–32} These data provided clinical evidence to support earlier animal studies demonstrating that PaO₂ fluctuations influenced proliferative retinal disease in newborn rats.³³

A recent meta-analysis showed a 52% reduction of severe ROP in studies targeting

oxygen saturations of 70-96%.³⁴ Several recent multi-centered randomized trials have sought to further clarify the relationship between oxygen exposure and development of ROP. One of the gold standard studies, the Surfactant, Positive Airway Pressure, Pulse Oximetry Randomized Trial (SUPPORT), compared oxygen target ranges of 85-89% with 91-95% as measured by pulse oximetry in 1,316 infants born between 24-28 weeks gestation.³⁵ Severe ROP occurred less frequently in the lower oxygen saturation group. However, these data also demonstrated significantly increased mortality in the lower oxygen saturation group (relative risk: 1.27).³⁵ Therefore, the data raised concern for clinical practice.¹⁹

Additional and somewhat conflicting work was published recently. The Benefits of Oxygen Saturation Targeting (BOOST) II group assessed rates of ROP in 1,187 preterm infants targeted to oxygen saturations of either 85-89% or 91-95% by pulse oximetry. The study was prematurely stopped due to an increased rate of death in infants with 85-89% oxygen saturations (23.1% vs 15.9%; relative risk, 1.45, $P=0.002$), but also found a reduced incidence of ROP in the 85-89% oxygen saturation group.³⁶ The Canadian Oxygen Trial (COT) also compared targeting oxygen saturation 85% to 89% versus to 91% to 95% with the primary outcome measure being death or disability at 18 months. Infants born between 23-28 weeks gestation, with SpO_2 of 85% to 89% as compared to those with SpO_2 of 91% to 95% had no significant difference in terms of death or disability at 18 months (adjusted odds ratio, 1.11; 95% CI, 0.80 to 1.54; $P=0.54$)³⁷ or in secondary outcome measures, including ROP and brain injury.³⁷ Thus, data from the COT, BOOST and SUPPORT do not provide clear guidance as to the optimal oxygen saturation level for preterm infants to reduce infant mortality, morbidity and ROP.

OTHER FACTORS THAT INFLUENCE OXYGENATION

Although the amount of oxygen delivered and resultant oxygenation are the primary focus in ROP research, other factors influence overall

oxygen delivery in the preterm infant. It is helpful to consider the oxyhemoglobin dissociation curve when relating oxygen saturation and partial pressure of oxygen in the fetus and infant. In the preterm infant, fetal hemoglobin (HbF) functions as the primary oxygen transport protein. Fetal hemoglobin has relatively high affinity for oxygen as compared to adult hemoglobin due to reduced affinity for 2,3-diphosphoglycerate (2,3-DPG). As a consequence, oxygen is released from red blood cells at lower PaO_2 levels than adults.

Another important issue is that preterm infants are transfused with adult packed red blood cells that have adult hemoglobin. Thus, transfusion changes oxygen delivery in the preterm infant. Baseline anemia in the preterm infant also impairs oxygen delivery to end organs. Estimation of blood oxygenation in the retina is complicated by dilution factors from the fetal circulation. Lung disease may reduce oxygenation of measured blood, therefore PaO_2 levels in the retinal vasculature can be estimated to be 30-40 mmHg or lower. The presence of reactive oxygen species (ROS) has also been shown to affect retinal angiogenesis in models of oxygen induced retinopathy.^{38,39} Finally changes in cardiovascular parameters such as heart rate, pH, and temperature can also alter oxygen delivery by shifting the oxyhemoglobin dissociation curve. These factors add to the complexity of determining accurate oxygen levels in the retinal and choroidal vasculature.

SUMMARY

Ideal parameters for post-gestational oxygen supplementation in preterm infants remain unclear. Infants exposed to low oxygen levels may be at increased risk of death, cerebral palsy, patent ductus arteriosus, pulmonary vascular resistance and apnea.^{2,37} Those exposed to high levels of oxygen however, are reported to have greater rates of morbidity including ROP and chronic lung disease.^{2,35-37}

There was no agreement in conclusions from the BOOSTII, SUPPORT, and COT trials. Reasons for this include differences in prenatal

Table 1. Summary of key studies informing the relationship of oxygen exposure to development of ROP

Trial	Duration	Enrollment criteria	Exclusion criteria	% Not meeting inclusion criteria	Geography	Average birth weight	Intervention	ROP outcome	Mortality outcome
STOP-ROP	1994-1999	Infants 30-48 weeks GA with pre-threshold ROP in one eye and median pulse oximetry <94% saturation	Median oxygen saturations >94% or congenital abnormality	34%	United States	726 gm	Infants randomized to pulse oximetry ranges of 89%-94% or 96%-99%	No statistically significant difference in ROP between 2 groups	Not assessed formally though 7 infants in lower oxygen tension group vs 9 infants in the higher tension group
SUPPORT	2005-2009	GA: 24-27 weeks 6 days at birth who underwent full resuscitation	Infants with major congenital abnormalities	6.6%	United States	825-836 gm	1) Randomized to receive early CPAP or early surfactant 2) Randomized to SaO ₂ of 85-89% or 91-95%	Decreased ROP in 85-89% SaO ₂ group	Increased mortality in 85-89% SaO ₂ group
BOOST II	2006-2011	GA: <28 weeks	1) unlikely to survive 2) major congenital abnormality 3) unavailable for follow up	9%	Australia, UK and New Zealand	826-837 gm	Randomized to SaO ₂ of 85-89% or 91-95%	Decreased ROP in 85-89% SaO ₂ group	Increased mortality when targeting oxygen saturations <90%
COT	2006-2012	GA: >23 weeks to 27 weeks and 6 days	1) not viable 2) persistent pulmonary hypertension 3) dysmorphic features or congenital malformations 4) cyanotic heart disease 5) unavailable for follow up	16%	Canada United States, Argentina Finland, Germany, and Israel	827-845 gm	Randomized to SaO ₂ of 85-89% or 91-95%		Targeting oxygen saturations of 85% to 89% compared with 91% to 95% had no significant effect on the rate of death or disability at 18 months

SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial; BOOST II, Benefits Of Oxygen Saturation Targeting; COT, Canadian Oxygen Trial; GA, gestational age; CPAP, continuous positive airway pressure

characteristics of populations enrolled into these clinical trials and potential differences in NICU technology including, measurement of oxygen saturation. There are also differences in the genetic makeup of the populations, the number of extremely preterm infants who survive, and in the diagnosis of ROP. The International Classification of ROP, although broadly adopted, depends on dilated retinal examination of preterm infants, a skill requiring adequately trained ophthalmologists, who are not always available for ROP examinations.⁸ As noted in Table 1, exclusion criteria differed among these trials. The COT restrictions to enrollment may have affected survival and

ROP outcomes. The BOOST and COT included infants from other areas of the world, which add factors of heterogeneity and potential variability in prenatal and neonatal management.

Clinical studies on the use of oxygen in ROP suggest that broad changes in oxygenation may cause too many events within the developing delicate preterm infant. It is clear that oxygen is a powerful drug in preterm infants. Greater study of the role of oxygen on molecular pathways within cells of the retina may lead to targeted treatments. In this regard, relevant animal models that accurately replicate the systemic profile of preterm infants would be useful.²¹

Conflicts of Interest

None.

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