# Oxygen Saturation and Retinopathy of Prematurity

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**KEYWORDS**

• Oxygen • Retinopathy of prematurity • Prematurity

**KEY POINTS**

- Retinopathy of prematurity (ROP) affects the infants at lower gestational ages and birth weight.
- Oxygen exposure in preterm infants is associated with ROP.
- Recent oxygen saturation targeting trials show increased mortality with lower target ranges; target ranges above 90% saturation are current suggested for premature infants.
- Prevention, early intervention and treatment regimens are needed to improve ROP outcomes.

## BRIEF HISTORY OF RETINOPATHY OF PREMATURITY

Retinopathy of prematurity (ROP) is a serious vasoproliferative disorder affecting premature infants. It was first described as "retrolental fibroplasia" because of the white Q5 appearance of the pupil in infants who survived but were blind.[1] The white appearance was due to retinal detachment. Early treatment for premature infants involved administration of oxygen into incubators. Oxygen use was curtailed following the Kinsey Study,[2] which assigned infants administered oxygen of more than 50% or less than 40% to 50%. The results showed that the infants in the restrictive group had less retinopathy and oxygen use was subsequently restricted resulting in less retinopathy. For infants less than 1000 g birthweight, the estimate of absolute numbers of infants affected with ROP was anticipated to increase secondarily to increased survival.[3]

## RETINOPATHY OF PREMATURITY EPIDEMIOLOGY AND PATHOLOGY

ROP occurs more commonly with lower gestational age (GA), and is associated with duration of oxygen exposure. Black infants are less likely to develop severe ROP.[4] Small for GA infants are at higher risk of development of ROP.[5]

Disclosure Statement: The author has no relationship with a commercial company that has a direct financial interest in subject matter or materials discussed in article or with a company making a competing product.

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Clin Perinatol ■ (2019) ■–■
https://doi.org/10.1016/j.clp.2019.05.008 perinatology.theclinics.com

Premature birth results in a relative hyperoxia compared with in utero. Further, the retinal vessels are not fully mature and the relative hyperoxia initially inhibits vessel growth. In the meantime, the retina grows in thickness. Over time, a gradual retinal hypoxia develops, and growth factors, including vascular endothelial growth factor, are released, resulting in excessive blood vessel growth. The result is ROP.

## RETINOPATHY OF PREMATURITY CLASSIFICATION AND TREATMENT STUDIES

With the advent of modern neonatal care, including neonatal intensive care units (NICUs) and mechanical ventilation, and additional technologies, smaller preterm infants were surviving and ROP increased in the 1970s.[3] During the 1980s, the International Classification of ROP was developed; this was the first attempt at standardizing the grading system for ROP[6] and this has been recently updated.[7] This classification was used in the Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) trial conducted in the mid-1980s.[8] The results of the CRYO-ROP trial now availed treatment for advanced ROP when previously none existed.

Laser therapy was then developed for ROP. Several smaller trials were conducted, and the ET-ROP (Early Treatment for Retinopathy of Prematurity) trial[9] showed reduced unfavorable visual acuity with earlier treatment from 19.5% to 14.5% ($P = .01$). Type 1 ROP was defined as follows: zone I, any stage ROP with plus disease; zone I, stage 3 ROP with or without plus disease; zone II, stage 2 or 3 ROP with plus disease.[9] Plus disease was defined as 2 or more quadrants (6 clock hours) of dilation or tortuosity of the peripheral retinal vessels.[9] Thus, the laser treatment occurred earlier than treatment occurred in the CRYO-ROP study. Further comparison between the ET-ROP and CRYO-ROP studies showed more zone I disease in the ET-ROP study.[10] There were more infants in the ET-ROP study with lower birth weights and lower GA, likely accounting for the increase in zone I disease.

## ADVENT OF OXYGEN SATURATION TARGETING TRIALS: SMALLER REPORTS THAT SPURRED LARGE TRIALS

A retrospective review of outcomes for infants admitted to NICUs in England showed that infants managed with lower oxygen saturation ranges (70%–90%) compared with higher ranges (88%–98%) in the first 8 weeks of life had lower rates of cryotherapy.[11] The infants in the lower saturation range did not have an increased risk of mortality or neurodevelopmental impairment.[11] Use of transcutaneous oxygen monitoring showed a decrease in ROP in a subgroup of infants $\geq$1100 g.[12] Chow and colleagues[13] showed that implementation of an oxygen policy to avoid higher oxygen saturations (93%–95%) and to prevent large swings in oxygen saturations for 2 to 8 weeks of age in infants 500 to 1500 g birth weight, resulted in a significant decrease in the rate of severe ROP and an improvement in survival over time.

The relationship of oxygen and ROP continued to be explored in the 1990s. The Supplemental Therapy with Oxygen to Prevent Retinopathy of Prematurity (STOP-ROP) trial[14] and the Benefits of Oxygen Saturation Targeting Study (BOOST)[15] were conducted to test the role of supplemental oxygen for ROP. The STOP-ROP trial[14] enrolled premature infants with prethreshold ROP in at least 1 eye to target oxygen saturations of 96% to 99% versus 89% to 94% saturation to test the hypothesis that a higher level would reduce the rate of progression of ROP to threshold disease. The trial enrolled 649 infants with an average GA at birth of 25.4 weeks and an average postmenstrual age of 35.4 $\pm$ 2.5 weeks. The progression of ROP from prethreshold to threshold disease was not reduced in the higher saturation group. Infants who did not have plus disease, defined as posterior pole dilation and/or tortuosity, at the time of

enrollment had less progression to threshold with supplemental oxygen. However, the supplemental oxygen group (96%–99%) had higher rates of pulmonary adverse events.[14]

The BOOST Study[15] was designed to look at 2 saturation targets; 91% to 95% or 95% to 98% begun at 32 weeks postmenstrual age with outcomes of improving growth and development at 1 year of age. There were 358 infants enrolled with no differences observed in growth or major developmental outcomes. The investigators concluded that optimal oxygen saturation range for preterm infants soon after birth should be determined with a large trial.[15]

## SATURATION TRIALS OF THE 2000S

Based on the conclusions from the BOOST trial, several large oxygen saturation–targeting trials were developed and executed. The investigators from these trials agreed to pool data and perform a prospective individual patient meta-analysis.[16] The meta-analysis[17] showed that death occurred in 484 (19.9%) of 2433 infants in the lower SpO2 target group and 418 (17.1%) of 2440 infants in the higher SpO2 target group (risk difference 2.8%; 95% confidence interval [CI] 0.6%–5.0%; relative risk (RR) Q6 1.17; 95% CI 1.04–1.31; $P = .01$). Treatment for ROP was administered to 220 (10.9%) of 2020 infants in the lower SpO2 target group and 308 (14.9%) of 2065 infants in the higher SpO2 target group (risk difference −4.0%; 95% CI −6.1% to −2.0%; RR 0.74; 95% CI 0.63–0.86; $P<.001$).[17] These trials would not have been conducted if a mortality difference had been anticipated in advance of the studies. Nevertheless, they have provided valuable clinical evidence to guide practice with respect to oxygen therapy. The individual trial results are described as follows.

The Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT)[18] was conducted from 2005 to 2009 in the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network. Primary outcome showed no difference in the primary outcome of death or ROP between a higher oxygen target saturation (91%–95%) and a lower oxygen target saturation (85%–89%). However, secondary outcome of ROP was lower in the lower saturation group compared with the higher saturation group. The death rate was higher in the lower saturation group, which was an unexpected finding. At follow-up at 18 to 22 months,[19] death or neurodevelopmental impairment was in 30.2% of the infants in the lower oxygen saturation group (185 of 612), versus 27.5% of those in the higher oxygen saturation group (171 of 622) (relative risk 1.12; 95% CI 0.94–1.32; $P = .21$).

The Canadian Oxygen Trial (COT)[20] was conducted from 2006 to 2012. There was no difference in the rate of retinopathy or death in the higher versus lower target saturation groups. Infants who were assigned to the lower target range, 298 (51.6%) died or survived with disability compared with 283 (49.7%) of the 569 infants assigned to the higher target range (odds ratio adjusted for center 1.08; 95% CI 0.85–1.37; $P = .52$).[20] The rates of death were 16.6% for those in the 85% to 89% group and 15.3% for those in the 91% to 95% group (adjusted odds ratio 1.11; 95% CI 0.80–1.54; $P = .54$).[20] Differences between baseline characteristics of patients in COT and SUPPORT may account for the different study results.

The Benefits of Oxygen Saturation Targeting (BOOST II) in New Zealand[21] was conducted from 2006 to 2012, in the United Kingdom from 2007 to 2014, and in Australia from 2006 to 2013.[22] Targeting an oxygen saturation below 90% in extremely preterm infants was associated with an increased risk of death in infants

whose treatment used the revised oximeter-calibration algorithm. The rate of death was significantly higher in the lower-target group than in the higher-target group (23.1% vs 15.9%; relative risk in the lower-target group 1.45; 95% CI 1.15–1.84; $P = .002$). Those in the lower-target group for oxygen saturation had a reduced rate of ROP (10.6% vs 13.5%; relative risk 0.79; 95% CI 0.63–1.00; $P = .045$). For the Australia and UK studies,[23] an interim analysis showed increased mortality at a corrected GA of 36 weeks. Enrollment was stopped after 1135 infants in Australia and 973 infants in the United Kingdom had been enrolled in the trial. The mortality rate in the lower oxygen saturation arm was 21.2% compared with 17.7% in the higher oxygen saturation arm (RR 1.20; 95% CI 1.01–1.43). No difference was shown in severe vision loss between the higher and lower saturation arms of the trial (0.4% vs 0.7%).

## CURRENT OXYGEN TARGET SATURATION PARAMETERS

The guidelines of the American Academy of Pediatrics (AAP)[24] as of 2007 stated, "The optimal range for oxygen saturation and $Pao_2$ that balances tissue metabolism, growth and development, and toxicity has not been elucidated fully for preterm infants receiving supplemental oxygen. Oxygen saturation values between 85% and 95% and $Pao_2$ values between 50 mm Hg and 80 mm Hg are examples of ranges pragmatically determined by some clinicians to guide oxygen therapy in preterm infants. Additional research is needed to determine the 'optimal' oxygen saturation and $Pao_2$ needed. Of note, even with careful monitoring, oxygen saturation and $Pao_2$ may fluctuate outside specified ranges, particularly in neonates with cardiopulmonary disease." This recommendation was published in 2007,[24] while the vast majority of oxygen saturation targeting studies were occurring around the world.

In 2012, shortly after the publication of the SUPPORT trial, the AAP recommendations[25] were updated to state, "Data from cohort studies initially suggested that lower saturation ranges may decrease ROP. However, 3 RCTs demonstrated that although a target saturation range of 85% to 89% was associated with a decrease in severe ROP, it was also associated with an increase in mortality, compared with a target saturation range of 91% to 95%. These findings resulted in early study closure of 2 of these 3 studies, and a recommendation to target a saturation range higher than 85% to 89%. Of note, even with careful monitoring, oxygen saturation and $Pao_2$ may fluctuate outside specified ranges, particularly in neonates with cardiopulmonary disease."[25]

A recent survey to assess variations in oxygen saturation targets in 2015 and 2016 was conducted across the networks of the International Network for Evaluating Outcomes in Neonates (iNeo).[26] The upper SpO2 target limit was 94% or 95% (range 90%–98%) in 68% of the NICUs. The lower SpO2 limit was 90%; however, there was considerable variation in saturation targets was found in this survey.

## GAPS IN KNOWLEDGE

Despite the rigorous oxygen saturation trials, there are still many areas in need of study for oxygen saturation for preterm infants to optimize outcomes. An NICHD workshop in 2006[27] identified several areas for study. The oxygen saturation trials did provide evidence for a saturation target that may cause harm. In the NEOPROM meta-analysis, infants assigned to 85% to 89% target saturation had a higher mortality.[17] Other questions that persist include the following: What is the therapeutic range of inspired oxygen? What is the toxic range of inspired

oxygen? What explains the variability in toxicity? How do specific disease processes affect toxicity?[27] Titrating a sweet spot that allows for maximal survival and minimal ROP based on age of the infant, GA at birth, and other factors still eludes physicians.

Minimization of saturation variability persists as a gap in knowledge. Preterm infants can have labile cardiorespiratory status. Development of automatic feedback systems are needed to maintain saturation at stable targets. Technology such as feedback devices to keep oxygenation constant, closed-loop oxygen controllers, or oxygen delivery systems with pulse oximetry regulation have the potential to advance care for preterm and sick infants. Defining the optimal saturation target for various populations of infants is needed. Further, investigation of target saturation at various developmental periods and GA are needed to better inform clinical practice.

## FUTURE OF OXYGEN AND RETINOPATHY OF PREMATURITY

Although lower GA and birthweight are strong predictors of the development of ROP, oxygen remains in the causal pathway. Additional prevention, early intervention, and treatment strategies are needed to relieve the burden of ROP.

**Best Practices**

*What is the current practice for oxygen management and ROP?*

Best Practice/Guideline/Care Path Objective(s)
- Avoid preterm birth
- AAP recommendation to target a saturation range higher than 85% to 89%
- Emerging evidence-based consensus to target the 91% to 95% saturation range
- Vigilance with oxygen saturation monitoring
- Screening for ROP in conjunction with ophthalmology
- Follow-up eye examinations at established intervals
- Intervention with laser treatment if Type I ROP develops

*What changes in current practice are likely to improve outcomes?*

- Prevention of preterm birth
- Further research to include the following:
  - Balance between adequate inspired oxygen versus toxicity at various developmental periods
  - Automated feedback systems to maintain saturation targets
  - Saturation target variability
  - Prevention and early intervention therapies

Major Recommendations
- AAP recommendation to target a saturation range higher than 85% to 89% but evidence-based emerging consensus to target the 91% to 95% saturation range
- ROP screening performed as per guidelines
- Treatment if Type 1 ROP occurs
- Appropriate follow-up

Rating for the Strength of the Evidence

Saturation targeting

Saturation targeting in the range of 91% to 95% is supported by an individual participant meta-analysis, which is the highest level of evidence.

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