Published in final edited form as:

JAMA Ophthalmol. 2019 April 01; 137(4): 423–424. doi:10.1001/jamaophthalmol.2018.6940.

Tailored vs Static Oxygen Saturation Targets to Prevent Retinopathy of Prematurity

Ann Hellström, MD, PhD, Anna-Lena Hård, MD, PhD, Lois E. H. Smith, MD, PhD

Department of Ophthalmology, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden (Hellström, Hård); Department of Ophthalmology, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts (Smith).

Oxygen supplementation is a risk factor for retinopathy of prematurity (ROP) but is also necessary for the survival of extremely preterm infants. Oxygen supplementation to preterm infants must balance these risks and benefits. Lower oxygen levels promote the vascular development of eyes, lungs, and other organs but are associated with increased mortality rates. Higher oxygen saturation levels are needed for extrauterine adaptation, energy generation, and survival but increase the risk of ROP. To our knowledge, the optimal oxygenation (including optimal oxygen saturation at different postnatal ages) is not known. In this issue of *JAMA Ophthalmology*, Shukla et al¹ begin to address the complexity of optimizing the balance between the risk factors of ROP and mortality rates by examining the association of biphasic vs static oxygen saturation targets with ROP.

The Neonatal Oxygenation Prospective Meta-analysis Collaboration compared, in 5 similar studies, a constant oxygen saturation (SpO₂) target of 85% to 89% vs 91% to 95% for all postnatal ages of preterm infants who required oxygen supplementation. The lower target was associated with less severe ROP that required treatment but also with increased mortality rates and an increased incidence of severe necrotizing enterocolitis.² However, only target ranges and not the infants' actual oxygenation levels were evaluated in association with the outcome. The measured SpO₂ levels showed an overlap between the study groups. After these studies were published, many clinics adopted the higher SpO₂ target range of 91% to 95% for all preterm infants from birth onward who require oxygen supplementation.

Retinopathy of prematurity is regarded as a 2-phase disease. In the first phase, hyperoxia suppresses oxygen-regulated vascular growth factors, such as vascular endothelial growth factor, preventing normal retinal vascularization during the first weeks of life, leaving the peripheral retinal avascular and prone to hypoxia. In the second phase, hypoxia causes an increase in vascular endothelial growth factor that leads to pathologic neovascularization. Thus one might speculate that lower oxygen saturation during the first weeks of life and higher targets later might reduce the incidence of severe ROP. A systematic review and meta-analysis by Chen et al³ supported a preventive association of early low and later higher

Corresponding Author: Lois E. H. Smith, MD, PhD, Department of Ophthalmology, Boston Children's Hospital, Harvard Medical School, 300 Longwood Ave, Boston, MA 02115 (lois.smith@childrens.harvard.edu).

Conflict of Interest Disclosures: None reported.

SpO₂ targets. Cayabyab et al.⁴ compared infants with gestational ages between 24 and 28 weeks during a period with a constant SpO₂ target of 90% to 94% up to 36 weeks postmenstrual age (PMA) and thereafter an SpO₂ target of more than 94% with a similar regimen but with SpO₂ targets of 83% to 90% before 33 weeks PMA. A reduced incidence of severe ROP was found in the infants with a lower SpO₂ target before 33 weeks PMA (34.9% vs 19.7%). This aligns with the results of Shukla et al.¹ In this study, preterm infants (with a gestational age at birth younger than or equal to 31 weeks) had a lower incidence of type 1 ROP warranting treatment when the SpO₂ target ranges were biphasic, with 85% to 92% for ages younger than 34 weeks' corrected gestational age and more than 95% for ages older than 34 weeks' corrected gestational age. The 2 studies compared populations during different periods with other differences in clinical practice that may affect ROP incidence.

The role of oxygen in ROP pathogenesis is complex and an increased risk of ROP after implementing constant SpO₂ targets of 91% to 95% has been reported.⁵ To our knowledge, it is unknown whether the increased risk is due to early hyperoxia. It might also be a result of alterations in oxygen saturation fluctuations, which are strongly associated with ROP, when the oxygen supply is increased after desaturations. There is also some contrary evidence that infants who later develop severe ROP tend to have less hyperoxia during the first weeks of life than those without ROP. It was reported that infants in a clinic with an SpO₂ target range of 85% to 95% who later developed severe ROP had a tendency to have lower SaO₂ levels early after birth compared with those with no or mild ROP. The difference, which was partly due to an increased frequency of intermittent hypoxic episodes, increased with time and became significant after 42 days of life.

On the other side of the equation, low oxygen saturation during the first 3 days of life has been associated with lower 90-day survival rates.⁶ It is possible that different infants have different oxygenation needs. At birth, those with the youngest gestational ages seem to have a less developed ability to use oxygen for oxidative phosphorylation than more mature infants.⁷ In the neonatal period, boys have higher levels of oxidative stress markers and lower levels of markers of antioxidant defense than girls,⁸ and infants who are small-for-gestational age at birth appear to be more vulnerable to hypoxia during the neonatal period.⁶ Transfusions with red blood cells that contain adult hemoglobin in preterm infants result in a reduced oxygen affinity, which should be considered when oxygen supplementation is regulated.

Shukla et al.¹ found an increase in any ROP (and an increase in severe ROP) as well as retarded retinal vascularization after implementing a constant high SpO₂ target range. The higher target range was also associated with a reduced incidence of patent ductus arteriosus. This study is an important first step in defining the use of oxygen while considering the timing of oxygen supplementation as well as the saturation targets. The use of lower SpO₂ targets early and higher during a later period has the potential to become a preventive strategy for ROP. Future research that prospectively evaluates oxygenation in different groups with regard to postnatal age and retinal development, gestational age at birth, sex, blood transfusions, and intrauterine growth restriction will confirm if personalized oxygen supplementation can be beneficial to minimize ROP and morbidity and mortality.

REFERENCES

1. Shukla A, Sonnie C, Worley S, et al. Comparison of biphasic vs static oxygen saturation targets among infants with retinopathy of prematurity [published online February 14, 2019]. *JAMA Ophthalmol*. doi:10.1001/jamaophthalmol.2018.7021
2. Askie LM, Darlow BA, Finer N, et al.; Neonatal Oxygenation Prospective Meta-analysis (NeOProM) Collaboration. Association between oxygen saturation targeting and death or disability in extremely preterm infants in the neonatal oxygenation prospective meta-analysis collaboration. *JAMA*. 2018;319(21):2190–2201. doi:10.1001/jama.2018.5725 [PubMed: 29872859]
3. Chen ML, Guo L, Smith LE, Dammann CE, Dammann O. High or low oxygen saturation and severe retinopathy of prematurity: a meta-analysis. *Pediatrics*. 2010;125(6):e1483–e1492. doi:10.1542/peds.2009-2218 [PubMed: 20498174]
4. Cayabyab R, Arora V, Wertheimer F, Durand M, Ramanathan R. Graded oxygen saturation targets and retinopathy of prematurity in extremely preterm infants. *Pediatr Res*. 2016;80(3):401–406. doi:10.1038/pr.2016.98 [PubMed: 27081928]
5. Manley BJ, Kuschel CA, Elder JE, Doyle LW, Davis PG. Higher rates of retinopathy of prematurity after increasing oxygen saturation targets for very preterm infants: experience in a single center. *J Pediatr*. 2016;168:242–244. doi:10.1016/j.jpeds.2015.10.005 [PubMed: 26548746]
6. Di Fiore JM, Martin RJ, Li H, et al.; SUPPORT Study Group of the Eunice Kennedy Shriver National Institute of Child Health, and Human Development Neonatal Research Network. Patterns of oxygenation, mortality, and growth status in the surfactant positive pressure and oxygen trial cohort. *J Pediatr*. 2017;186:49–56.e1. doi:10.1016/j.jpeds.2017.01.057 [PubMed: 28279433]
7. Ravera S, Podestà M, Sabatini F, et al. Mesenchymal stem cells from preterm to term newborns undergo a significant switch from anaerobic glycolysis to the oxidative phosphorylation. *Cell Mol Life Sci*. 2018;75(5): 889–903. doi:10.1007/s00018-017-2665-z [PubMed: 28975370]
8. Lavoie JC, Tremblay A. Sex-specificity of oxidative stress in newborns leading to a personalized antioxidant nutritive strategy. *Antioxidants (Basel)*. 2018;7(4):E49. doi:10.3390/antiox7040049 [PubMed: 29584624]