Seminars in Perinatology ▮ (2016) ▮▮▮–▮▮▮

Available online at www.sciencedirect.com

Seminars in Perinatology

www.seminperinat.com

Pharmacologic interventions for the prevention and treatment of retinopathy of prematurity

Kay D. Beharry[a,b,c], *Gloria B. Valencia, MD*[a], *Douglas R. Lazzaro, MD*[b,c], *and Jacob V. Aranda, MD, PhD, FRCPC*[a,b,c,*]

[a]*Division of Neonatal–Perinatal Medicine, Department of Pediatrics, State University of New York, Downstate Medical Center, Brooklyn, NY*

[b]*Department of Ophthalmology, State University of New York, Downstate Medical Center, Brooklyn, NY*

[c]*State University of New York Eye Institute, Brooklyn, NY*

ARTICLE INFO

Keywords:
Drug Interventions
Retinopathy of Prematurity
Oxygen

ABSTRACT

Retinopathy of prematurity (ROP), a significant morbidity in prematurely born infants, is the most common cause of visual impairment and blindness in children and persists till adulthood. Strict control of oxygen therapy and prevention of intermittent hypoxia are the keys in the prevention of ROP, but pharmacologic interventions have decreased risk of ROP. Various drug classes such as methylxanthines (caffeine), VEGF inhibitors, antioxidants, and others have decreased ROP occurrence. The timing of pharmacologic intervention remains unsettled, but early prevention rather than controlling disease progression may be preferred. These drugs act through different mechanisms, and synergistic approaches should be considered to maximize efficacy and safety.

Introduction

Retinopathy of prematurity (ROP) is a developmental vascular disorder characterized by abnormal growth of retinal blood vessels in the incompletely vascularized retina of extremely low gestational age neonates (ELGANs) who are <1250 g, <28 weeks gestation.[1–3] In the United States, ROP afflicts about 16,000 ELGANs annually[1] and remains the third leading cause of childhood blindness (14%) with much higher rates in developing countries.[5] Incomplete retinal vascularization due to prematurity and oxygen are key factors in ROP; however, the etiology of this "new" form of ROP is multivariate and complex and involves hypersensitivity of the immature retina to changes in oxygen.[4,6,7]

Pathophysiology of ROP

In humans, the retina develops in utero where tissue oxygen is low.[7] Vascular precursor cells are laid from 12 to 21 weeks gestational age creating a scaffold for future vessel development. The vessels emerge from the optic disk and follow a VEGF template established by astrocytes which populate the retina before the vessels.[8] Angiogenesis begins at approximately 16–17 weeks gestational age, with new vessels budding from existing vessels. The metabolic demands of the developing retina exceed the oxygen supplied by the choroidal circulation resulting in "physiologic hypoxia," and thus stimulate angiogenesis.[7] Vasoactive factors, such as insulin-like growth factor (IGF)-1, vascular endothelial growth factor

This work was supported by the NIH-Eunice Kennedy Shriver National Institute of Child Health & Human Development, Grant no. 1U54HD071594.

*Correspondence to: Department of Pediatrics & Ophthalmology, State University of New York, Downstate Medical Center, 450 Clarkson Ave, Box 49, Brooklyn, NY 11203.

E-mail address: jaranda@downstate.edu (J.V. Aranda).

http://dx.doi.org/10.1053/j.semperi.2015.12.006
0146-0005/

(VEGF), and erythropoietin (Epo), in addition to maternally derived factors, stimulate new vessel formation. The vessels reach the nasal ora serrata by 36 weeks and the temporal ora serrata by 40 weeks. In ELGANs, the retinal vasculature is immature and thus vulnerable to oxidative damage. Early studies by Ashton et al.[9] demonstrated that exposure to oxygen causes vaso-obliteration and vasoproliferation when room air breathing was resumed. Those early studies led to a two-phase hypothesis of ROP: (1) phase 1 or vaso-obliteration begins at preterm birth with the transition from an intrauterine to extrauterine environment causing a rise in PaO_2 of 30–35 mmHg to 55–80 mmHg and loss of placental and maternal growth factors. During this phase, exposure to supplemental oxygen, required for treatment of respiratory distress syndrome, further suppresses retinal growth factors that are already compromised due to preterm birth and poor nutrition,[10] thus leading to arrest and retraction of the developing retinal vessels, or vaso-obliteration; and (2) phase 2 or vasoproliferation begins at approximately 32–34 weeks.[11] As the infant matures, the avascular retina becomes metabolically active, inducing a second phase, or retinal neovascularization.[3] This phase of ROP is driven by hypoxia and subsequent upregulation of VEGF and IGF-I which leads to abnormal vascular overgrowth into the vitreous, retinal hemorrhages, retinal folds, dilated and tortuous posterior retinal blood vessels, or "Plus" disease, and retinal detachment. ELGANs with chronic lung disease experience numerous alterations in their O_2 saturations or apneas.[12,13] Infants who experience the greatest fluctuations in their PaO_2 seem to be at a higher risk for the development of threshold ROP.[6,13] In these infants with "new" ROP, intermittent hypoxia (IH) occurs during supplemental oxygen treatment or phase 1, thus worsening the outcomes during phase 2. Indeed, this was demonstrated in a rat model that utilized brief episodes of hypoxia during hyperoxia, simulating apnea of prematurity.[14–17] The fluctuating oxygen model also shows a higher incidence of intravitreal neovascularization[18] with corresponding high levels of retinal VEGF[19] and vitreous fluid growth factors.[14,15] The pattern of IH may also play a role in the development of ROP[13] and OIR.[14–17] Clustering IH episodes resulted in a more severe form of OIR with increased retinal hemorrhages, vascular tufts, leaky vessels, vascular tortuosity, and vascular overgrowth, compared to dispersed IH episodes. This may be due to differences in exposure time of the retina to hypoxia at a given time point. Clustering episodes of brief hypoxia or grouping of desaturations with minimal time for recovery between episodes causes the retina to remain hypoxic for a longer period of time, thus leading to a more exaggerated increase in VEGF resulting in characteristics consistent with "Plus" disease.[14] In light of these new findings, the phase 1/phase 2 hypothesis of ROP originally proposed in 1954 by Ashton et al.[9] may need to be redefined with respect to "new" ROP and IH.

Oxygen

Oxygen is the most commonly used drug in neonatal care for respiratory support.[20] The widespread use of unrestricted oxygen in preterm infants began in the early 1940s in response to observations that inspired oxygen improved the irregular breathing pattern of premature infants.[21,22] This led to the first epidemic of ROP, described in 1942 by Terry.[23] and then known as retrolental fibroplasia or fibroblastic overgrowth behind the crystalline lens. In 1951, it was suggested that oxygen use was associated with ROP.[24] This was confirmed in 1952 in humans[25] and later in animals.[26] By 1953, approximately 10,000 infants worldwide were blinded.[21] The first multicenter randomized clinical trial to study ROP started in 1953 and involved 18 centers. The study enrolled infants <1500 g in two arms: (1) $FiO_2 \geq 50\%$ for 28 days and (2) $FiO_2 < 50\%$. In 1954, one of the centers reported that blindness was prevented if oxygen did not exceed 40%. However, 6 years later, review of autopsies revealed that curtailed use of oxygen increased the incidence of mortality such that for every eye sight gained, 16 lives were lost.[27] Despite the introduction of transcutaneous oxygen monitoring and pulse oximetry in the 1960s–1980s, and many nonrandomized and randomized clinical trials, the optimum range of oxygenation in preterm infants remains elusive and controversial. The phase 1 (hyperoxia)/phase 2 (hypoxia) hypothesis of ROP led to the premise that administration of oxygen during phase 2 would increase tissue oxygen, decrease VEGF, and curtail vessel overgrowth. This hypothesis was tested in the Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP) randomized clinical trial in 2000.[28] The study randomized 649 infants with prethreshold ROP and O_2 saturation $<94\%$ at 35 weeks to oxygen saturation targets of 89–95% or 96–99%. The STOP-ROP study failed to decrease progression of the disease or reduce the number of infants requiring peripheral ablative surgery and showed no differences in the development of threshold ROP. ELGANs experience continuous fluctuations in arterial O_2 saturation; therefore, increasing inspired oxygen may not be an appropriate approach.[29,30] Instead, low and stable oxygen therapy may be more beneficial.[2] The Australian Benefits of Oxygen Saturation Targeting (BOOST) randomized, double-blind, multicenter trial involving 358 preterm infants, kept the saturation ranges at 91–94% or 95–98%. The incidence of severe ROP was comparable between the groups.[31] Five large multicenter, masked, randomized, control trials (collectively known as The Neonatal Oxygen Prospective Meta-Analysis or NeOPRoM Collaboration) enrolled approximately 5000 ELGANs <28 weeks, compared 85–89% versus 91–95%. In the United States, the Surfactant Positive Pressure and Pulse Oximetry (SUPPORT) trial reported that SpO_2 levels of 85–89% was associated with increased mortality and a higher incidence of severe ROP was found in the 91–95% group.[32] This was reflected in the BOOST II trial (Australia, New Zealand, and United Kingdom) after interim analysis, and enrollment was stopped.[33] The Canadian Oxygen Trial (COT) reported no difference in mortality or severe ROP.[34] A recent meta-analysis of all published randomized trials evaluating the effect of restricted versus liberal oxygen exposure in preterm infants shows no difference in ROP.[35] After over 70 years of oxygen use, and despite large multicenter, randomized clinical trials, there is still no consensus regarding optimal oxygen therapy for ELGANs. Oxygen remains the most commonly used drug in neonatal intensive care units worldwide[36] and the incidence of severe ROP has not appreciably declined.