Published in final edited form as:

Expert Rev Ophthalmol. 2010 October 1; 5(5): 583–585. doi:10.1586/eop.10.60.

Optimum oxygen therapy to prevent retinopathy of prematurity

Waldemar A Carlo and

Division of Neonatology, University of Alabama at Birmingham, 1700 6th Avenue South, 176F Suite 9380R, Birmingham, AL 35294-7335, USA, Tel.: +1 205 934 4680, Fax: +1 205 934 3100, wcarlo@pediatrics.uab.edu

Rosemary D Higgins

The Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, USA

Keywords

blindness; developmental disabilities; hyperoxia; oxygen inhalation therapy; retinopathy of prematurity

Retinopathy leading to blindness and other visual disabilities continues to result in long-term neurodevelopmental impairment in former preterm infants. Up to one in four of the most prematurely born infants (<25 weeks) develop retinopathy of prematurity stage 3 or more with plus disease [1]. With exposure to hyperoxia, even higher rates of retinopathy have been reported. Approximately 2–3% of survivors of extreme prematurity (<26 weeks) become blind despite state-of-the-art care [2]. However, selection of oxygenation goals in preterm infants to prevent retinopathy of prematurity is limited by the lack of appropriately controlled studies.

Efforts to prevent or reduce the incidence and severity of retinopathy of prematurity started in the 1940s and 1950s when it was suspected that excessive oxygen supplementation was a cause of retinopathy. Clinical trials carried out in the 1950s confirmed that restriction of the concentration of oxygen supplementation reduced the relative risk (RR) of retinopathy by approximately 50% [3,4]. However, these trials also reported trends for increased mortality as a result of oxygen restriction [3,4]. Restriction of oxygen concentration became common practice, but several subsequent reports raised concerns that mortality may have increased with oxygen restriction, which, in one of the studies, was estimated to result in an excess of 16 deaths per case of blindness prevented [5].

Subsequent studies evaluated oxygenation levels rather than just the concentration of oxygen supplemented to preterm infants, as had been done in the trials in the 1950s. A multicenter

© 2010 Expert Reviews Ltd

Correspondence to: Waldemar A Carlo.

Financial & competing interests disclosure

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

observational study using intermittent blood gas sampling [6] reported that the occurrence of retinopathy was unexpectedly unrelated to the level of arterial oxygen (PaO_2) but was associated with the concentration of oxygen supplementation and the duration of supplemental oxygen exposure.

With new techniques for continuous monitoring of oxygenation, the association of oxygenation and retinopathy became more evident. A parallel cohort study using transcutaneous oxygen monitoring supported the expected association of retinopathy with exposure to high arterial oxygen levels ($> 80 \text{ mmHg}$) [7]. Using continuous pulse oximetry, several observational studies reported that with lower oxygen saturation targeting, the incidence of retinopathy decreased [8–10]. In these and other studies, targeted saturations to prevent retinopathy varied widely (70–97%). Furthermore, many clinicians have not used the upper alarm limits of the saturation monitors, and even higher oxygen saturations are often tolerated or used for unproven clinical indications such as improved growth [11].

However, all recent studies of oxygen supplementation to prevent retinopathy of prematurity up to now were of low-level evidence (not randomized). Only goals rather than actual oxygenation levels achieved were reported in all studies. Furthermore, despite the concern raised by the early randomized controlled trials and clinical experience that restriction of the concentration of oxygen supplementation would lead to an increase in mortality, many of these and other similar studies did not report the mortality data.

In order to determine if targeting of oxygen saturations at lower levels than usual reduces retinopathy of prematurity, we conducted a multicenter randomized controlled trial in the Eunice Kennedy Shriver National Institute of Child Health and Human Development. Many experts target oxygen saturations of 83–98% in preterm infants needing oxygen supplementation, with lower limits of 83–92% and upper limits of 92–98% reported in a multicenter study of target oxygen saturations in infants at 28 weeks' gestation [12]. Thus, we designed a randomized controlled trial to test the effect of targeting oxygen saturations of 85–89% versus 91–95% in very premature infants of 24–27 weeks gestation. The intervention was started within the first 2 h after birth.

The randomization, intervention and outcomes assessment were masked. Electronically altered pulse oximeters that displayed saturations of 88–92% for both targeted oxygen saturation ranges using an offset of 3% were used. For example, an oxygen saturation display of 90% corresponded to an actual oxygen saturation of 87% in the lower oxygen saturation target groups (85–89%) but corresponded to an actual oxygen saturation of 93% in the higher oxygen saturation target group (91–95%).

All surviving infants were followed by ophthalmologists trained in the diagnosis of retinopathy of prematurity. Examinations began by 33 weeks of postmenstrual age and continued until the study outcome was reached or resolution occurred. Resolution was defined as fully vascularized retinas or immature vessels in zone 3 for two consecutive examinations in each eye. Threshold retinopathy of prematurity (called 'new type 1 threshold' by the Early Treatment of Retinopathy Cooperative Group) [13,14] was diagnosed if any of the following findings were present:

In zone 1, stage 3 retinopathy of prematurity, even without plus disease (i.e., two quadrants of dilated veins and tortuous arteries in the posterior pole), or plus disease with any stage of retinopathy of prematurity;

In zone 2, plus disease with stage 2 retinopathy of prematurity or plus disease with stage 3 retinopathy of prematurity.

Surgical ophthalmologic intervention was recorded if any of the following occurred: laser therapy, cryotherapy, both laser therapy and cryotherapy, scleral buckling, or vitrectomy. The primary outcome was death before discharge or severe retinopathy as defined by threshold retinopathy, ophthalmologic surgery or the use of bevacizumab treatment for retinopathy.

A total of 1316 infants were enrolled. Their baseline characteristics were similar. Severe retinopathy among survivors to discharge, transfer or 1 year was decreased in the lower oxygen saturation group (8.6%) compared with the higher oxygen saturation group (17.9%; RR: 0.52; 95% CI: 0.37–0.73; $p < 0.001$; number needed to treat: 11). However, death before discharge occurred in 130 of the 654 infants (19.9%) in the lower oxygen saturation group versus in 107 of the 662 infants (16.2%) in the higher oxygen saturation group (RR: 1.27; 95% CI: 1.01–1.60; $p = 0.04$; number needed to harm: 27). The combined outcome of severe retinopathy and/or death before discharge did not differ between the lower and higher oxygen saturation groups (28.3 vs 32.1%; RR: 0.90; 95% CI: 0.76–1.06; $p = 0.21$). Other major outcomes did not differ significantly between the two treatment groups. It is important to note that even though the oxygen saturation targets were 85–95%, a larger proportion of the saturation values were above 95% in higher oxygen saturation groups and a larger proportion of the saturation values were below 85% in the lower oxygen saturation group.

Thus, this large trial indicates that while retinopathy can be decreased substantially by targeting oxygen saturation in the range of 85–89%, there is a significantly increased risk of death with the practice. Several studies have reported increased retinopathy when oxygen saturations above 95% are tolerated. The current trial with better levels of evidence indicates that even within the common target range of up to 95%, there is an increased risk of retinopathy.

So what should clinicians do? Because this trial shows that oxygen saturation targeting markedly affects retinopathy of prematurity, clinicians should develop guidelines or protocols that minimize hyperoxia. As infants in the higher oxygen saturation target group spent more time with saturation above the upper target, clinicians may want to put more effort into developing strategies to prevent hyperoxia. Furthermore, as saturations below the low target limits were more common in the lower saturation group, prevention of saturations below 85% may be important to prevent the excess mortality.

In summary, this large, well-designed and masked randomized controlled trial shows that appropriate oxygen targeting has the potential to substantially decrease severe retinopathy. There appears to be potential opportunities for improved targeting of saturations that could result in decreased retinopathy without adverse effects. Clinicians should use the data from this study to develop processes for improved targeting of oxygen saturations.

Acknowledgments

This work was funded in part by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Cooperative Multicenter Neonatal Research Network Grant (U10 HD034216).

Biographies

Waldemar A Carlo

Rosemary D Higgins

References

1. Hintz SR, Kendrick DE, Vohr BR, Poole WK, Higgins RD. National Institute of Child Health and Human Development Neonatal Research Network. Changes in neurodevelopmental outcomes at 18 to 22 months' corrected age among infants of less than 25 weeks' gestational age born in 1993–1999. *Pediatrics*. 2005; 115:1645–1651. [PubMed: 15930228]
2. Vohr BR, Wright LL, Poole WK, McDonald SA. Neurodevelopmental outcomes of extremely low birth weight infants <32 weeks' gestation between 1993 and 1998. *Pediatrics*. 2005; 116:635–643. [PubMed: 16143580]
3. Duc, G.; Sinclair, JC. Oxygen administration. In: Sinclair, JC.; Bracken, MB., editors. *Effective Care of the Newborn Infant*. NY, USA: Oxford University Press; 1992. p. 178-194.
4. Askie LM, Henderson-Smart DJ, Ko H. Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants. *Cochrane Database Syst. Rev.* 2009; 1:CD001077. [PubMed: 19160188]
5. Bolton DP, Cross KW. Further observations on cost of preventing retrolental fibroplasia. *Lancet*. 1974; 303:445–448. [PubMed: 4131442]
6. Kinsey VE, Arnold HJ, Kalina RE, et al. PaO₂ levels and retrolental fibroplasia: a report of the cooperative study. *Pediatrics*. 1977; 60:655–668. [PubMed: 578921]
7. Flynn JT, Bancalari E, Snyder ES, et al. A cohort study of transcutaneous oxygen tension and the incidence and severity of retinopathy of prematurity. *N. Engl. J. Med.* 1992; 326:1050–1054. [PubMed: 1549150]
8. Tin W, Milligan DW, Pennefather P, Hey E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. *Arch. Dis. Child Fetal Neonatal Ed.* 2001; 84:F106–F110. [PubMed: 11207226]
9. Chow LC, Wright KW, Sola A. Can changes in clinical practice decrease the incidence of severe retinopathy of prematurity in very low birth weight infants? *Pediatrics*. 2003; 111:339–345. [PubMed: 12563061]
10. Anderson CG, Benitz WE, Madan A. Retinopathy of prematurity and pulse oximetry: a national survey of recent practices. *J. Perinatol.* 2004; 24:164–168. [PubMed: 14999216]

11. Ellsberry DL, Acarregui MJ, McGuinness GA, Klein JM. Variability in the use of supplemental oxygen for bronchopulmonary dysplasia. *J. Pediatr.* 2002; 140:247–249. [PubMed: 11865280]
12. Hagadorn JI, Furey AM, Nghiem TH, et al. Achieved versus intended pulse oximeter saturation in infants born less than 28 weeks' gestation: the AVIOx study. *Pediatrics.* 2006; 118:1574–1582. [PubMed: 17015549]
13. Hardy RJ, Good WV, Dobson V, et al. Multicenter trial of early treatment for retinopathy of prematurity: study design. *Control. Clin. Trials.* 2004; 25:311–325. [PubMed: 15157731]
14. Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. *Arch. Ophthalmol.* 2003; 121:1684–1694. [PubMed: 14662586]