Published in final edited form as:

J AAPOS. 2007 April ; 11(2): 170–174. doi:10.1016/j.jaapos.2006.08.012.

Incidence of Severe Retinopathy of Prematurity Before and After a Modest Reduction in Target Oxygen Saturation Levels

David K. Wallace, MD, MPH¹, Kathleen A. Veness-Meehan, MD², and William C. Miller, MD, PhD, MPH³

¹ Duke Eye Center, Durham, NC

² Department of Pediatrics, The University of North Carolina, Chapel Hill, NC

³ Departments of Medicine and Epidemiology, The University of North Carolina, Chapel Hill, NC

Abstract

Background—Previous studies suggest that reducing target oxygen saturation levels to 85–93% decreases the incidence of severe retinopathy of prematurity (ROP). Our aim was to determine if a more modest reduction in target oxygen saturation levels also reduces ROP incidence.

Methods—One neonatal intensive care unit instituted new oxygen saturation guidelines that changed target levels from the upper 90's to 90–96%. We conducted a retrospective cohort study to determine the proportion of eyes that progressed to (1) threshold or type I ROP and (2) stage 3. These proportions were compared between two groups of all eligible infants born up to 10 months before (higher O₂ group, n = 46) and up to 16 months after (lower O₂ group, n = 59) the policy change. Binomial regression was used to calculate relative risks adjusted for birth weight, gestational age, apnea, days of mechanical ventilation, and length of hospital stay.

Results—Sixteen of 90 eyes (18%) in the higher O₂ group developed threshold or type I ROP versus 16 of 118 eyes (14%) in the lower O₂ group (adjusted relative risk = 0.66, 95% CI = 0.29, 1.51). Twenty-two of 88 eyes (25%) in the higher O₂ group developed stage 3 ROP versus 26 of 118 eyes (22%) in the lower O₂ group (adjusted relative risk = 0.76, 95% CI = 0.43, 1.37).

Conclusion—We observed a small but statistically insignificant reduction in the incidence of severe ROP after a modest reduction in target oxygen saturation levels to 90–96% in the first several weeks of life.

Introduction

In retinopathy of prematurity (ROP), abnormal retinal vascular development in premature infants may lead to retinal detachment and permanent visual loss. ROP, formerly known as retrolental fibroplasia (RLF), is the second leading cause of blindness in children in the United States after cortical visual impairment.¹ Peripheral retinal ablation by laser or cryotherapy is effective in many cases in preventing retinal detachment, but those eyes that develop a retinal detachment have a very poor visual prognosis.² Therefore, strategies to prevent ROP are needed, and one causative and potentially modifiable factor is supplemental oxygen use.

Corresponding Author and Reprint Requests: David K. Wallace, MD MPH; Duke University Eye Center; P.O. Box 3802, DUMC, Durham, NC 27710; telephone #919-684-4584; fax #919-684-6096; E-mail: david.wallace@duke.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Oxygen was first recognized to cause severe ROP and blindness in the 1950's.³ At that time, the incidence of ROP was very high because premature infants were exposed to unmonitored, high concentrations of oxygen. After this association was recognized, oxygen was severely restricted throughout the 1960's. This strategy dramatically reduced the incidence of ROP; however, it had the unexpected effect of increasing severe brain damage and death.⁴ Since that time, technological advances have allowed continuous monitoring of arterial oxygen saturation levels.

Recently, many neonatal intensive care units have reduced target oxygen saturation levels *more modestly* in an attempt to decrease the incidence of ROP while avoiding increases in neurodevelopmental morbidity or mortality. Many neonatal units have adopted new oxygen saturation policies to reduce the amount of supplemental oxygen given to premature infants. Implementation of these guidelines appears to have reduced the incidence of ROP.^{5–6}

At the beginning of 2004, our neonatal intensive care unit instituted new oxygen saturation guidelines with a targeted range of 90–96% for infants ≤ 30 weeks gestational age at birth. Before then, oxygen saturation levels were generally kept in the upper 90's. These new guidelines represented a more modest reduction in oxygen saturation targets than guidelines previously studied.^{5–6} The purpose of our study was to compare the risk (cumulative incidence) of severe ROP (threshold or type I ROP) before and after this change in target oxygen saturation levels. Our study advances previous work by assessing the effect of potentially confounding variables such as birth weight and gestational age.

Subjects and Methods

We used a retrospective cohort study design. Eligibility criteria were: (1) birth weight less or equal than 1250 grams, (2) no more than one week (7 days) of the first 6 weeks of life spent at another hospital, and (3) serial ROP examinations performed for a period of time sufficient to determine if the outcome measures were present or absent (primary outcome = threshold or type I ROP;⁷ secondary outcome = stage 3). These outcomes were considered to be absent if they had not appeared by an examination performed at 40.5 weeks postmenstrual age or later, or if there was complete retinal vascularization, or incomplete vascularization or ROP in zone III. The criterion of 40.5 weeks postmenstrual age was chosen a priori because it represented an age when approximately 85% of infants with ROP would have reached threshold,⁸ while not excluding too many infants. Results of eye examinations were recorded using the International Classification of ROP.^{9,10} More than 95% of examinations were performed by one of the coauthors (DKW), who was a certified examiner for the Early Treatment for Retinopathy of Prematurity (ETROP) study.⁷ We collected data from the charts of all eligible infants born on or after October 1, 2002, except for those born between August 1, 2003, and December 31, 2003, which was the period of time when our neonatal unit was transitioning to the new oxygen saturation protocol. The higher oxygen group included infants born between October 1, 2002, and July 31, 2003. Infants born before October 1, 2002, were excluded because they participated in the ETROP Clinical Trial.⁷ The lower oxygen group included infants born between January 1, 2004, and April 30, 2005. Power calculations were not done, since the sample size was limited by the number of eligible infants. All eligible infants were included. Institutional Review Board approval was obtained and included waiver of informed consent.

Until late 2003, oxygen saturation was generally kept in the upper 90's, and oxygen saturations were frequently in the range of 98–100%. The new oxygen saturation policy started late in 2003 and was fully implemented by January 1, 2004. For infants born ≤ 30 weeks postmenstrual age, the target oxygen saturation was 90–96%, and the alarm limits were set at a low of 89% and a high of 97%. The alarm sounded when 100 “saturation-seconds” occurred, defined as the time in seconds multiplied by the percentage above or below the limits. For example, the

alarm sounded when the oxygen saturation was 85% (4% below the lower limit) for 25 seconds, or 79% (10% below the lower limit) for 10 seconds. The nursing staff attempted to maintain these new target oxygen saturation levels as long as the infants were on oxygen. Although they were educated with regard to the target levels, no effort was made to confirm that they were adhering to these guidelines.

Potentially confounding variables (covariates) were identified by a priori discussion among co-authors of possible differences in neonatal care between the higher and lower target oxygen groups. The differences identified were (1) more frequent use in the lower oxygen group of vitamin A supplementation and (2) high flow oxygen delivered via nasal cannula to reduce apneic episodes. Beginning on September 27, 2004, all infants 1000g or less at birth who were on supplemental oxygen at 24 hours of age received 12 doses over 4 weeks of 5000 international units of vitamin A intramuscularly. Therefore, data were collected on the use of vitamin A as well as the presence of apnea. Apnea was consistently documented in patients' charts when cessation of breathing occurred for 20 seconds or more based on cardiorespiratory monitoring. We assessed other covariates because they were established strong risk factors for ROP and could be measured accurately. These variables included birth weight, gestational age at birth, days of mechanical ventilation, and total length of stay in the hospital. Mechanical ventilation was a surrogate for presence and severity of lung disease, and length of stay in the hospital was used as a marker of general health.

The primary measure of effect was the relative risk (risk ratio), defined as the risk (cumulative incidence) of the outcome (primary = laser criteria of threshold or type I ROP, secondary = stage 3 ROP) in the exposed (lower oxygen) group divided by the risk of the outcome in the unexposed (higher oxygen) group. Binomial regression analysis was done to calculate crude and adjusted risk ratios using generalized estimating equations (GEE), which allowed inclusion of data from both eyes while accounting for the correlation between eyes of individual infants. Analyses were conducted using SAS 9.1 (Cary, NC). Birth weight was described by 3 categories: ≤ 750 grams, 751–1000 grams, and 1001–1250 grams. Days of mechanical ventilation was stratified into 3 categories: 0–7 days, 8–28 days, and ≥ 29 days. Total length of stay in our hospital was described by 3 categories: 0–60 days, 61–90 days, and ≥ 91 days. Apnea was described as present or absent. Gestational age at birth was treated as linear, because the risk ratio estimates for both outcomes were monotonic over 4 categories of gestational age (≤ 25 weeks, 26–27 weeks, 28 weeks, and ≥ 29 weeks). Continuous values were not used for other variables because categorical risk ratio estimates were not monotonic. Vitamin A could not be included as a covariate because no infants in the higher oxygen group received vitamin A supplementation.

We used a generalized linear model with a log link and binomial distribution (binomial regression) to estimate the risk ratio of the relationship between oxygen exposure and each outcome. First, each covariate was tested separately in a model which included only the exposure and the outcome. From these variables, the covariates that changed the risk ratio estimate by at least 10% were included in a full multivariable model. We used backward elimination to assess the effect of each covariate on the risk ratio estimate of the oxygen effect. Covariates were removed one at a time, and in each case the variable with the highest p value was removed first. If removal of the covariate changed the risk ratio estimate by less than 10%, then it was kept out of the model and the next covariate was removed. This process was repeated until removal of a covariate resulted in a change in estimate of 10% or greater. We examined both laser criteria and stage 3 as outcomes.

Results

Study Population

One hundred ten eyes of 55 infants in the higher oxygen group and 162 eyes of 81 infants in the lower oxygen group had a birth weight less or equal than 1250 grams and spent no more than one of the first 6 weeks of life at another hospital. Of these, 90 eyes of 46 infants in the higher oxygen group and 118 eyes of 59 infants in the lower oxygen group had an outcome determined and were included in the primary analyses. In the higher oxygen group, 20 of 110 eyes (18%) in 11 patients were excluded because an outcome was not determined; of these, one infant died (2 eyes), one infant developed endophthalmitis in one eye prior to ROP screening, and 9 infants (17 eyes) were transferred to another hospital or discharged and followed elsewhere prior to an outcome examination. (An outcome had been determined prior to discharge in one eye but not in the other eye of one infant.) In the lower oxygen group, 44 of 162 eyes (27%) in 22 patients were excluded because an outcome was not determined; of these, 3 infants died (6 eyes) and 19 infants (38 eyes) were transferred to another hospital or discharged and followed elsewhere prior to an outcome examination. One infant in the higher oxygen group was excluded because his target oxygen saturation was 92–98%; he was not exposed to the new oxygen policy because his gestational age at birth was 31 weeks. One infant in the higher oxygen group was excluded only from the analysis with stage 3 as the outcome because the interval between two examinations was too long to be certain that stage 3 did not appear and then regress without detection. The Table shows that infants in the lower oxygen group had a lower mean birth weight (873 versus 945 grams) that was not statistically significant ($p = 0.06$).

Primary Outcome (Criteria for Laser Treatment)

Sixteen of 90 eyes (18%) in the higher O₂ group developed threshold or type I ROP compared to 16 of 118 eyes (14%) in the lower O₂ group. (unadjusted risk ratio 0.78, 95% CI = 0.32, 1.89). After adjustment for birth weight, length of hospital stay, and duration of mechanical ventilation, the risk ratio was 0.67 (95% CI = 0.30, 1.51). With adjustment for length of hospital stay, the adjusted risk ratio was 0.66 (95% CI = 0.29, 1.51, $p = 0.3$), a relative reduction of 34%. (Relative reduction = $1 - \text{adjusted risk ratio} = 1 - 0.66 = 0.34$)

Secondary Outcome (Stage 3 ROP)

Twenty-two of 88 eyes (25%) in the higher O₂ group developed stage 3 ROP compared to 26 of 118 eyes (22%) in the lower O₂ group, corresponding to an unadjusted risk ratio of 0.90 (95% CI = 0.46, 1.78). After adjustment for birth weight, gestational age, length of hospital stay, duration of mechanical ventilation, and apnea, the risk ratio was 0.83 (95% CI = 0.47, 1.48). In a reduced model, the adjusted risk ratio was 0.76 (95% CI = 0.43, 1.37, $p = 0.4$) with adjustment for birth weight and length of hospital stay, corresponding to a relative reduction in incidence of stage 3 ROP by 24%. (Relative reduction = $1 - \text{adjusted risk ratio} = 1 - 0.76 = 0.24$)

Discussion

We used a retrospective cohort design to investigate whether a modest reduction in target oxygen saturation levels reduced the incidence of ROP in one nursery. After adjustment, our relative risk point estimates suggested a modestly protective effect of lower oxygen target saturation levels on the development of severe ROP. However, this single-center study had a limited sample size. Therefore, these estimates were imprecise and were not statistically significant.

Other studies have reported decreases in the incidence of severe ROP after target oxygen saturation levels were reduced, although the magnitudes of these reductions have been quite variable. Chow and associates found a reduction in the incidence of stage 3 or 4 ROP from 12.5% in 1997 to 2.5% in 2001 and a decrease in laser treatment from 4.5% to 0% after implementation of a strict oxygen management policy with saturation limits of 85% to 93% for infants ≤ 32 weeks gestation.⁵ Tin and associates conducted an observational cohort study to compare the incidence of severe ROP in infants with a target oxygen saturation range of 88–98% to those with a target range of 70–90%.⁶ The risk of severe ROP was 27.7% (95% CI = 17.3 to 40.2%) in the higher oxygen group versus 6.2% (95% CI = 1.7 to 15.0%) in the lower oxygen group. VanderVeen and associates studied the impact of changing oximetry alarm limits to 85–93% with target saturations of 90–92% for those infants ≤ 32 weeks gestation. They reported a reduction in the incidence of prethreshold ROP in at least one eye from 17.5% (44/251 infants) to 5.6% (4/72 infants).¹¹ Britt and Sandoval reported a reduction in the incidence of severe ROP after institution of a policy to keep oxygen saturation between 85 and 93% for infants ≤ 30 weeks gestation. The incidence of stage 3 or more advanced ROP decreased from 49% (18/37) to 15% (5/33), and the need for laser decreased from 38% (14/37) to 15% (5/33). (abstract) These studies were similar to ours in that most of them used a historical control group; however, they differed from ours in that they did not adjust for confounding variables. By identifying and adjusting for confounding variables, we increased the comparability of our two groups. This type of design and analysis is particularly important when historical control groups are used, since advances in medical care and shifting patient populations can result in groups that are not comparable.

In comparison to the aforementioned studies, our relative risk point estimates suggest a smaller reduction in the incidence of severe ROP. One possible reason is that our target oxygen saturation levels in the “lower” oxygen group were higher than that of the other studies. That is, there may be a dose-response relationship between target oxygen saturation levels and risk of severe ROP. We do not know the typical target oxygen saturation ranges of other neonatal intensive care units, but our target ranges were higher than that of other studies. A second possibility is that our nursery did not have procedures to insure adherence with the new oxygen policy. In contrast, Chow and associates implemented several additional steps, including monitoring of fraction of inspired oxygen at birth and during in-hospital transport, avoidance of hyperoxia and repeated episodes of hypoxia-hyperoxia, and creation of teams of neonatal nurses and respiratory therapists to help monitor adherence with the policy.⁵

The hypothesis that lower target oxygen saturation levels reduce the incidence of severe ROP is biologically plausible. Premature infants are exposed to much higher blood oxygen concentrations in the neonatal nursery compared to the intrauterine environment. Oxygen is a potent vasoconstrictor, and prolonged vasoconstriction can lead to vasoobliteration and peripheral retinal ischemia, initiating a cascade of events culminating in neovascularization.^{12,13} In fact, this mechanism is well-established in the laboratory, and high oxygen levels are used to create rat models of ROP.^{14–16} Relative hyperoxia probably has its most detrimental effect on retinal vascular development early in life, so we chose the first 6 weeks as the critical time of exposure in this study. Tin et al. required that infants were cared for in one of their units for at least the first 4 weeks of life.⁶ Chow et al. used saturation goal limits from birth until 2 to 8 weeks of age, depending on the gestational age at birth.⁵

This study must be viewed in light of some limitations. Our sample size was relatively small because it was based on the number of eligible infants in our neonatal nursery during the time period of interest. Therefore, our estimates of effect were imprecise, and they were not statistically significant. As a result, we cannot conclude with certainty that reducing target oxygen saturation decreased the incidence of severe ROP in our nursery. In addition, the small sample size and short follow-up time did not allow us to assess possible adverse effects of

reducing target oxygen levels, such as neurodevelopmental deficits or mortality. Two studies have found no difference in mortality or neurodevelopmental outcomes in infants randomized to higher versus lower target oxygen saturation levels.^{6,17}

It is also possible that we had exposure misclassification (infants in the lower oxygen group not actually staying within their target ranges) as a result of partial lack of adherence to the new oxygen saturation policy, since we did not formally assess compliance with the policy. This misclassification would likely be a differential type, affecting the lower O₂ group more than the higher O₂ group, since the more stringent target oxygen saturation guidelines implemented for the lower O₂ group represented a change in practice. This type of misclassification would likely bias our results toward the null hypothesis of no difference in severe ROP between groups. Because we did not measure oxygen saturation in this study, we cannot know with certainty that the two groups differed in their actual oxygen saturation levels. However, we do know that the lower O₂ group was exposed to a new oxygen saturation policy with a greater emphasis on preventing high saturation levels than the higher O₂ group.

Another limitation is that we were unable to adjust for all potential confounding variables. There were no infants in the higher oxygen group who received vitamin A supplementation, so we were unable to adjust for this variable. However, the association between vitamin A and decreased ROP is relatively weak and controversial.^{18,19} Because our study did not include randomization, we were also unable to control for unknown or unrecognized confounding variables. We cannot measure the impact of this limitation on our results, but we acknowledge that the potential for confounding exists despite our efforts to adjust for important, recognized covariates.

With regard to other potential sources of bias, this study was not conceived until 2005, so there were very few patients examined with knowledge that the results would be used for a study. It is notable that more infants in the lower oxygen group were excluded because they were transferred before an outcome could be determined. These infants were likely healthier and less likely to develop severe ROP, which could bias our results toward the null hypothesis of finding no difference. However, our adjusted analysis should adequately account for this potential difference between groups.

In conclusion, we found a small, statistically insignificant decrease in ROP incidence after implementing a policy of modest reduction in target oxygen saturation levels to 90–96%. Results from other studies support the premise that greater reductions in target oxygen saturation levels result in larger decreases in ROP incidence. However, reducing target oxygen saturation levels is not without potential harm, such as increasing the risks of neurodevelopmental deficits and/or death, outcomes that were not examined in this study. Our results reinforce the need for an adequately powered, multi-center, prospective randomized clinical trial to control for potential confounding variables and assess long-term outcomes and adverse events.²⁰

Acknowledgments

Supported by a K23 Grant from the National Eye Institute (K23 EY015806) Presented at the 32nd Annual Meeting of the American Association for Pediatric Ophthalmology and Strabismus, Keystone, Colorado, March, 2006.

References

1. Steinkuller PG, Du L, Gilbert C, et al. Childhood blindness. J of AAPOS 1999;3:26–32. [PubMed: 10071898]
2. Quinn GE, Dobson V, Barr CC, Davis BR, Palmer EA, Robertson J, Summers CG, Trese MT, Tung B. Visual acuity of eyes after vitrectomy for retinopathy of prematurity: follow-up at 5 1/2 years. The

- Cryotherapy for Retinopathy of Prematurity Cooperative Group. *Ophthalmology* 1996;103:595–600. [PubMed: 8618758]
3. Patz A, Hoeck LE, De La Cruz E. Studies on the effect of high oxygen administration in retrolental fibroplasia: I, nursery observations. *Am J Ophthalmol* 1952;35:1248–53. [PubMed: 12976495]
 4. Cross KW. Cost of preventing retrolental fibroplasia? *Lancet* 1973;2:954–6. [PubMed: 4126572]
 5. Chow LC, Wright KW, Sola A. CSMC Oxygen Administration Study Group. Can changes in clinical practice decrease the incidence of severe retinopathy of prematurity in very low birth weight infants? *Pediatrics* 2003;111:339–45. [PubMed: 12563061]
 6. Tin W, Milligan DWA, 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]
 7. 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;121:1684–94. [PubMed: 14662586]
 8. Palmer EA, Flynn JT, Hardy RJ, et al. Incidence and early course of retinopathy of prematurity. *Ophthalmology* 1991;98:1628–40. [PubMed: 1800923]
 9. The Committee for the Classification of Retinopathy of Prematurity. An international classification of retinopathy of prematurity. *Arch Ophthalmol* 1984;102:1130–4. [PubMed: 6547831]
 10. An International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity Revisited. *Archives of Ophthalmology* 2005;123:991–999. [PubMed: 16009843]
 11. VanderVeen DK, Mansfield TA, Eichenwald EC. Lower oxygen saturation alarm limits decreases the severity of retinopathy of prematurity. *J of AAPOS* 2006;:-—.
 12. Pierce EA, Foley ED, Smith LEH. Regulation of retinal vascular endothelial growth factor by hyperoxia and hypoxia: A possible etiology for retinopathy of prematurity. *Inv Ophthalmol Vis Sci* 1995;36:S871.
 13. Hellstrom A, Engstrom E, Hard A, et al. Postnatal serum insulin-like factor I deficiency is associated with retinopathy of prematurity and other complications of premature birth. *Pediatrics* 2003;112:1016–20. [PubMed: 14595040]
 14. Penn JS, Thum LA. Oxygen-induced retinopathy in the rat. *Basic Life Sci* 1988;49:1025–8. [PubMed: 3250464]
 15. Ricci B. Oxygen-induced retinopathy in the rat model. *Doc Ophthalmol* 1990;74:171–7. [PubMed: 2209374]
 16. McCollm JR, Geisen P, Hartnett ME. VEGF isoforms and their expression after a single episode of hypoxia or repeated fluctuations between hyperoxia and hypoxia: relevance to clinical ROP. *Mol Vis* 2004;10:512–20. [PubMed: 15303088]
 17. Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM. Oxygen-saturation targets and outcomes in extremely preterm infants. *New England Journal of Medicine* 2003;349:959–67. [PubMed: 12954744]
 18. Shenai JP, Kennedy KA, Chytil F, Stahlman MT. Clinical trial of vitamin A supplementation in infants susceptible to bronchopulmonary dysplasia. *J Pediatr* 1987;111:269–77. [PubMed: 3302193]
 19. Wardle SP, Hughes A, Chen S, Shaw NJ. Randomised controlled trial of oral vitamin A supplementation in preterm infants to prevent chronic lung disease. *Arch Dis Child Fetal Neonatal Ed* 2001;84:F9–F13. [PubMed: 11124916]
 20. Cole CH, Wright KW, Tarnow-Mordi W, Phelps DL. Pulse Oximetry Saturation Trial for Prevention of Retinopathy of Prematurity Planning Study Group. Resolving our uncertainty about oxygen therapy. *Pediatrics* 2003;112:1415–9. [PubMed: 14654618]

Table

Characteristics of patients in the Higher Oxygen (O₂) Group (born between 10-1-02 and 7-31-03 and target oxygen saturation in the upper 90s) and the Lower O₂ Group (born between 1-1-04 and 4-30-05 and target oxygen saturation range of 90–96%)

	Higher O ₂ Group	Lower O ₂ Group	P value
Number of infants	46	59	-
Number of eyes	90	118	-
Mean birth weight, grams	945	873	0.06
Mean gestational age, weeks	27	27	0.4
Mean duration of mechanical ventilation, days	22	26	0.6
Mean length of hospital stay, days	79	92	0.2
Apnea, <i>n</i> (%)	42 (91%)	57 (97%)	0.4
Vitamin A supplementation, <i>n</i> (%)	0	21 (36%)	<0.001