

# A PHYSIOLOGIC REDUCED OXYGEN PROTOCOL DECREASES THE INCIDENCE OF THRESHOLD RETINOPATHY OF PREMATURITY

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## ABSTRACT

**Purpose:** To report the incidence of threshold retinopathy of prematurity (ROP) in very low birth weight premature infants from three neonatal intensive care units (NICUs) before and after implementation of a physiologic reduced oxygen protocol (PROP).

**Methods:** Prospective, observational study of data from three NICUs: Cedars-Sinai Medical Center (CSMC), Los Angeles; Good Samaritan Hospital (GSH), Los Angeles; and National University Hospital (NUH), Singapore. PROP was implemented to keep oxygen saturation values by pulse oximeter (SpO<sub>2</sub>) between 83% and 93% (as described in *Pediatrics* 2003;111:339-345). The incidence of threshold ROP in the year before and the year after implementation of PROP was compared. Data from the transition year were not included in the analysis.

**Results:** The incidence of threshold ROP decreased in each center: CSMC, 3.3% to 0.0% (3/92 to 0/88); GSH, 14.8% to 4.9% (8/54 to 2/41); and NUH, 6.7% to 0.0% (3/45 to 0/30). Overall, the incidence of threshold ROP decreased from 7.3% to 1.3%. ( $P < .05$ ). The 95% confidence interval was 4.3% to 12% for the pre-PROP group and 0.05% to 4.76% for the post-PROP group.

**Conclusions:** Physiologic hypoxia is the normal fetal state. Exposure of newborn premature infants to hyperoxia down-regulates retinal vascular endothelial growth factor. This arrests the normal retinal vascular migration and causes vaso-obliteration, the first phase of ROP. The hypothesis is that maintaining SpO<sub>2</sub> values between 83% and 93% in the immediate postgestation life, combined with strict control of oxygen fluctuations, prevents the early vaso-obliterative phase and subsequent development of severe ROP. Significant reduction of threshold disease after implementation of PROP in all three centers supports the hypothesis.

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## INTRODUCTION

Use of oxygen in neonatal units began in the early 1940s, based on observations that increasing the fraction of inspired oxygen (FiO<sub>2</sub>) imparts a more regular breathing pattern to infants.<sup>1,2</sup> Newly designed incubators in the late 1940s enabled maintenance of high O<sub>2</sub> (oxygen) concentrations for prolonged intervals.<sup>2</sup> By the early 1950s, blindness from retrolental fibroplasia (RLF) was an epidemic,<sup>3</sup> occurring in over 10,000 premature babies.<sup>1</sup> By the mid-1950s, oxygen was implicated as a cause of blindness from RLF.<sup>4-6</sup> The National Institutes of Health sponsored a multicenter randomized control trial comparing "routine oxygen" to "curtailed oxygen" in babies weighing less than 1,500 g. The results were conclusive: the rate of cicatricial eye disease was reduced by two thirds with curtailed oxygen.<sup>3</sup> Subgroup analysis suggested the risk of eye damage was related to the duration of oxygen exposure, but no correlation was found with the level of FiO<sub>2</sub>. Nonetheless, an FiO<sub>2</sub> of 40% was adopted as the upper limit of what was "safe."<sup>1</sup> Pulse oximetry was unavailable at the time,<sup>1</sup> and bluish skin color of neonates was found to be an unreliable indicator of hypoxia.<sup>7</sup> Blindness from RLF was reduced significantly with curtailed oxygen delivery, but the inability to monitor blood oxygen saturation resulted in increased infant morbidity and mortality.

In the 1960s, concern over the risks of increased mortality, and cerebral palsy with curtailed oxygen protocols, resulted in a liberalization of oxygen delivery.<sup>8-15</sup> At the same time, cryotherapy studies suggested that in some infants the disease is treatable. Unfortunately, even when disease regression occurs with treatment, the visual outcome is poor in a significant proportion of children.<sup>16-18</sup> By the 1980s, a second retinopathy of prematurity (ROP) epidemic had developed,<sup>9</sup> which, in part, was related to increased survival of infants of very low birth weight, but increased oxygen delivery also was a factor.<sup>19</sup> Studies showed that low birth weight and gestational age are the single most important predictors for the development and severity of ROP and correlate with the area of avascular retina at birth.<sup>20-24</sup>

Use of pulse oximetry has facilitated control of oxygen fluctuations and more targeted overall O<sub>2</sub> saturations in neonates.<sup>25-27</sup> Recent results reported in *Pediatrics* in 2003 showed a dramatic reduction of severe ROP after introduction of a protocol of reduced oxygen saturation for premature infants of very low birth weight.<sup>28</sup> The present study was undertaken to ascertain if prevention of severe ROP translated to other centers that adopted the protocol of physiologic reduced oxygen saturation for very low birth weight premature infants.

From the Cedars-Sinai Medical Center, Los Angeles, California (Dr Wright, Dr Sami); Stroger Hospital of Cook County, Chicago, Illinois (Dr Thompson); Keck School of Medicine, University of Southern California, Los Angeles (Dr Wright and Dr Ramanathan); National University Hospital, National University of Singapore (Dr Joseph); and Singapore National Eye Centre, National University Hospital, Singapore (Dr Farzavandi). Supported by the Wright Foundation for Pediatric Ophthalmology and Strabismus. This study was conducted at Cedars-Sinai Medical Center and Good Samaritan Hospital, Los Angeles, California, and National University Hospital, Singapore. The authors disclose no financial interests in this article.

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Bold type indicates AOS member.

**METHODS**

This was an observational study of data that was prospectively collected from three neonatal intensive care units (NICUs): Cedars-Sinai Medical Center (CSMC), Los Angeles; Good Samaritan Hospital (GSH), Los Angeles; and National University Hospital (NUH), Singapore. Institutional review board approval was obtained at all three centers for data collection and analysis. Prior to the protocol, the oxygen saturation goals at the three NICUs were as follows: CSMC, > 90%; GSH, 89% to 94%; and NUH, 90% to 95%. A physiologic reduced oxygen protocol (PROP) was implemented in all three NICUs to keep oxygen saturation values by pulse oximeter (SpO<sub>2</sub>) between 83% and 93%, as previously described.<sup>28</sup> All three centers were site visited by one of the authors (K.W.W.). NICU staff were trained to minimize fluctuations in SpO<sub>2</sub> and to adjust the FiO<sub>2</sub> in small increments. The infants were examined by an experienced pediatric ophthalmologist at each institution. The indications for screening and the timing of examination followed the International Classification of ROP (ICROP) and the American Academy of Pediatrics guidelines.<sup>29,30</sup> Fundus examination was performed using indirect ophthalmoscopy with an eyelid speculum in place and with scleral depression. Diode laser photocoagulation was performed for threshold ROP.<sup>16,31-34</sup>

The data were collected and analyzed in different birth weight categories (500 to 749 g, 750 to 999 g, 1,000 to 1,249 g, 1,250 to 1,500 g). Infant mortality rate was defined as all infant deaths at any age that occurred before discharge from the NICU. Babies with severe cardiovascular disease or congenital deformities, who could not be placed on the reduced oxygen protocol, were excluded from the sample. The incidence of threshold ROP in the year before and the year after implementation of the protocol was compared. Data from the transition year were not included in the analysis.

**RESULTS**

The incidence of threshold ROP decreased in each center: CSMC, 3.3% to 0.0% (n = 3/92 to 0/88); GSH, 14.8% to 4.9% (n = 8/54 to 2/41); NUH, 6.7% to 0.0% (n = 3/45 to 0/30). Overall, the incidence of threshold ROP decreased from 7.3% to 1.3% (Table 1). The *P* value for the combined statistic (N = 14/191 to 2/159) is *P* < .05. The 95% confidence interval was 4.3% to 12% for the pre-PROP group and 0.05% to 4.76 % for the post-PROP group. Infant mortality rates did not change significantly at all three centers after implementation of the reduced oxygen protocol.(N = 15/191 to 15/159) (Table 2).

**TABLE 1. INCIDENCE OF RETINOPATHY OF PREMATURITY (ROP) AT THREE CENTERS IN THE YEAR BEFORE AND AFTER IMPLEMENTATION OF THE PHYSIOLOGIC REDUCED OXYGEN PROTOCOL FOR INFANTS WEIGHING BETWEEN 500 AND 1,500 G**

CENTER	TRANSITION YEAR*	% CHANGE IN THRESHOLD ROP
CSMC	1998	3/92 (3.3%) to 0/88 (0%)
GSH	2002	8/54 (14.8%) to 2/41 (4.9%)
NUH	2002	3/45 ( 6.7%) to 0/30 (0%)

CSMC = Cedars-Sinai Medical Center; GSH = Good Samaritan Hospital; NUH = National University Hospital.

\*Transition year is the year the physiologic reduced oxygen protocol was instituted.

**TABLE 2. INFANT MORTALITY RATES AT THREE CENTERS IN THE YEAR BEFORE AND AFTER IMPLEMENTATION OF A PHYSIOLOGIC REDUCED OXYGEN PROTOCOL FOR INFANTS WEIGHING BETWEEN 500 AND 1,500 G**

CENTER	TRANSITION YEAR	% CHANGE IN INFANT MORTALITY
CSMC	1998	12/92 (13.0 %) to 13/88 (14.8%)
GSH	2002	1/54 ( 1.9 %) to 1/41 ( 2.4%)
NUH	2002	2/45 ( 4.4 %) to 1/30 ( 3.3 %)

CSMC = Cedars-Sinai Medical Center; GSH = Good Samaritan Hospital; NUH = National University Hospital.

\*Transition year is the year the physiologic reduced oxygen protocol was instituted.

## DISCUSSION

Optimal oxygen saturations for low birth weight premature infants are still not well established.<sup>35,36</sup> In utero, the fetus is in a stable, nonfluctuating state of relative hypoxia with a partial pressure arterial oxygen (PaO<sub>2</sub>) of 22 to 25 mm Hg.<sup>37</sup> Vascular endothelial growth factor (VEGF) expression is induced by this state of hypoxia, thus stimulating normal vessel growth throughout the body, including the retina. Normal fetal retinal hypoxia has been termed “physiological hypoxia” by Chan-Ling and associates.<sup>38</sup>

The pathogenesis of ROP is biphasic: (1) an early vaso-obliterative phase followed by (2) a late proliferative or neovascular phase.<sup>39</sup> The first phase is caused by early exposure of immature retina to hyperoxia, which down-regulates VEGF production and inhibits normal retinal vascular migration.<sup>40</sup> Sustained hyperoxia results in vaso-obliteration of existing vessels.<sup>40</sup> Repeated episodes of hyperoxia-hypoxia may also contribute to abnormal regulation of VEGF and the pathogenesis of ROP.<sup>41,42</sup> Early vaso-obliteration and arrest of retinal vessel growth cause ischemia of the peripheral retina. The second proliferative phase occurs later as peripheral ischemic retina up-regulates VEGF, which in turn stimulates neovascularization at the border between the vascular and avascular retina. In humans this second proliferative phase occurs approximately 6 to 12 weeks after birth, or at 32 to 38 weeks gestation.<sup>21,39</sup>

Our hypothesis is that a physiologic reduced oxygen protocol in the immediate postgestation life of low birth weight (<1,500 g) premature infants prevents the early vaso-obliterative phase and subsequent development of severe ROP. More physiologic low oxygen levels should allow for more normal levels of retinal VEGF, thus stimulating normal vessel growth into peripheral retina. Reduction of threshold disease in all three centers supports the hypothesis. Recently published guidelines based on findings of the Early Treatment for Retinopathy of Prematurity Study (ETROP)<sup>43,44</sup> recommend earlier treatment. However, we have found drastically reduced numbers of infants requiring laser treatment despite the more recent guidelines. A recent survey of neonatal practices, related to the use of pulse oximetry in infants less than 1,500 g, supports our clinical findings and the above hypothesis. The study found statistically significant reduced rates of threshold ROP when max SpO<sub>2</sub> was less than 92% after the first 2 weeks of age.<sup>45</sup> The data presented here, from three separate centers, in addition to several other recent reports, including a large study by Tin and associates<sup>46</sup> (Table 3), show a clear association between combined reduction of overall oxygen saturation and fluctuation with significant decrease in the incidence and treatment for threshold ROP.

**TABLE 3. SUMMARY OF STUDIES EXAMINING EFFECT OF REDUCED OXYGEN PROTOCOLS ON THE INCIDENCE OF THRESHOLD RETINOPATHY OF PREMATURITY (ROP)**

STUDY	SUBJECT POPULATION	SPO <sub>2</sub> GROUPS	% LASER THERAPY
Tin <sup>46</sup> (2001)	<27 wk	Low 70%-90% High 88%-98%	6% 27%
Chow <sup>28</sup> (2003)	500-1,500 g	Low 85%-93% High 90%-98%	1.3%-0 % 4.5%
Anderson <sup>45</sup> (2004)	<1,500 g	Low <92% High >92%	1.3% 3.3%
VanderVeen* (2005)	<1,250 g or <28 wk	Low 85%-93% until 32 wk Target of 90%-92% High 87%-97% No specified target	60% reduction in prethreshold and threshold ROP compared to the high O <sub>2</sub> group

\*VanderVeen DK, Mansfield T, Eichenwald EC. Oxygenation parameters and retinopathy of prematurity in very low birth weight infants—Brigham and Women's Neonatal Unit and Children's Hospital of Boston. Poster presented at AAPOS annual meeting, 2005.

In addition to VEGF, adequate insulin-like growth factor I (IGF-I) levels also appear to be necessary for normal retinal vessel maturation.<sup>47</sup> Preterm birth interrupts the source of maternal IGF-I, and premature babies appear unable to produce IGF-I in sufficient quantities.<sup>48,49</sup> Clinically, low IGF-I levels may correlate with the development of ROP.<sup>50</sup> In contrast to VEGF, which is oxygen-dependent, IGF-I is a non-oxygen-dependent growth factor and should not have been affected by the protocol of physiologic hypoxia used in this study. We cannot explain our results showing a significant reduction of severe ROP based on changes in IGF-I.

Recent studies suggest that infant resuscitation with room air is as effective as 100% oxygen and may, in fact, be associated with reduced mortality rates.<sup>51</sup> Healthy preterm infants appear to maintain O<sub>2</sub> saturations greater than 95% most of the time.<sup>52</sup> However, such levels of oxygen may not be suitable for neonates of very low birth weight and less than 30 weeks gestation.<sup>28,46,53-58</sup> Even brief exposure to high FiO<sub>2</sub> after birth appears to adversely influence long-term cell growth and development,<sup>13</sup> as newborns may be particularly sensitive to oxidative stress.<sup>59-63</sup> The physiologic reduced oxygen protocol emphasizes the importance of controlling oxygen from birth and the use of pulse oximetry in the delivery room. There is a growing body of literature that supports a view that excessive use of oxygen appears to increase infant mortality, lung disease, and ROP, and reduced oxygen protocols do not appear to

alter the incidence of cerebral palsy.<sup>13,46</sup> Studies by Tin and associates<sup>46</sup> and Chow and colleagues<sup>28</sup> found no increased mortality rates and significantly reduced chronic lung disease rates in the lower SpO<sub>2</sub> groups.

Which is more important in relation to ROP prevention: reducing fluctuation in arterial oxygen saturation, or the overall oxygen saturation limits? The answer is not clear. Several studies (both human and animal models) have cited variability of oxygen saturation levels in the first weeks of life to be a significant predictor of the incidence and severity of ROP.<sup>41,64-68</sup> A prospective multicenter study may help to answer this question.<sup>69</sup>

For now, it is encouraging that a physiologic reduced oxygen protocol implemented immediately after birth appears to significantly reduce the risk for development of threshold ROP in premature infants of birth weight 500 to 1,500 g, as demonstrated in three separate NICUs. Low O<sub>2</sub> saturation levels do not appear to be associated with increased rates of brain and lung damage or infant mortality. Indeed, pulmonary and mortality outcomes appear to improve with reduced, perhaps more physiologic, arterial oxygen saturation protocols.<sup>13,28,46</sup>

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## PEER DISCUSSION

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DR WILLIAM V. GOOD: The relationship of oxygen to retinopathy of prematurity (ROP) and to neonatal disease and survival is complex, interesting, and highly important. Since the early 1950's, oxygen has been incriminated, maligned, touted, and ignored as a treatment or cause for retinopathy of prematurity and other neonatal diseases. In one particularly large and well-controlled trial, the STOP-ROP Study, oxygen was studied as a potentially therapeutic agent in the management of prethreshold ROP. Although that study did not show any great benefit on the disease, it also did not demonstrate any harm as far as ROP measures were concerned.

The latest iteration of oxygen's effects on ROP is presented in this report by Dr Wright and his colleagues. These authors, and others, have studied oxygen restriction in the first hours and days of a premature infant's life and have data which suggests that modest restriction of oxygen reduces the rate at which eyes ultimately require laser treatment for advanced disease. To remind the audience, any such ablative treatment occurs at least 6 weeks, and often 12 weeks, after this oxygen intervention.

Dr. Wright and his colleagues are to be congratulated for continuing to push this idea forward. Their work has already spawned studies in the United Kingdom, New Zealand, and Australia. Many researchers in this country are also interested in pursuing studies on an oxygen treatment intervention. As with most preliminary studies, and I believe this study should be considered preliminary, it is important to consider problems in the interpretation of this data.

But before I address some of these concerns, it should be acknowledged that the study reported herein is based on a plausible basic science mechanism, and that is, that early exposure to oxygen downregulates VEGF-1, a prerequisite to normal retinal vessel development.<sup>1</sup> Subsequently, in response to terminal arteriole obliteration and hypoxia, it is likely that an overproduction of growth factors occurs, and normal vessel development regulation is altered, resulting in pathological neovascularization. Therefore, oxygen restriction could, in theory, reduce the terminal arteriole obliteration and reduce these undesirable downstream effects. It is also important to note that future ROP studies should address prevention of the disease, as this one does, and not treatment effect after the disease has developed. The Early Treatment for Retinopathy of Prematurity Study demonstrated a reduction in the rate of blindness to approximately 14% in high risk prethreshold ROP.<sup>2</sup> However, ocular morbidity still occurs, even with favorable outcomes, so prevention of the disease is desirable.

Concerns about this study of Wright and colleagues fall along several lines. The report here does not provide any baseline characteristics for the infants. Therefore, the control group could differ substantially from the experimental group. For example, if the average birth weight of control infants is even 50 grams less than the experimental group, this could have an effect on the incidence and severity of ROP. Comparable mean birth weights for 2 groups could occur in significantly different groups of children, if one group has a disproportionate number of large or very low birth weight infants. Other risk factors for ROP should also be reported, for example, ethnicity, gestational age, and inborn or outborn status.

Second, the study uses inclusion criteria of infants <1500 grams. This means that a very large number of infants in the study are at almost no risk for developing ROP, thus increasing the denominator of the equation: ROP in infants/all infants. A huge sample size is needed to detect any effect of any treatment intervention. The sample size here is too small to draw any strong conclusions.

The authors offer reassurance that mortality rates did not change with oxygen restriction, but mortality rates are subject to the same issues as described above for average birth weights. Furthermore, all organ systems are prone to injury with too little, or too much oxygen, so we need a great deal more information before we can decide whether oxygen manipulation is safe.

Lastly, it is worth noting that the changes in oxygen saturation for the treatment group in this study are modest, compared to the control group. Comparisons of 83-93 saturation in the treatment arm with >90, or 90-95, may not show much difference when

measuring the incidence of ROP, because in real-world neonatology, it takes a very concerted effort and discipline to restrict oxygen. Nurses and doctors would much rather see oxygen saturation on the high side, and will always err in this direction when infants desaturate. Also, infants who are healthy (larger birth weight) with no pulmonary disease should run oxygen saturations near 100% on room air, even from birth.

I congratulate the authors on their thoughtful work, and for reminding us that such a vital drug, oxygen, is also potentially dangerous when administered inappropriately.

**REFERENCES:**

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1. Smith LE. Pathogenesis of retinopathy of prematurity. *Growth Horm IGF Res* 2004;14 Suppl A:S140-S144.
2. Good WV. Final results of the Early Treatment for Retinopathy of Prematurity (ETROP) randomized trial. *Trans Am Ophthalmol Soc* 2004;102:233-248.

DR EDWARD L.RAAB: You have shown that the rate of reaching threshold has decreased. Can you tell us when those that reached threshold reached it? The early treatment study encourages us to do, if anything, more frequent exams. If reaching threshold, especially in zone 1 disease, is gradual rather than rapid, would this allow us to do somewhat fewer exams without affecting quality of care?

DR KENNETH W.WRIGHT: As Dr Good suggests, the numbers are small but it is hard to have large numbers in a clinical study of this nature. It would be nice to know, before and after implementation of the new protocol, exactly what the oxygen parameters really were, but that is hard to confirm. When we look back in 1998, the information we had to work was sparse so we really need to do a prospective study. Cynthia Cole of Boston and I have submitted two NIH planning grants for \$100,000 to evaluate this issue prospectively but both were turned down and we were surprised. The NIH and others might be concerned about untoward effects if we reduce oxygen. Around the United States and the world, however, we are turning the oxygen down, and the outcomes have improved. I predict that we are going to see a dramatic reduction in ROP now that worldwide we are turning the oxygen down. But I do agree with Dr Good that it would be ideal to have a more controlled prospective study, although this might not happen. We operate on congenital cataracts the first week of life but there is no prospective study to prove that protocol. So with ROP, I think we are all going to begin to lower the oxygen and we will probably see ROP decline significantly.