Use of a Supplemental Oxygen Protocol to Suppress Progression of Retinopathy of Prematurity

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PURPOSE. To compare progression of retinopathy of prematurity (ROP) before and after institution of an oxygen therapy protocol to inhibit active proliferation and progression of ROP in premature infants.

METHODS. A retrospective cohort study was performed of premature infants undergoing ROP screening before (cohort A) and after (cohort B) implementation of an oxygen therapy protocol to inhibit further progression for those with stage 2 ROP or worse. Statistical analysis with χ2, Fisher’s exact test, or Wilcoxon rank sum test was performed; and logistic regression models were created to determine the odds ratio of cohort B developing ROP progression beyond stage 2, compared to cohort A, adjusting for other risk factors for ROP.

RESULTS. In cohort A, without oxygen therapy protocol (2002–2007), 44% (54/122) of infants progressed beyond stage 2, compared to 23% (24/103) of infants after protocol implementation (cohort B, 2008–2012) (P = 0.001). No significant differences between cohort A and B were found for gestational age, birth weight, survival, sepsis, bronchopulmonary dysplasia, oxygen at discharge, or need for diuretics. Infants with stage 2 ROP in cohort B, with oxygen therapy protocol, had significantly decreased risk of ROP beyond stage 2 (odds ratio 0.37, 95% confidence interval 0.20–0.67;  P = 0.0013), compared to cohort A, correcting for differences in birth weight and necrotizing enterocolitis.

CONCLUSIONS. Progression from stage 2 to stage 3 ROP in premature infants was significantly decreased after implementation of an oxygen therapy protocol, without a corresponding increase in pulmonary morbidity. This study suggests that appropriate oxygen therapy may play a role in inhibiting progression of stage 2 ROP, potentially decreasing the risk of lifelong visual loss in this vulnerable population.

Keywords: retinopathy of prematurity, very low-birth-weight infants, oxygen therapy, prematurity, neonatal outcomes, bronchopulmonary dysplasia, visual loss

Exposing premature infants to supplemental oxygen is a risk factor for development of retinopathy of prematurity (ROP).1 However, the role of oxygen in the development of ROP is complex. The possibility that higher levels of oxygen would prevent progression of ROP later in the course of treatment after ROP has already developed has been studied in the Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP) trial.2 This trial has shown that using supplemental oxygen to target higher oxygen saturation levels for infants with prethreshold (moderate to severe) ROP reduces the progression to threshold (severe) disease, but does not show a significant decrease in requirement for laser therapy.2 Among all infants with prethreshold ROP, infants in the higher saturation group experienced a lower rate of progression to threshold disease (41% vs. 48%,  P = 0.032). Among the subgroup of infants with prethreshold ROP without plus disease, the rate of progression decreased even further to 32.3% in the higher saturation group from 45.6% in the conventional group ( P = 0.004). However, infants in the higher saturation group experienced higher rates of hospitalization at 50 weeks postmenstrual age (PMA) as well as higher rates of oxygen and diuretic use at this time.1,3 The decrease in progression of retinopathy with the use of higher oxygen saturation levels reported in the STOP-ROP trial has been suggested but not globally accepted as a reason to implement targeted supplemental oxygen therapy in infants with stage 2 or higher ROP.1,3

Based on these findings, a quality improvement initiative was undertaken at the University of Iowa Neonatal Intensive Care Unit (NICU) to use targeted oxygen therapy in infants with ROP. Infants with stage 2 or greater ROP were started on a targeted supplemental oxygen protocol to reduce the progression of ROP. The purpose of this study was to compare the rates of progression of ROP in infants with stage 2 ROP before and after 2008 when the targeted oxygen therapy protocol was initiated, and to compare pulmonary outcomes between the two groups.

METHODS

Participants
We reviewed the medical records of all inborn very low-birth-weight (VLBW) infants who underwent ROP screening from
January 1, 2002, to December 31, 2012, at the University of Iowa NICU. Patients were divided into two epochs by birth date: before and after a targeted supplemental oxygen protocol was initiated as a quality improvement project on January 1, 2008. This retrospective analysis was approved by the University of Iowa Institutional Review Board. The University of Iowa NICU participated in the NICHD Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) between October 27, 2006, and February 10, 2009.5

Table 1. Current Target Oxygen Saturations in the NICU for Infants Without Active ROP

<table>
<thead>
<tr>
<th>Postmenstrual Age</th>
<th>Alarm Limits</th>
<th>Target Saturation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤26 wk</td>
<td>80%–93%</td>
<td>84%–93%</td>
</tr>
<tr>
<td>27–31 wk</td>
<td>80%–95%</td>
<td>86%–94%</td>
</tr>
<tr>
<td>≥32 wk</td>
<td>85%–98%</td>
<td>90%–95%</td>
</tr>
<tr>
<td>≥32 wk RA or nasal cannula ≤ 1 LPM</td>
<td>90%</td>
<td>&gt;94%</td>
</tr>
</tbody>
</table>

Adjust O2 by 5% increments. If the patient requires >70% O2 on nasal CPAP or while intubated, please notify medical team. If high alarming on 21% O2, may change upper alarm limit with order. LPM, liter per minute; RA, room air.

Retinopathy of Prematurity Screening

Eye examinations were performed by trained pediatric ophthalmologists with indirect ophthalmoscopy who alerted the NICU staff to the findings. Prethreshold ROP was defined as any stage 2 or stage 3 ROP in zones 1 or 2, as classified by the 2006 policy statement published in Pediatrics.7

Table 2. Practice Guidelines for Using Oxygen to Inhibit Active Proliferation and Progression of Retinopathy of Prematurity

<table>
<thead>
<tr>
<th>Goal: To use oxygen in a safe manner to:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Inhibit abnormal neovascularization of the retina in premature infants with active ROP that is “prethreshold”</td>
</tr>
<tr>
<td>2. Minimize the risk for abnormal retinal vascular tissue undergoing reactivation and progression before full retinal vascularization</td>
</tr>
</tbody>
</table>

Degree of ROP based on Policy Statement of Pediatrics 20067:

- Threshold ROP was defined as follows and indicated the initiation of increased oxygen therapy:
  - Zone I: Stage 3 no plus disease
  - Zone II: Stage 2 or 3 with plus disease

Oxygen therapy: Oxygen intake should be increased as soon as the diagnosis of “prethreshold” or “threshold” ROP is made. The goal is to target oxygen saturation greater than or equal to 97% until ROP is improving.

Oxygen management: Goal to avoid oxygen toxicity

- Intubated or NPCPAP: Oxygen should not be increased above 50–60%.
- High-flow nasal cannula oxygen (>1 LPM): The effective FiO2 being delivered needs to be calculated and should not be increased above 0.50–0.60.
- To minimize the risk of reactive or progression, oxygen should not be weaned below 35–40% or the effective FiO2 < 0.35–0.40.
- An oxygen floor is used to minimize the hypoxic fluctuation, which could worsen active ROP.
- Low-flow nasal cannula (≤1 LPM): The patient should be placed on 100% oxygen and should not be weaned until ROP improves.
- Patients on the protocol, the oximeter lower alarm limit should be set at 90% to limit hypoxic events.

NPCPAP: nasal pharyngeal continuous positive airway pressure.

Statistical Analysis

Gestational age at birth, birth weight (BW), sex, SCPsis, necrotizing enterocolitis (NEC), survival, highest stage of ROP, and PMA at stage 2 and stage 3 were documented. For eye findings, the presence of plus disease, need for peripheral laser ablation, and retinal detachment were documented, as well as the refraction at 12 months of age and presence of unequal vision or strabismus on the latest eye examination for the patient. Markers for bronchopulmonary dysplasia (BPD), defined as the use of oxygen at 36 weeks, oxygen supplementation at discharge, use of diuretics, use of oral azithromycin, and/or use of theophylline at discharge, were documented.

Statistical analysis was performed by using SAS software 9.3 (Cary, NC, USA) with χ2, Fisher’s exact test, or Wilcoxon rank sum test as indicated, and we used multiple logistic regression modeling to assess the impact of oxygen treatment to suppress ROP on progression from stage 2 to 3, adjusting for factors that differed between the two cohorts by a standard univariate P value < 0.20.12

Results

Screening eye examinations for ROP were performed on 1112 VLBW inborn infants from January 1, 2002, to December 31, 2012. Overall incidence of ROP was 54.2% (580/1112) and the highest stage of ROP reached was as follows: 13.9% stage 1
**Table 3.** Incidence of ROP During the Period 2002–2012

<table>
<thead>
<tr>
<th>Incidence of ROP</th>
<th>Total</th>
<th>Epoch 1</th>
<th>Epoch 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLBW infants</td>
<td>n = 1284</td>
<td>n = 721</td>
<td>n = 563</td>
</tr>
<tr>
<td>Retinal examination</td>
<td>1112 (86.6%)</td>
<td>596 (82.7%)</td>
<td>516 (91.7%)</td>
</tr>
<tr>
<td>ROP Any ROP</td>
<td>380 (34.2%)</td>
<td>184 (30.9%)</td>
<td>196 (38.0%)</td>
</tr>
<tr>
<td>Stage 1</td>
<td>155 (13.9%)</td>
<td>62 (10.4%)</td>
<td>93 (18.0%)</td>
</tr>
<tr>
<td>Stage 2</td>
<td>153 (13.8%)</td>
<td>71 (11.9%)</td>
<td>82 (15.9%)</td>
</tr>
<tr>
<td>Stage 3</td>
<td>69 (6.2%)</td>
<td>49 (8.2%)</td>
<td>20 (3.9%)</td>
</tr>
<tr>
<td>Stage 4</td>
<td>5 (0.3%)</td>
<td>2 (0.3%)</td>
<td>1 (0.2%)</td>
</tr>
</tbody>
</table>

Infants classified by highest stage of ROP showing cohort A and B.

ROP (155); 13.8% stage 2 ROP (153); 6.2% stage 3 ROP (69); and 0.3% stage 4 ROP (3). Table 3 shows the analysis of the total incidence of ROP by stage over the 10 years and then divided into each epoch (epoch 1, January 1, 2002–December 31, 2007; epoch 2, January 1, 2008–December 31, 2012).

There were 225 infants diagnosed with ≥stage 2 ROP: 122 born in epoch 1, (cohort A) 103 born in epoch 2 (cohort B). The median gestational age for both cohorts was the same: 25 weeks (interquartile range [IQR] 24, 27). The median BW was not significantly different between cohorts (cohort A, 706 g [IQR 604, 878]; cohort B, 755 g [624, 969]). The incidence of sepsis was similar between epochs; however, there were more cases of NEC diagnosed in cohort B (4/103) than cohort A (2/122), P = 0.04. Table 4 shows comparison of the clinical characteristics and outcomes of both epochs. Infants enrolled in the SUPPORT trial were equally distributed between the epochs: 17/122 in cohort A, 11/103 in cohort B, P = 0.4720.

We found a significant reduction in the progression of ROP using a targeted supplemental oxygen protocol. Before the implementation of the oxygen therapy protocol, that is, cohort A (January 1, 2002–December 31, 2007), 44% (54/122) of infants progressed beyond stage 2 as compared to only 23% (24/103) in cohort B, infants after protocol implementation (January 1, 2008–December 31, 2012) (P = 0.001). Given the difference in NEC incidence between the epochs, and the trend toward lower birth weight in cohort A, a logistic regression model was created to adjust for the effects of NEC and BW. Compared to cohort A, infants in cohort B, with stage 2 ROP who were treated with the oxygen therapy protocol, had significantly decreased risk of ROP progressing to stage 3 or worse (odds ratio [OR] 0.37; 95% confidence interval [CI] 0.20–0.67; P = 0.0013). Plus disease also occurred less frequently in cohort B; however, this difference was not statistically significant (cohort A, 18.9%; cohort B, 12.6%; P = 0.2). Despite the reduction in ROP progression to stage 3 or worse, the need for laser peripheral ablative therapy was similar in the two cohorts (cohort A, 13.9%; cohort B, 12.6%). All cases were treated with indirect diode laser.

Pulmonary outcomes including the use of supplemental oxygen at 36 weeks, oxygen use at discharge, and need for diuretics, theophylline, or prophylactic azithromycin were reviewed and no statistically significant differences were found between cohort A and B.

Age-appropriate vision was assessed at the last available examination for each patient. Eye examinations at ≥12 months of age were available for 70% of the patients (157/225). No statistically significant differences were found between epochs for the incidences of amblyopia or unequal vision as assessed by fixation preference or subjective vision (difference of two lines or greater than two lines) (P = 0.4). There was also no difference in the occurrence of strabismus (14 subjects in cohort A, 10 subjects in cohort B, P = 0.4). In children with subjective vision evaluated, all had vision better than 20/200, except for one child who had light perception vision secondary to cortical visual loss in the second epoch.

**Table 4.** Overall Comparison of Baseline Patient Characteristics and Outcomes Between Cohort A and Cohort B

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Cohort A</th>
<th>Cohort B</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (wk), median</td>
<td>25 (24, 27)</td>
<td>25 (24, 27)</td>
<td>0.89*</td>
</tr>
<tr>
<td>Birth weight (grams), median</td>
<td>706 (604, 878)</td>
<td>755 (624, 969)</td>
<td>0.17*</td>
</tr>
<tr>
<td>Mortality rate</td>
<td>6/122</td>
<td>2/103</td>
<td>0.46†</td>
</tr>
<tr>
<td>Culture-positive sepsis</td>
<td>2/122</td>
<td>4/103</td>
<td>0.42†</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>2/122</td>
<td>8/103</td>
<td>0.05‡</td>
</tr>
<tr>
<td>Pulmonary medications at discharge‡</td>
<td>38/122</td>
<td>37/103</td>
<td>0.45‡</td>
</tr>
<tr>
<td>Supplemental oxygen at 36 wk</td>
<td>117/121</td>
<td>102/103</td>
<td>0.38‡</td>
</tr>
<tr>
<td>Supplemental oxygen at discharge‡</td>
<td>107/121</td>
<td>94/101</td>
<td>0.24‡</td>
</tr>
<tr>
<td>Laser treatment</td>
<td>17/122</td>
<td>13/102</td>
<td>0.85</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>2/122</td>
<td>1/102</td>
<td>1.0†</td>
</tr>
<tr>
<td>Plus disease present</td>
<td>23/122</td>
<td>13/103</td>
<td>0.23</td>
</tr>
<tr>
<td>Postmenstrual age (wk) at stage 2</td>
<td>35 (34, 37)</td>
<td>35 (34, 37)</td>
<td>0.61*</td>
</tr>
<tr>
<td>Postmenstrual age (wk) at stage 3</td>
<td>36.5 (35, 38)</td>
<td>56 (39)</td>
<td>0.51*</td>
</tr>
<tr>
<td>Progression from stage 2 to 3</td>
<td>54/122</td>
<td>24/103</td>
<td>0.001§</td>
</tr>
</tbody>
</table>

* Wilcoxon test.
† Fisher’s exact test.
‡ Diuretics or theophylline.
§ χ².
Oxygen Suppression of ROP

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of infants with prethreshold ROP without plus disease (46% to 32% in the low saturation versus high saturation groups). Adjusted for birth weight and NEC, the odds of developing severe ROP in our subjects were significantly lower after initiation of the oxygen therapy protocol (OR 0.37; 95% CI 0.20–0.67; P = 0.001). Despite the increased oxygen creates worse pulmonary outcomes, we did not find this to be the case in our retrospective study of increased oxygen supplementation. There were no statistically significant differences found in discharge pulmonary medications, discharge oxygen requirement, or oxygen requirement at 36 weeks.

Unlike the STOP-ROP trial, we did not find a statistically significant increase in pulmonary morbidity in infants placed on our targeted supplemental oxygen therapy protocol. In the STOP-ROP trial, infants in the high saturation group experienced significantly increased pulmonary morbidities at 50 weeks PMA, including higher rate of oxygen use (47% vs. 37%) and diuretic use (36% vs. 24%). Although we did not formally assess infants at 50 weeks PMA owing to the observational nature of our study, there was no difference in the use of supplemental oxygen at either 36 weeks PMA or at hospital discharge. Additionally, there was no difference in the use of respiratory medications at discharge. We found a higher rate of NEC in cohort B, during epoch 2 of the targeted supplemental oxygen therapy protocol. Despite the increase in NEC, a potential risk factor for worse ROP, the patients in cohort B still had less ROP progression.

Our study was limited in that it was a retrospective cohort study, rather than a randomized controlled trial, which limited our ability to control for nonsystematic changes in clinical practice over the 9-year span of this study. However, the only unit-wide systematic practice intervention made during this time was the introduction of our supplemental oxygen therapy to suppress progression of ROP.

An additional limitation was that the primary outcome of interest (progression from stage 2 to worse ROP) was determined by review of clinical eye examination reports. We were unable to determine if the effect of therapy was different between patients with prethreshold versus threshold ROP, as the examinations did not routinely include clock hours of ROP. Since the Early Treatment Retinopathy of Prematurity (ETROP) study introduced plus disease as treatment criteria,15 the clock hours of ROP are not routinely mentioned on screening eye examinations. It is important to note that the University of Iowa NICU was participating in the SUPPORT trial during part of both epochs (October 27, 2006–February 10, 2009). Although the SUPPORT trial did study the impact of oxygen saturation limits on the incidence of ROP, it did not study the impact of saturation limits on progression of ROP once diagnosed. Additionally, a similar proportion of each cohort was enrolled (17/122 in cohort A, 11/105 in cohort B, P = 0.4720). Given that SUPPORT was a randomized trial, the equality of participation in both cohorts should prevent bias. Our clinical guidelines for patients not enrolled were not affected by participating in the SUPPORT trial, and we made no changes in our oxygen saturation limits after publication of the results of the SUPPORT trial.

It is interesting that despite reducing the odds of progressing from stage 2 ROP to stage 3 in the second epoch, there was no statistically significant decrease in the number of infants requiring laser treatment for threshold or type 1 ROP, a finding that was also consistent with the results from the STOP-ROP Trial. One might then ask whether the increased oxygen protocol is useful if it does not decrease the number of children requiring treatment. From our clinical experience, some individual infants are spared the need for laser, based on this oxygen protocol, although the numbers for the group as a whole may not achieve significance. In addition, it has long been noted that a better anatomic and visual outcome is expected from eyes treated at stage 2 than at stage 3 or severe posterior ROP (ETROP study). Although longer-term follow-up is needed to validate this, it is reasonable to expect better long-term vision in eyes that did not progress to stage 3, even if they still required treatment for stage 2 plus disease. Another possibility for not finding a significant decrease in the number of patients needing laser therapy is that new recommendations for timing of treatment in ROP went into effect at approximately the same time as the second epoch in our study. The recommendation changed from treating at threshold, defined as 5 contiguous or 8 discontinuous clock hours of stage 3 with plus, to treating at type 1, an earlier stage defined as any plus disease with stage 2 or 3 in zones 1 or 2. Thus, while fewer patients in epoch 2 may have reached the more severe threshold designation, they were still recommended for treatment under the new guidelines.

A limitation to the use of supplemental oxygen to suppress ROP is diagnosing stage 2 ROP in order to find the cases to use a targeted oxygen therapy protocol. If screening protocols could more accurately detect ROP at the start of stage 2, one could hypothesize that there might ultimately be an improvement in those children needing laser or with retinal detachment. It is also unknown if the need for laser therapy could be reduced by implementing the targeted oxygen therapy protocol at stage 1 ROP, rather than the more severe stage 2. Related to this, a smaller proportion of VLBW infants in epoch 1 (82.7%) received at least one screening examination than those in epoch 2 (91.7%). There was no change in screening protocol in our unit during this time, and thus the reasons for this are unclear. This may have increased the risk of ascertainment bias, that is, missing cases of ROP. However, our intention was to study the impact of our oxygen protocol on progression after the diagnosis of stage 2 ROP, not the overall incidence of ROP in the population. Missing cases should impact primarily the incidence, not the rate of progression, in the cases detected.

Because there are known risks to both oxygen desaturation and excessive use of oxygen, we designed our oxygen therapy protocol to limit episodes of both hypoxia and hyperoxia. We designed the protocol to include specific oxygen saturation targets with a wide range of alarm settings to minimize the need for excessive adjustment of FiO2 for transient episodes of desaturation. For each patient, we assigned an FiO2 limit or floor below which the oxygen level was not to be weaned in order to minimize bursts of hypoxia, which have been known to cause worsening of ROP.10,11,11 Conversely, to minimize hyperoxic exposure, our protocol included limiting the effective oxygen exposure to FiO2 ≤ 0.50–0.60 even if this meant that some infants did not consistently achieve the desired oxygen saturation of ≥97%. We believe that limiting the amount of oxygen exposure among infants treated with our protocol minimized the risk of significant pulmonary exacerbation even if infants were unable to achieve targeted saturations owing to their degree of lung disease. As a retrospective study, the rate and occurrence of desaturations could not be collected, since continuous pulse oximeter data are not routinely downloaded and stored in the medical record.

An additional limitation of our study was lack of complete data on all subjects’ visual outcomes owing to loss to follow-up after the initial screening eye examinations. Additionally, there were some patients who were followed up past 12 months of age, but were too young to have their subjective vision tested. However, in the group that was old enough to have subjective vision testing, there were no children that had severe blindness or were legally blind (< 20/200 vision) owing to ROP.

In conclusion, our data showed that the selective use of a standardized protocol to deliver targeted supplemental oxygen
therapy in infants with stage 2 ROP can be a safe and effective method of decreasing the progression of active ROP. Standardized protocols are most effective when used in a collaborative manner in a multidisciplinary team approach between ophthalmology and neonatology providers in selective patients. These findings would support the use of a standardized targeted supplemental oxygen therapy approach to inhibit the progression of ROP.

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References