Achieved oxygen saturations and retinopathy of prematurity in extreme preterms

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ABSTRACT

Objective To identify achieved oxygen saturations (SpO_2) associated with increased risk of severe retinopathy of prematurity (ROP).

Design This is a secondary analysis of the Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)randomised controlled trial. SpO_2 was recorded up to 36 weeks' postmenstrual age. Saturations through 9 postnatal weeks were explored graphically, and logistic regression models were created to predict severe ROP.

Setting 20 centres of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network.

Patients 984 surviving infants of 24–27 weeks' gestational age born in 2005–2009.

Interventions SUPPORT targeted SpO_2 to a lower (85%–89%) or higher (91%–95%) range through 36 weeks' postmenstrual age or off respiratory support.

Main outcome measures Severe ROP defined as threshold ROP, ophthalmological surgery or bevacizumab treatment.

Results There were statistically significant interactions between duration of oxygen supplementation and percentage of time in certain achieved saturation ranges. Specifically, for infants who spent at least 2 weeks on oxygen in postnatal weeks 1–5, a higher percentage of time at 91%–96% SpO_2 was associated with increased odds of severe ROP. For infants who spent at least 3 weeks on oxygen in postnatal weeks 6–9, a higher percentage of time at 97%–100% SpO_2 was associated with increased odds of severe ROP. Other significant risk factors were lower gestational age and birth weight, non-Hispanic white versus black race, prospectively defined severe illness, late-onset sepsis or meningitis, and clinical centre.

Conclusions Among extremely preterm survivors to discharge, the association between SpO_2 and severe ROP depended on the timing and duration of oxygen supplementation.

What is already known on this topic?

- Retinopathy of prematurity (ROP) was associated with unrestricted oxygen use in the 1950s.
- However, the specific oxygen saturations associated with the development of severe ROP in extremely preterm infants are unknown.

What this study adds?

- Among infants of 24–27 weeks' gestational age, the relationship between achieved oxygen saturations and severe ROP depended on the timing and duration of oxygen supplementation.
- For infants requiring oxygen past 5 postnatal weeks, the percentage of time spent with saturations of 97%–100% may be a modifiable risk factor.

INTRODUCTION

Retinopathy of prematurity (ROP) is a cause of visual disabilities in preterm infants. ROP risk increases with decreasing gestational age (GA), and an association between ROP and unrestricted oxygen use in preterm infants was established in the 1950s.[1] In 2005–2009, the Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT) randomised 1316 infants of 24 0/7–27 6/7 weeks' GA to oxygen saturation (SpO_2) target ranges of 85%–89% or 91%–95% (with suggested alarms set at 84% and 96% in both groups).[2] Among survivors to discharge, the lower target group had a reduced risk of severe ROP (relative risk 0.52, 95% CI 0.37 to 0.73, $p<0.001$) and shorter duration of oxygen supplementation (mean 59.8 vs 67.4 days, $p<0.001$)[2]; however, the lower target group had an unexpected increase in mortality.[2] The Benefits of Oxygen Saturation Targeting II (BOOST II) trials in Australia and the UK were terminated early for similar mortality findings. Those trials also reported a decrease in ROP with a lower target range.[3]

Previous data had suggested that SpO_2 in the upper part of the recommended and generally accepted range at the time (85%–95%)[4] might increase the risk of ROP relative to the lower part of the range.[5–7] Although a multicentre observational study published in 1977 did not find an association between partial pressure of oxygen concentrations and retinopathy,[8] a single centre cohort study in the 1980s using transcutaneous oxygen monitoring supported an association between retinopathy and arterial oxygen levels ≥80 mm Hg.[9] Since then,

pulse oximetry has largely supplanted transcutaneous oxygen tension for continuous clinical monitoring of oxygenation.

SUPPORT hypothesised that ROP would be decreased by targeting SpO_2 at 85%–89% compared with 91%–95%. However, oxygen targets are difficult to maintain in critically ill infants due to their labile clinical status. Thus, as expected,[10] actual saturations while on supplemental oxygen differed from the targets, and the achieved saturations in the two randomised groups overlapped.[2] This study tested the hypothesis that there were specific achieved oxygen saturations associated with increased risk of severe ROP.

SUBJECTS AND METHODS

This was a secondary analysis of the SUPPORT trial data with prespecified outcomes. Infants were examined by ophthalmologists trained in the diagnosis of ROP beginning at 31–33 weeks' postmenstrual age (PMA) and continuing until severe ROP outcome was reached or resolution occurred.[2 11] Resolution was defined as fully vascularised retinas or immature vessels in zone 3 on two consecutive examinations in each eye. Threshold ROP (called 'Type 1 ROP' by the Early Treatment for Retinopathy of Prematurity Cooperative Group[12 13]) was defined as any of the following: (1) zone 1: stage 3 ROP without plus disease (ie, two or more quadrants of dilated veins and tortuous arteries in the posterior pole), or plus disease with any stage of ROP; and (2) zone 2: plus disease with stage 2 or 3 ROP. Surgical ophthalmological intervention included laser therapy, cryotherapy, scleral buckling or vitrectomy. Severe ROP was defined as threshold ROP, ophthalmological surgery or bevacizumab treatment.

Respiratory support data, including mode of support and fractional inspired oxygen (FiO_2), were collected on study forms. Through February 2006, these data were collected every 8 hours during the first 14 days of life and once a day from 15 days through 36 weeks' PMA or death, transfer or discharge, whichever occurred first. After February 2006, the data were collected every 2 hours for the first 14 days and every 6 hours thereafter to facilitate monitoring of treatment adherence.

Treatment assignment was masked using specially designed pulse oximeters with skewed display algorithms such that, for both treatment groups, SpO_2 values in the target range were displayed as 88%–92% (a maximum variation of 3% from the actual value)[2]; the recommended alarm settings were 84% and 96% in both groups. Oximeter averaging time was set to 16 s, and sensitivity was set to normal mode. Displayed SpO_2 was sampled every 10 s, and display values were transformed to actual SpO_2 for analysis. Where there was not one-to-one correspondence between display and actual values,[14] quadratic and cubic spline interpolation methods were used.

Study pulse oximeters were discontinued at 36 weeks' PMA or when the infant was on room air and off ventilatory support or continuous positive airway pressure for 72 hours, whichever occurred earlier. However, if respiratory support was resumed prior to 36 weeks' PMA, the study oximeter was placed back on the infant. Since saturations on room air cannot be controlled, this analysis included SpO_2 data collected only during oxygen supplementation, identified based on whether the infant was receiving oxygen at the closest time point for which respiratory support data were collected on daily study forms. Saturation data collected after the ophthalmological outcome were excluded from this analysis.

Demographic and neonatal characteristics of infants with and without severe ROP were compared using Student's t-tests and X^2 tests. Kaplan-Meier survival curves were generated for the probability of oxygen supplementation through 12 postnatal weeks. Hours on oxygen with various SpO_2 values were estimated by postnatal week, assuming SpO_2 remained constant over the 10 s sampling interval. Graphs were used to identify periods when SpO_2 differed between infants with and without severe ROP, and informed a logistic regression model to predict severe ROP based on per cent of time while on oxygen at specific SpO_2 values during selected postnatal age intervals. Because infants born at 27 weeks' GA had SpO_2 data only through 9 postnatal weeks, only data through week 9 were used in modelling for all infants. The model included total hours on supplemental oxygen during the time interval, and demographic and neonatal characteristics. When infants were not receiving oxygen support, time on oxygen at specific SpO_2 values was set to zero for modelling purposes. Demographic and neonatal characteristics were

Table 1 Characteristics of infants with and without severe ROP

Characteristics		Severe ROP (n=132)	No severe ROP (n=852)	P value
Perinatal characteristics				
Gestational age at birth (weeks), mean±SD		25.4±0.9	26.4±1.0	<0.001
Birth weight (g), mean±SD		715.1±142.4	871.9±186.9	<0.001
Male, n (%)		74 (56.1)	447 (52.5)	0.44
Race/Ethnicity, n (%)	Non-Hispanic black	41 (31.1)	329 (38.6)	0.30
	Non-Hispanic white	57 (43.2)	334 (39.2)	
	Hispanic	27 (20.5)	161 (18.9)	
	Other/Unknown	7 (5.3)	28 (3.3)	
Any antenatal steroids, n (%)		129 (97.7)	814 (95.5)	0.24
Comorbidities				
Severe illness (FiO_2 >0.4 and on a ventilator for >8 consecutive hours) in the first 14 days, n (%)		83 (62.9)	191 (22.4)	<0.001
PVL prior to ROP determination, n (%)		12 (9.1)	35 (4.1)	0.013
IVH grade 3–4 prior to ROP determination, n (%)		19 (14.4)	76 (8.9)	0.048
NEC prior to ROP determination, n (%)		16 (12.1)	69 (8.1)	0.13
LOS/Meningitis prior to ROP determination, n (%)		68 (51.5)	248 (29.1)	<0.001

FiO_2, fractional inspired oxygen; IVH, intraventricular haemorrhage; LOS, late-onset sepsis; NEC, Bell's stage II or III necrotising enterocolitis; PVL, periventricular leucomalacia; ROP, retinopathy of prematurity.

selected prospectively and included known risk factors for ROP and comorbidities impacting supplemental oxygen use. Model covariates were clinical centre, sex, race and ethnicity, GA, birth weight, antenatal steroid exposure, severe illness (defined prospectively as FiO_2 >0.4 and ventilator use for >8 consecutive hours in the first 14 days of life), periventricular leucomalacia (PVL) (increased echogenicity or cysts in the periventricular region), grade III or IV intraventricular haemorrhage (severe IVH), Bell's stage II or III necrotising enterocolitis (NEC), and culture-positive late-onset sepsis or meningitis. Comorbidity diagnoses after the ophthalmological outcome were excluded. Similar analyses used weeks' PMA in place of weeks' postnatal age. Statistical tests were two-sided and p values <0.05 were considered statistically significant. Analyses were performed using SAS V.9.4.

RESULTS

SUPPORT enrolled 1316 infants, and 1079 survived to discharge. Among survivors, 984 (92%) had an ophthalmological outcome. Of these, 132 (13%) had severe ROP, including 22 infants who did not have threshold ROP but were treated with ophthalmological surgery or bevacizumab. Ninety-five per cent (932/984) of infants with outcome data also had SpO_2 data (128/132 (97%) with severe ROP and 804/852 (94%) without). Missing SpO_2 data resulted from technical issues such as lost or corrupted files. Infants without SpO_2 data had higher GA and birth weight and none had NEC (see online supplementary table S1).

Infants with severe ROP had lower GA and birth weight, and were more likely to have PVL, severe IVH, late-onset sepsis or meningitis, and severe illness, compared with infants without severe ROP (table 1). Based on data from respiratory support forms, 97% (128/132) of infants with severe ROP received oxygen through the sixth postnatal week (figure 1); two others were transferred before 6 weeks, and subsequent respiratory support was unknown. In comparison, 68% (577/852) of infants without severe ROP still received oxygen at 6 weeks. Of the 288 infants who were not confirmed to be on oxygen at 6 weeks, only 4 (1.4%) developed severe ROP.

Among infants receiving supplemental oxygen, those with severe ROP spent more total hours per infant per week at 91%–96% SpO_2, particularly in weeks 1–5, and more hours at 97%–100% SpO_2, particularly in weeks 6–9, compared with those without severe ROP (figure 2; see online supplementary tables S1A,B and S2). Total hours per infant per week on oxygen at 97%–100% SpO_2 increased over the first 5 weeks in both groups (figure 3). After 5 weeks, there was increased separation between infants with and without severe ROP in hours at 97%–100% SpO_2 (figure 3). In week 6, infants with severe ROP spent a median of 24 hours (IQR 17–44 hours) at

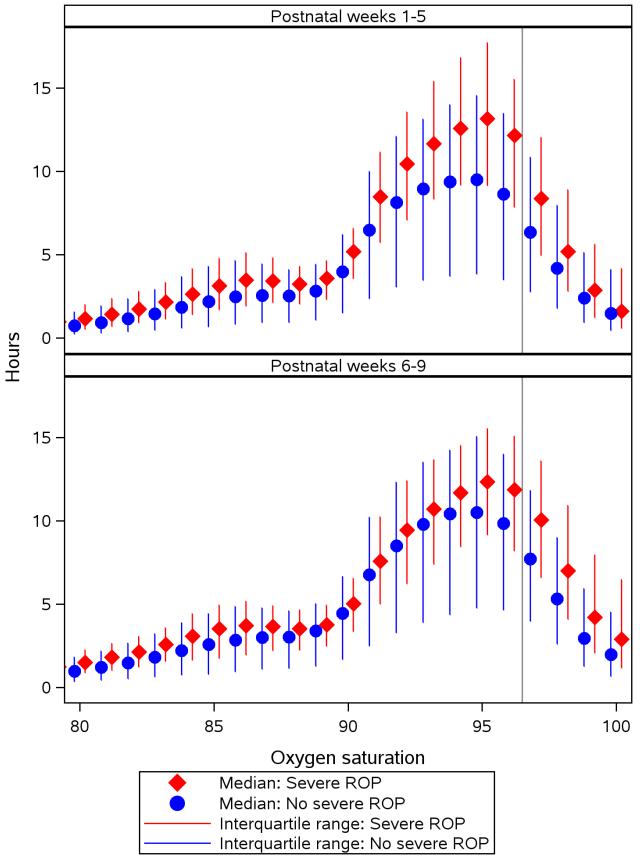

Figure 2 Total hours per week each infant spent at each oxygen saturation value during time on supplemental oxygen in postnatal weeks 1–5 and 6–9, by severe retinopathy of prematurity (ROP).

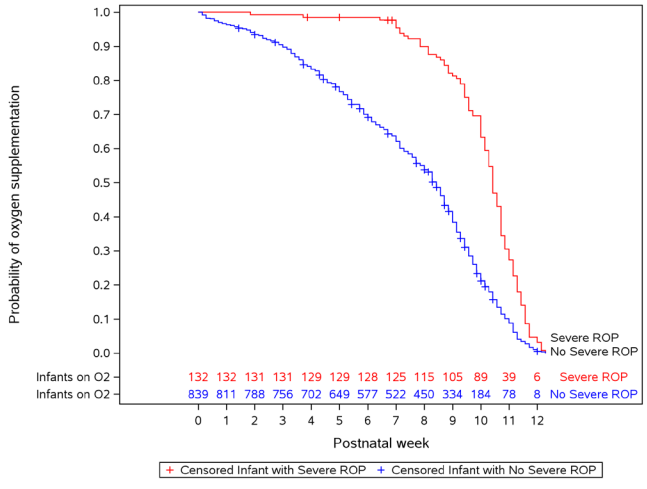

Figure 1 Survival curve for probability of oxygen supplementation through 12 postnatal weeks, by severe retinopathy of prematurity (ROP).

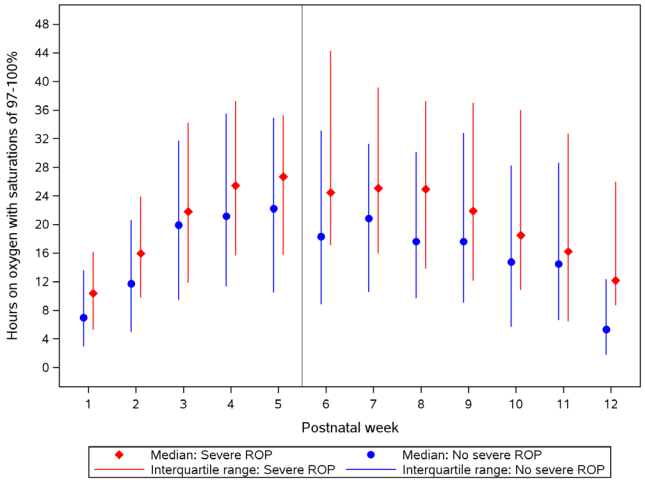

Figure 3 Total hours with saturations of 97%–100% for each infant during time on supplemental oxygen, by postnatal week and severe retinopathy of prematurity (ROP).

97%–100% SpO_2 compared with 18 hours (IQR 9–33 hours) for infants without severe ROP. Infants with more than 20 hours (the overall median) vs 20 or fewer hours at 97%–100% SpO_2 in week 6 had lower GA and birth weight, were more likely to be non-Hispanic white compared with non-Hispanic black race, and were more likely to have had severe illness in the first 2 postnatal weeks (see online supplementary table S2). In week 9, infants with severe ROP spent a median of 22 hours (IQR 12–37 hours) at 97%–100% SpO_2 compared with 18 hours (IQR 9–33 hours) for infants without severe ROP.

Based on the graphical findings, a logistic regression model was created that (1) accounted separately for time on oxygen at 1–5 weeks and 6–9 weeks, because nearly all infants with ROP were still on oxygen at 6 weeks, and (2) examined the specific saturation ranges that differed during those postnatal weeks between infants with and without severe ROP. The model predicted severe ROP based on total hours of oxygen supplementation at 1–5 weeks, the percentage of that time with SpO_2 of 91%–96%, and their interaction; total hours of oxygen supplementation at 6–9 weeks, the percentage of that time with SpO_2 of 97%–100%, and their interaction; and prespecified perinatal risk factors. The interaction terms were significant at the $p<0.05$ level, indicating that the association between severe ROP and the specific SpO_2 ranges depended on the duration of time spent on supplemental oxygen (see online supplementary table S3). For infants who spent at least 2 weeks on oxygen in postnatal weeks 1–5, a higher percentage of time at saturations of 91%–96% was associated with increased odds of severe ROP (figure 4). For infants who spent at least 3 weeks on oxygen in postnatal weeks 6–9, a higher percentage of time at saturations of 97%–100% was associated with increased odds of severe ROP (figure 4).

Other risk factors significantly associated with severe ROP were lower GA and birth weight, non-Hispanic white compared with non-Hispanic black race, severe illness, late-onset sepsis or meningitis, and clinical centre (see online supplementary table S3). Analyses using PMA in place of postnatal age did not demonstrate the same strength of association between time at SpO_2 values and severe ROP (data not shown).

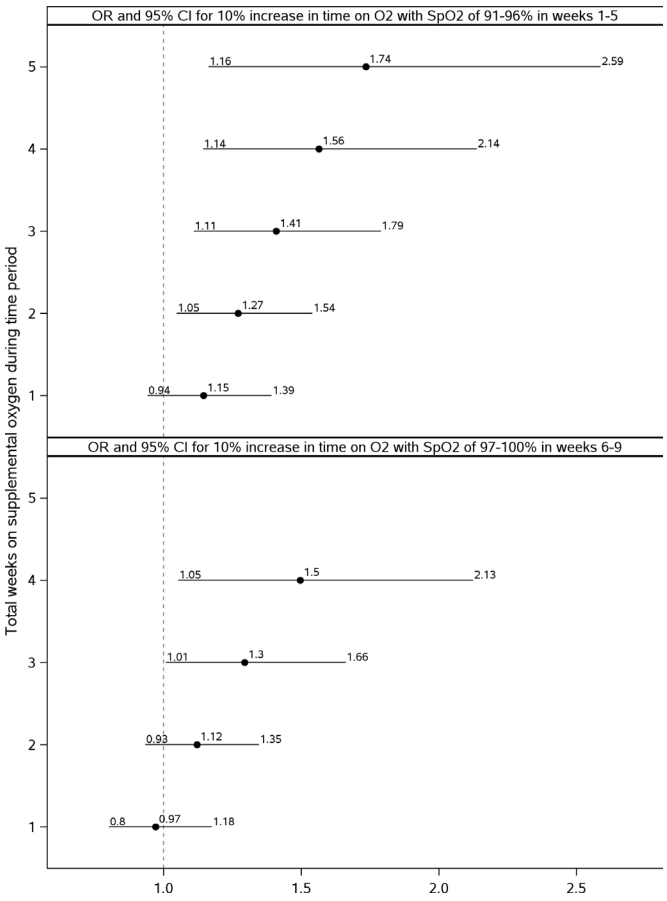

Figure 4 Results of logistic regression model to predict severe retinopathy of prematurity (ROP). Adjusted ORs and 95% CIs are shown for the effect of percentage of time on oxygen with saturations of 91%–96% during postnatal weeks 1–5 and percentage of time on oxygen with saturations of 97%–100% during postnatal weeks 6–9. Because there were significant interactions in the logistic regression model, ORs and CIs for the effect of the percentage of time spent in the saturation ranges are presented separately for infants spending 1, 2, 3, 4 or 5 weeks on supplemental oxygen during the specified postnatal time period.

DISCUSSION

Previous large studies of SpO_2 levels and ROP reported targeted, rather than achieved, saturations.[5 6] We found that the relationship between achieved saturations and severe ROP depended on the timing and duration of supplemental oxygen. A greater percentage of time on oxygen at 91%–96% SpO_2 in weeks 1–5 was associated with severe ROP for infants who spent at least 2 weeks on oxygen. The SUPPORT primary analysis found an unexpected increase in mortality with saturation targets below 91%.[2] Together, these findings imply that increased severe ROP may be an unavoidable consequence of targeting higher saturations to avoid mortality. However, this study also found that infants on room air by 6 weeks had a very low incidence of severe ROP (1.4%). Thus, infants healthy enough to be off oxygen by 6 weeks may have low risk of severe ROP regardless of earlier saturations. For infants still receiving oxygen 3 or more weeks past the 5-week mark, the association between severe ROP and a higher percentage of time at 97%–100% SpO_2 in weeks 6–9 may point to a modifiable risk factor, particularly given the increased stability of most infants past 5 weeks.

ROP proceeds in two phases (I: vasoconstrictive; II: vasoproliferative), during which similar SpO_2 may have different effects. Data suggest that supplemental oxygen poses a risk during phase I, prior to vasoproliferation.[15] ROP phase II begins to develop after 32 weeks' PMA but has a wide range of onset.[15] The Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP) study found that an SpO_2 target of 96%–99% implemented at a mean (±SD) PMA of 35.4±2.5 weeks did not increase ROP severity for infants with prethreshold ROP.[16] We found an association between severe ROP and exposure to 97%–100% SpO_2 in weeks 6 through 9, or 30–33 weeks through 33–36 weeks PMA, earlier than the average age at which infants in STOP-ROP were randomised. Extremely preterm infants may be more vulnerable to harm from higher saturations during this earlier period.

In a single-centre study of pulse oximeter data continuously recorded through 8 weeks of age, hyperoxaemic events >95% SpO_2 for 10 or more seconds were less frequent in week 2 and weeks 4–8 in infants requiring laser treatment for ROP compared with those with no ROP or mild ROP.[17] The authors speculated that this was because infants not requiring laser treatment spent more time on room air, where an SpO_2 of 94%–100% is common.[17] The High Oxygen Percentage in Retinopathy of Prematurity (HOPE-ROP) study suggests that

spontaneous high saturations (>94%) on room air do not have the same detrimental effect as high saturations during oxygen support.[18] Consistent with this, we found that infants who were on room air by 6 weeks had a very low incidence of severe ROP.

While some studies have found that timing of ROP onset corresponds with PMA,[19 20] both the SUPPORT study and a Swedish study of infants at 22–26 weeks' GA found it to be more closely associated with postnatal age.[11 21] In a previous analysis, the postnatal age of ROP onset in SUPPORT did not differ between lower and higher GA infants, and infants of lower GA had onset at earlier PMA.[11] This is consistent with the weaker association in this study between severe ROP and SpO_2 measured at specific weeks' PMA compared with postnatal weeks.

In SUPPORT, severe ROP was not diagnosed prior to 6.4 weeks of age,[11] consistent with other studies that found onset of type 1 ROP or need for treatment did not occur before 6 or 8 weeks, respectively.[20 22] In this study, exposure to 97%–100% SpO_2 increased over the first 5 postnatal weeks for infants with and without severe ROP, which may be due to an improvement in the infants' clinical condition over time or other factors. Exposure to 97%–100% SpO_2 decreased more quickly in weeks 6–12 in infants without severe ROP. Observational studies have found an association between duration of oxygen supplementation and severe ROP.[23 24] It is possible that infants on respiratory support longer are more likely to receive oxygen during a window of increased risk from higher saturations.

Saturations >96% are above the range typically recommended, either before SUPPORT[4] or subsequently. Guidance for oxygen targeting in extremely low birthweight infants published in 2016 concluded that 'a target saturation range of 90% to 95% may be safer than 85% to 89% at least for some infants. However, the ideal oxygen saturation range for extremely low birthweight infants remains unknown'.[25] It is challenging to keep infants within a target range for a variety of reasons. First, less stable infants may be maintained at higher saturations to avoid intermittent hypoxic episodes. Second, studies supporting an association between higher saturation targets during ROP phase II and decreased progression to severe ROP[15 26 27] have led some neonatal intensive care units to routinely increase saturation targets for the most extremely preterm infants from around 33 weeks' PMA until the retina has stabilised. This practice may lead to decreased concern about higher saturations even before that. Third, bedside personnel may be less consistent, and staffing ratios may decrease, with increasing postnatal age of the infants. A study of infants enrolled in BOOST II at The Royal Women's Hospital, Melbourne found that upper alarm limits on study oximeters were correctly set on 79.8% of the days prior to 32 weeks' PMA in contrast with 65.6% in weeks 32–36.[28] Although SUPPORT recommended alarm settings of 84% and 96%, the alarms could be changed at the discretion of the healthcare team, and data on actual alarm settings were not collected. These factors and unknown others may have contributed to some infants spending more time at higher saturations beginning around 6 weeks.

The strengths of this study include prospective collection of detailed neonatal, respiratory and SpO_2 data on a large cohort of extremely preterm infants, and rigorous monitoring and evaluation of the ophthalmological outcome. The study included 20 clinical centres, which increases its generalisability over single-site studies. Because sites differ with respect to unmeasured characteristics, clinical centre was included as a covariate in statistical modelling to obtain risk factor estimates that are averaged over the centres.

A limitation is that saturations were only recorded through 36 weeks' PMA; thus, data after 9 weeks are not available for infants of higher GA. In order to include consistent data for all infants, only data through 9 weeks (33 weeks' PMA for 24-week GA infants) were used in statistical modelling. It may be that higher saturations while on oxygen beyond 9 postnatal weeks are associated with severe ROP, but this was not tested. Infants spending more time with higher saturations may also have more desaturations, but oxygen fluctuations were not examined in this analysis.

Identification of oximeter data during oxygen supplementation may be imprecise, since it is based on respiratory data collected at intervals of 2–6 hours. Since infants with low oxygen requirement can go in and out of oxygen supplementation, inclusion of time on room air may have increased or decreased the estimated number of hours with a high SpO_2. Missing saturation data may have an impact on the results, although this impact is expected to be small since most missing SpO_2 data occurred in infants with higher GA and birth weight who did not have severe ROP.

It is possible that the data for actual SpO_2 values of 91%–96% are influenced by the transformation from masked to actual values. However, in both the lower and higher target saturation groups, SpO_2 values of 97% and higher were not masked (actual values were displayed on the study oximeters and captured in the resulting data sets). Thus, we do not expect that the oximeter masking had a substantial impact on our results regarding saturations of 97%–100%. A previously published characteristic of the study oximeters reduced the frequency of saturations of 87%–90% and may have impacted the data used in this study.[29]

In conclusion, the relationship between achieved SpO_2 and severe ROP in this study depended on the timing and duration of oxygen supplementation. For infants requiring oxygen past 5 postnatal weeks, the percentage of time spent with saturations of 97%–100% may be a modifiable risk factor for severe ROP, particularly given the increased stability of most infants past 5 weeks.

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