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ORIGINAL ARTICLE

Temporal quantification of oxygen saturation ranges: an effort to reduce hyperoxia in the neonatal intensive care unit

MJ Bizzarro[1], FY Li[2], K Katz[2], V Shabanova[2], RA Ehrenkranz[1] and V Bhandari[1]

OBJECTIVE: To reduce exposure to hyperoxia and its associated morbidities in preterm neonates.
STUDY DESIGN: A multidisciplinary group was established to evaluate oxygen exposure in our neonatal intensive care unit. Infants were assigned target saturation ranges and signal extraction technology implemented to temporally quantify achievement of these ranges. The outcomes bronchopulmonary dysplasia/death, retinopathy of prematurity (ROP)/death, severe ROP and ROP requiring surgery were compared in a pre- versus post-intervention evaluation using multivariate analyses.
RESULT: A total of 304 very low birth weight pre-initiative infants were compared with 396 post-initiative infants. Multivariate analyses revealed decreased odds of severe ROP (adjusted odds ratio (OR): 0.41; 95% confidence interval (CI): 0.24–0.72) and ROP requiring surgery (adjusted OR 0.31; 95% CI: 0.17–0.59) post-initiative. No differences in death were observed.
CONCLUSION: Significant reductions in severe ROP and ROP requiring surgery were observed after staff education and implementation of new technology to quantify success in achieving targeted saturations and reinforce principles and practices.

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INTRODUCTION

Very low birth weight (VLBW) neonates often require supplemental oxygen and experience intermittent periods of hypoxia and hyperoxia. In the setting of hyperoxia, production of reactive oxygen species may cause significant cellular damage.[1] Preterm neonates are deficient in the quantity and function of antioxidants, creating an imbalance termed oxidative stress.[1] Oxidative stress has been implicated in the development of several neonatal disease processes including bronchopulmonary dysplasia (BPD)[2–4] and retinopathy of prematurity (ROP).[5–7]

BPD and ROP account for a significant amount of morbidity in preterm neonates.[8–11] Although many factors contribute to the pathogenesis of each disease, exposure to supplemental oxygen and sustained periods of hyperoxia are common to both. Several institutions have demonstrated that efforts to limit hyperoxia in preterm neonates can be effective in reducing BPD and ROP.[12–15] We conducted a quality improvement effort in our neonatal intensive care unit (NICU) aimed at regulating the use of supplemental oxygen in the preterm population and, ultimately, reducing BPD and ROP. A major focus of this initiative was the use of pulse oximetry with signal extraction technology to temporally quantify success or failure in achieving target oxygen saturation (SpO_2) ranges. We report the design, implementation and results of that initiative.

METHODS

The NICU at Yale-New Haven Children's Hospital (YNHCH) is a 54-bed level IV[16] NICU for infants with complex medical and surgical conditions. There are ~4500 annual live births at Yale-New Haven Hospital with 800 to 900 admissions, both inborn and outborn, to the NICU.

Pre-initiative practices

In 2004, we established goal SpO_2 parameters in our NICU whereby VLBW infants requiring supplemental oxygen were assigned a target SpO_2 range of 88 to 96% and those in room air, 88 to 100%. Upper and lower SpO_2 alarm limits were set to match this range with the bedside nurse documenting a single and presumably representative SpO_2 value as part of the scheduled vital signs. Desaturation episodes were noted by placing a checkmark in an assigned column on the infant's bedside paper flow sheet. Frequency and severity criteria for recording such episodes were entirely subjective. Episodes of hyperoxia were not documented. Flow sheet data were reviewed by the medical staff to determine whether or not SpO_2 goals were being met and, at times, to assist with respiratory management.

In the delivery room, the default fraction of inspired oxygen (FiO_2) used for resuscitation was set at 1.0 in both term and preterm infants. Pulse oximetry was available but not routinely utilized during all neonatal resuscitations.

Designing and implementing an intervention

In 2006, an internal review of NICU-specific outcomes revealed that rates of BPD and severe ROP in our VLBW population were above the 50th percentile for pooled data from level III and IV NICUs. These data combined with several published reports outlining safe and successful efforts aimed at reducing BPD and ROP through limiting hyperoxia[12,14,15] resulted in the formation of the 'Oxidative Stress Initiative Committee.' The multidisciplinary committee was convened in January of 2007 and comprised physicians, neonatal nurse practitioners, physician assistants, registered nurses and respiratory therapists. A physician and nurse were identified to lead the initiative. Several steps were involved in this process including a detailed review of existing center-specific data and practices, discussion and analyses of relevant medical literature, creation of an evidence-based guideline, implementation of a new system for monitoring

[1]Division of Perinatal Medicine, Department of Pediatrics, Yale University School of Medicine, New Haven, CT, USA and [2]Yale Center for Analytical Sciences, New Haven, CT, USA. Correspondence: Dr MJ Bizzarro, Division of Perinatal Medicine, Department of Pediatrics, Yale University School of Medicine, 333 Cedar Street, PO Box 208064, New Haven, CT 06520-8064, USA.
E-mail: matthew.bizzarro@yale.edu
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oxygen saturations and development and implementation of a unit-wide educational program.

After a review of the then-current medical literature, unit-based guidelines for the use of supplemental oxygen were revised in March 2007. The decision was made to maintain relatively wide target SpO_2 ranges to facilitate compliance at the bedside. The target SpO_2 ranges for VLBW infants were changed from 88 to 96 to 85 to 93% for those requiring supplemental oxygen and from 88 to 100 to 85 to 100% for those in room air. Exceptions were made for specific populations (for example, those with certain types of congenital heart disease) and a written order from a licensed independent practitioner for upper and lower SpO_2 limits was mandated for every patient. Upper and lower SpO_2 alarm limits were set 1% above and 1% below the desired range with a particular emphasis on the principle that both high and low alarms be responded to with equal urgency. Random audits were conducted to determine if specified orders for SpO_2 ranges matched the alarm limits set on the monitor. Noted discrepancies were addressed with the appropriate staff member(s).

The written guideline, in an effort to standardize practice and limit potentially unnecessary interventions, provided specific details for when and how to respond to periods of hypoxia or hyperoxia. For example, for infants requiring supplemental oxygen it was stressed that an SpO_2 of 80 to 84% for a short duration in the setting of a stable respiratory and heart rate warranted observation and assessment but not immediate intervention. Any sustained SpO_2 of $<84\%$ or $\geqslant 94\%$, however, necessitated assessment and adjustment of supplemental oxygen in increments or decrements of between 2 and 5%.

In addition to guidelines for the NICU, management of oxygen use in the delivery room was also addressed. Our resuscitation area was outfitted with oxygen blenders and the default FiO_2 for resuscitation, previously set at 1.0, was changed to 0.40. Pulse oximeters were to be placed on the right hands of all infants requiring resuscitation. Education regarding acceptable SpO_2 parameters in the first few minutes of life was conducted and guidelines for when and how to escalate supplemental oxygen in the delivery room were drafted.

Quantifying achievement of target saturations

Masimo Signal Extraction Technology (Masimo Corporation, Irvine, CA, USA) was acquired and implemented for its ability to more accurately measure SpO_2 via algorithms and adaptive filters during episodes of motion or severe hypoxia.[17,18] The system also had the ability to generate histograms and temporal data, which proved vital to our process. It enabled us to quantify, for set time intervals, the percentage of time each patient was spending within, above and below their target SpO_2 range which, to some extent, served as a measure of compliance. The overall goal was to maintain each infant within their desired range for $\geqslant 75\%$ of the day. Interval SpO_2 range data were collected from the monitoring system (Figure 1), documented in the clinical flow sheet, and presented and discussed as part of clinical work rounds to assist with management. For example, if the histogram in Figure 1 represents 24 h of pulse oximetry data from a VLBW infant on supplemental oxygen (that is, target SpO_2 range 85 to 93%), the data indicate that the infant spent at least 50% of that 24-h period above range. This information could then be used as an opportunity to reinforce the risks of hyperoxia to the entire medical team, to identify any barriers to maintaining the infant within his/her target range with the bedside nurse and respiratory therapist, and to reinforce

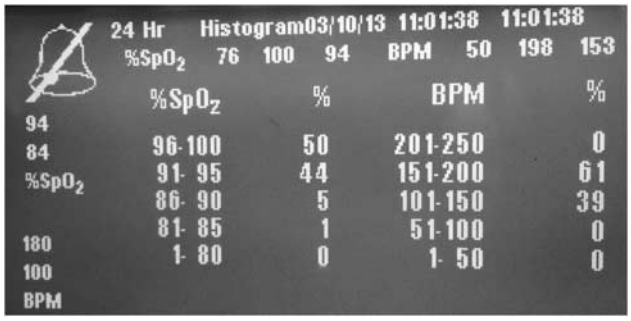

Figure 1. Signal extraction technology pulse oximeter display. Display from the Masimo Signal Extraction Technology pulse oximeter monitor depicting the percentage of time spent within various SpO_2 and heart rate ranges over a 24-h period.

the written guideline aimed at decreasing supplemental oxygen in the setting of hyperoxia. Alternatively, if an infant was determined to have spent a significant percentage of time below their targeted range, the potential need for more respiratory support could be evaluated and discussed. The use of oximeter data therefore helped not only to monitor success but also to ingrain new concepts into the NICU culture.

The educational effort conducted to implement these practices incorporated ~ 225 staff members across all disciplines in the NICU and was led by members of the Oxidative Stress Initiative Committee. The curriculum included background education on the potential dangers of oxygen exposure in the preterm neonate as well as a comparison of BPD and ROP rates in our NICU to national benchmarks. The written guideline was reviewed with staff members and feedback was encouraged. Where appropriate, this feedback was utilized to modify the guideline. Education in the use of the new pulse oximeter was also conducted. This entire process from formation of the committee to completion of staff education spanned ~ 9 months.

Patient population and data collection

In an effort to determine the impact of our intervention, pre- and post-initiative data were collected and compared. The pre-initiative period was defined from 1 January 2004 through 31 December 2006 and the post-initiative period from 1 January 2008 through 31 December 2011. The period of time from 1 January through 31 December 2007 was considered transitional.

The NICU at YNHCH maintains an electronic database of all long-term admissions. This database was accessed for the purpose of this investigation and additional data were collected from the medical record. All inborn VLBW neonates and those outborn VLBW neonates transferred to YNHCH within 48 h of birth were included. The primary outcomes of interest were BPD or death, ROP or death, severe ROP and ROP requiring laser surgery. Demographic data including gestational age (GA), birth weight (BW), gender and race were also collected as was the presence of multiple gestations, the use of antenatal steroids, method of delivery and need for intubation in the delivery room. Specific neonatal morbidities such as respiratory distress syndrome, early and late-onset sepsis, intraventricular hemorrhage, periventricular leukomalacia, patent ductus arteriosus, and necrotizing enterocolitis (NEC) were also included as was duration of NICU stay and death.

Definitions

Respiratory distress syndrome was defined as respiratory distress in a preterm neonate with a characteristic chest radiograph and the need for intubation and surfactant administration. A laboratory-confirmed bloodstream infection was defined according to criteria from the Center for Disease Control and Prevention.[19] Although the definition for a commensal species-related laboratory-confirmed bloodstream infection was modified in 2008,[20] the previous definition was utilized to maintain consistency throughout the study period. Sepsis was further defined by timing of the laboratory-confirmed bloodstream infection with early-onset occurring at $\leqslant 72$ h of life and late-onset at >72 h of life. Intraventricular hemorrhage was graded based on the classification system developed by Papile *et al.*[21] and included all grades. Periventricular leukomalacia was determined by screening ultrasonography interpreted by a pediatric radiologist. A patent ductus arteriosus was determined by an echocardiogram interpreted by a pediatric cardiologist. NEC was defined according to the modified Bell's staging and included those cases $\geqslant$ stage IIA.[22]

BPD was defined as the need for supplemental oxygen at 36 weeks post menstrual age in association with characteristic radiographic changes.[8,23] ROP was diagnosed by a single experienced pediatric ophthalmologist throughout the entire study period and staged according to the criteria established by the International Committee for Classification of ROP.[24] Severe ROP was defined as $\geqslant$ stage 3 disease or any stage with plus disease present.[24,25] ROP surgery included only laser surgery.

Data analysis

Frequency, proportion, mean and s.d. were used to describe the characteristics of the cohort as appropriate. The effect of our initiative was assessed by introducing the dichotomous variable 'period' which defined the pre-initiative period as 1 January 2004 through 31 December 2006 and post-initiative period as 1 January 2008 through 31 December 2011. In unadjusted analyses, the primary outcomes BPD or death, ROP or death, severe ROP and ROP requiring surgery were compared between

Table 1. A description and comparison of variables by period

Variable	*2004–2006* (n = *304*)	*2008–2011* (N = *396*)	*Total* (N = *700*)	P-*value*[a]
GA (weeks)	26.4 ± 2.3	26.5 ± 2.1	26.5 ± 2.2	0.82
BW (g)	914 ± 282	900 ± 274	906 ± 278	0.49
Male	161 (53.0)	214 (54.0)	375 (53.6)	0.78
Outborn	24 (7.9)	32 (8.1)	56 (8.0)	0.93
Race				0.68
Caucasian	179 (58.9)	245 (61.9)	424 (60.6)	
African American	118 (38.8)	141 (35.6)	259 (37.0)	
Hispanic	59 (19.4)	67 (21.5)	126 (18.0)	
Asian	8 (2.3)	10 (2.5)	18 (2.6)	
Antenatal steroids	266 (87.5)	367 (92.7)	633 (90.4)	0.02
Cesarean section	204 (67.1)	304 (77.3)	508 (72.9)	0.003
Multiple gestation	100 (32.9)	149 (37.6)	249 (35.6)	0.20
Intubated in delivery room	201 (66.1)	241 (60.9)	442 (63.1)	0.15
Surfactant administered	252 (82.9)	295 (74.5)	547 (78.1)	0.008
RDS	230 (75.7)	295 (74.5)	525 (75.0)	0.79
Pneumothorax	39 (12.8)	35 (8.8)	74 (10.6)	0.09
5-min Apgar score	8 (6–9)	7 (6–9)	8 (6–9)	0.33
Early-onset sepsis	10 (3.3)	10 (2.5)	20 (2.9)	0.55
Late-onset sepsis	61 (20.1)	39 (9.8)	100 (14.3)	<0.0001
IVH[b]	75 (26.8)	94 (24.6)	169 (25.5)	0.52
PVL[c]	8 (2.8)	11 (2.9)	19 (2.8)	0.97
PDA	67 (22.0)	78 (19.7)	145 (20.7)	0.45
NEC	46 (15.1)	35 (8.8)	81 (11.6)	0.01
BPD[d]	70 (30.8)	84 (26.7)	154 (28.4)	0.29
BPD or death	147 (48.4)	165 (41.7)	312 (44.5)	0.08
ROP	116 (38.2)	160 (40.4)	276 (39.4)	0.55
ROP or death	189 (62.2)	229 (57.8)	418 (59.7)	0.25
Severe ROP[e]	57 (24.6)	50 (15.4)	107 (19.2)	0.006
ROP surgery[f]	42 (36.2)	27 (16.9)	69 (25.0)	0.0003
Length of stay	72.5 ± 56.9	83.1 ± 67.0	78.5 ± 63.0	0.05
Death	77 (25.3)	81 (20.5)	158 (22.6)	0.13

Abbreviations: BW, birth weight; GA, gestational age; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; PVL, periventricular leukomalacia; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity.
[a]Represents a comparison of post- and pre-initiative period.
[b]Missing data of 38 infants (24 in pre- and 14 in post period) were excluded.
[c]Missing data of 32 infants (20 in pre- and 12 in post period) were excluded.
[d]Percentages are calculated excluding 158 deaths.
[e]One hundred and forty-two deaths without an eye exam were excluded (73 in pre- and 69 in post period).
[f]Percentages are among 276 who had any stage ROP.
Data are presented as mean (s.d.) for continuous variables and N (column%) for categorical variables.

pre- and post-initiative periods as were other important demographic and clinical characteristics using independent Student's *t* test, χ^2-test or Fisher's exact test, where appropriate. Further multivariate logistic regression analyses were performed on each primary outcome, with time period as the primary independent predictor variable. The models were built manually based on retaining clinical and demographic factors known to be associated with the outcomes of interest, as well as variables that differed between the two time periods. All the statistical analyses were performed using software SAS 9.2 (Cary, NC, USA). Statistical significance was set at $\leqslant 0.05$, two sided.

This project was designed in 2007 solely as a quality improvement initiative and was thereby exempt from review by our Human Investigation Committee. In 2011, however, the comparison of pre- and post-initiative data for the purpose of publication was submitted and approved by the Human Investigation Committee of the Yale University School of Medicine.

RESULTS

A total of 304 infants in the pre-initiative period were compared with 396 infants in the post-initiative period. The entire cohort had a mean GA and BW of 26.5 weeks and 906 g, respectively, 53.6% were male and 60.6% Caucasian. BPD was diagnosed in 28.4% and ROP in 39.4% of the entire cohort. Severe ROP was diagnosed in 19.2% of all infants who had an eye exam and 25.0% of those with any stage of ROP required laser surgery (Table 1).

When infants in the pre- and post-initiative periods were compared by bivariate analyses, antenatal steroid use and Caesarian section delivery were significantly higher in the post-initiative period (Table 1). Fewer infants in the post-initiative period received surfactant. The proportion of VLBW infants with late-onset sepsis and with NEC was significantly lower in the post-initiative period, but the duration of NICU stay was, on average, 10 days longer (Table 1). No significant differences in rates of intraventricular hemorrhage, periventricular leukomalacia or death were observed between periods. No statistically significant differences in the proportion of infants with BPD or death as well as all-stage ROP or death were observed, although there was a trend toward a reduction of BPD or death in the post-initiative period ($P = 0.08$; Table 1). Significant reductions in both severe ROP and ROP requiring laser surgery were noted (Table 1).

In the adjusted analyses, no significant effect from our initiative was observed on the outcome BPD or death (Table 2A). Lower BW, male gender, surfactant administration, the presence of a patent ductus arteriosus, NEC and pneumothorax, however, were all determined to be independent risk factors for BPD or death. Trends toward a protective effect from the use of antenatal steroids and a deleterious effect from late-onset sepsis were also observed (Table 2A).

When ROP or death was assessed as the outcome of interest in a multivariate model, a near statistically significant effect from our initiative was determined ($P = 0.06$; Table 2B). Of note, the magnitude of association (that is, odds ratio (OR)) and the significance of the initiative were strengthened in the presence of BW in the model ($P = 0.25$ in unadjusted and $P = 0.06$ in adjusted analyses); this was due to the overall lower BW in the sample of children considered in the analysis for the post-intervention period as compared with the pre-intervention period, especially

Table 2A. Multivariate logistic regression analysis for the outcome BPD or death, $N = 700$

Effect	*OR*	*95% CI*	P-*value*
Period (post vs pre)	0.85	0.59, 1.22	0.38
GA (weeks)	0.94	0.82, 1.08	0.37
BW (100 g)	0.73	0.65, 0.82	<0.0001
Male	1.81	1.25, 2.61	0.002
Race			0.48
Caucasian	1.06	0.72, 1.54	0.78
Asian	0.52	0.16, 1.67	0.27
African American	1.00	—	
Antenatal steroids	0.57	0.30, 1.06	0.07
Surfactant	3.07	1.71, 5.51	0.0002
Pneumothorax	3.13	1.72, 5.70	0.0002
PDA	1.68	1.08, 2.63	0.02
NEC	2.08	1.18, 3.68	0.01
Late-onset sepsis	1.65	0.97, 2.80	0.06

Abbreviations: BPD, bronchopulmonary dysplasia; BW, birth weight; CI, confidence interval; GA, gestational age; NEC, necrotizing enterocolitis; OR, odds ratio; PDA, patent ductus arteriosus.

Table 2B. Multivariate logistic regression analysis for the outcome ROP or death, $N = 700$

Effect	*OR*	*95% CI*	P-*value*
Period (post vs pre)	0.64	0.40, 1.01	0.06
GA (weeks)	0.57	0.48, 0.68	<0.0001
BW (100 g)	0.67	0.59, 0.76	<0.0001
Race			0.02
Caucasian	1.92	1.21, 3.06	0.006
Asian	0.93	0.19, 4.51	0.93
African American	1.00	—	
Outborn	2.76	1.06, 7.22	0.04
PDA	2.16	1.15, 4.07	0.02
Late-onset sepsis	3.01	1.40, 6.44	0.005

Abbreviations: BW, birth weight; CI, confidence interval; GA, gestational age; OR, odds ratio; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity.

among children who did not experience ROP or death (1098 g vs 1165 g). Lower GA, lower BW, Caucasian race (compared with African American), outborn status, the presence of a patent ductus arteriosus and late-onset sepsis were all associated with an increased risk of ROP or death (Table 2B).

Severe ROP was assessed among 558 VLBW infants who underwent an eye exam. This analysis excluded 142 infants who died before having an exam. After adjusting for other factors, the post-initiative period was associated with significantly lower odds of severe ROP (Table 3A). Lower GA and BW, and pneumothorax were all associated with a significantly increased risk (Table 3A). A similar finding was determined when ROP requiring laser surgery was assessed among those with any stage ROP. The post-initiative period again had a protective effect, whereas lower BW and GA, male gender and respiratory distress syndrome were all associated with a significantly increased risk (Table 3B).

Table 3A. Multivariate logistic regression analysis for severe ROP, $N = 558$

Effect	*Adjusted OR*	*95% CI*	P-*value*
Period (post vs pre)	0.41	0.24, 0.72	0. 002
GA (weeks)	0.65	0.52, 0.80	0.0001
BW (100 g)	0.65	0.53, 0.80	<0.0001
Male	1.71	0.98, 2.96	0.06
Race			0.20
Caucasian	1.44	0.82, 2.54	0.20
Asian	0.30	0.03, 2.93	0.30
African American	1.00	—	
Surfactant	4.31	0.97, 19.17	0.06
Pneumothorax	2.76	1.12, 6.83	0.02

Abbreviations: BW, birth weight; CI, confidence interval; GA, gestational age; OR, odds ratio; ROP, retinopathy of prematurity.

Table 3B. Multivariate logistic regression analysis for the outcome ROP surgery, $N = 276$

Effect	*Adjusted OR*	*95% CI*	P-*value*
Period (post vs pre)	0.31	0.17, 0.59	0.0003
GA (weeks)	0.75	0.57, 0.98	0.04
BW (100 g)	0.75	0.58, 0.97	0.03
Male	1.95	1.04, 3.65	0.04
Race			0.97
Caucasian	1.01	0.53, 1.93	0.98
Asian	0.74	0.07, 7.77	0.80
African American	1.00	—	
RDS	5.53	1.20, 25.56	0.03

Abbreviations: BW, birth weight; CI, confidence interval; GA, gestational age; OR, odds ratio; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity.

DISCUSSION

Oxygen exposure has been linked to an increased risk of both ROP and BPD in preterm neonates.[2–7] In ROP, interruption and subsequent abnormal neovascularization of the retina is believed to be the direct result of changes in oxygen tension in the neonate and its effects on vascular growth factors.[11] In our investigation, we observed a significant reduction in severe ROP and ROP necessitating surgery that coincided with an effort to limit hyperoxia in VLBW infants. Similar efforts have been previously described with comparable results.[12,26,27] Deulofeut *et al.*[12] outlined the effect of a change in practice in their NICU whereby target SpO_2 ranges for preterm infants requiring supplemental oxygen previously set at 92 to 100% were decreased to 85 to 93%. Data were collected prospectively from 502 infants with BW $\leqslant$1250 g. The authors noted a statistically significant decrease in all-stage ROP with no differences in intraventricular hemorrhage, periventricular leukomalacia or death across study periods.[12]

Chen *et al.*[26] conducted a meta-analysis aimed at evaluating the association between SpO_2 and ROP in infants with GA $\leqslant$32 weeks. Ten studies incorporating 3088 infants were included. A stratification analysis was performed given significant heterogeneity in lower and higher SpO_2 ranges investigated in each study. The authors determined that infants with a low SpO_2 limit of $\leqslant$83% in the first several weeks after birth had the lowest relative risk (RR) of developing severe ROP (RR: 0.34, 95% confidence interval (CI): 0.18, 0.65). No differences in mortality were observed.[26]

The National Institute for Child Health and Human Development's Neonatal Research Network conducted the prospective, randomized multicenter SUPPORT trial comparing a lower target oxygen saturation range (85 to 89%) to a higher target range (91 to 95%) in infants with GA 24 0/7 to 27 6/7 weeks.[27] The primary outcome of interest was severe ROP or death. A total of 1316 infants were enrolled in the study with 654 in the lower saturation group and 662 in the higher. Severe ROP or death did not differ between groups. However, when survivors were assessed, severe ROP was found to be significantly reduced in the lower target saturation group (8.6% vs 17.9%; RR: 0.52; 95% CI: 0.37 to 0.73; $P < 0.001$).[27]

Despite our success in reducing severe ROP, a comparable effect on BPD was not observed. The development of BPD is believed to be the end result of many factors. Poor nutrition and growth as well as pre- and post-natal infections, surgery, hyperoxia and ventilator-induced trauma can create an imbalance in pro- and anti-inflammatory cytokines resulting in lung injury and, subsequently, abnormal alveolarization and vascular development.[28] In our multivariate analyses, the risk of BPD was related to many variables other than prematurity, including intubation and surfactant administration, patent ductus arteriosus, NEC and late-onset sepsis. It is therefore possible that by targeting a single risk factor, we were unable to significantly alter the onset and progression of disease. Of note, from 2008 to 2011 additional successful quality-improvement initiatives and practice changes were conducted in our NICU, including a successful and sustained initiative aimed at reducing late-onset sepsis,[29] a concerted movement toward the use of non-invasive ventilation[30] and an effort aimed at the introduction of early enteral nutrition. Despite this, we were still unable to significantly influence the overall incidence of BPD or death. Prior investigations have suggested that genetic factors may have a role in the development of BPD.[31] It is possible that we have reached our limit in the ability to influence environmental factors, and future progress necessitates efforts to identify and target genetic factors related to the onset and progression of the disease.

It is also possible that the ideal target SpO_2 range for the prevention of BPD and ROP is not identical. The SUPPORT trial compared infants with an SpO_2 range of 85 to 89% to those with a range of 91 to 95%. Although a significant reduction in severe ROP was noted among survivors in the low saturation group, no significant differences in BPD were observed (adjusted RR for BPD or death: 0.91; 95% CI: 0.83, 1.01).[27] The BOOST trial randomized 358 infants <30 weeks' gestational age to a standard (91 to 94%) or high (95 to 98%) saturation group and compared groups with respect to several measures of growth and neurodevelopmental outcome.[32] A significantly increased risk of BPD was observed in the high SpO_2 group, with no significant differences in ROP, growth, major neurodevelopmental impairments or death noted.[32]

The ideal target SpO_2 range for the preterm infant therefore remains somewhat elusive. Based on findings from randomized controlled trials,[27,32] most NICUs adopted target SpO_2 ranges in their preterm population somewhere between 85 and 95%. Although targeting the lower end of this range may be of some perceived benefit in preventing severe ROP, the SUPPORT trial reported a higher rate of death before discharge in their group with a targeted SpO_2 range of 85 to 89% (19.9% vs 16.2%; RR: 1.27; 95% CI: 1.01, 1.60; $P=0.04$). This equated to $\sim$ one additional death for every two cases of severe ROP prevented by targeting a SpO_2 of 85 to 89%.[27] These findings have raised considerable concerns. In our initiative, we targeted an SpO_2 range of 85 to 93% in VLBW infants requiring supplemental oxygen. Unlike SUPPORT, we observed a significant reduction in severe ROP with no increase in mortality after implementing this strategy. However, not only were our SpO_2 ranges wider than those in the SUPPORT trial, but there was significant overlap between targeted ranges in our pre- and post-initiative periods (88% to 96% vs 85% to 93%). It is also possible that infants in our post-initiative period actually spent the majority of time in the upper portion of their targeted ranges (that is, 90 to 93%) with little true exposure to low SpO_2. The SUPPORT trial demonstrated this effect, reporting an actual median oxygen saturation for infants in their low saturation group of close to 91%.[27] Lastly, our cohort does not represent a randomized sample and instead compares two cohorts from different time periods. It was therefore not possible to control for all known and unknown confounding variables related to death when assessing this outcome.

In addition to those just described, there are some limitations to the interpretation of our results. We were unable to include and control for all known and unknown confounding variables, including practice changes, for both BPD and ROP, given the retrospective nature of our investigation. Also, although we were able to monitor and report the percentage of time each infant in the post-initiative period spent within and outside of their desired SpO_2 ranges, these data were only used for patient management and not collected for the purpose of analysis. By study design, similar data was not available from the pre-initiative period for comparison. We therefore cannot quantify compliance with target SpO_2 ranges and whether or not success was truly achieved in limiting hyperoxia.

Despite some of these limitations, we were able to demonstrate a significant reduction in the incidence of severe ROP and ROP requiring laser surgery in our NICU that directly coincided with our effort to limit hyperoxia. We believe that introduction of signal extraction technology was a major key to this success. Although we are not the first group to demonstrate that implementation of this technology can result in a reduction in severe ROP,[33] we are not aware of another report outlining the use of this monitoring in a method similar to ours. We also believe that other aspects of our approach to limiting hyperoxia likely improved our success. In a multicenter cohort study, Hagadorn *et al.*[34] reported significant variability from center-to-center in achieving target saturation ranges with the majority of infants remaining outside their desired SpO_2 range for more than half of the time. The authors determined that the use of wider SpO_2 target ranges and alarm limits set close to the desired upper and lower target limits, both of which were important aspects of our protocol, were associated with higher success in achieving target SpO_2 ranges.[34] In addition, we believe that the ability to quantify time spent within, above and below desired SpO_2 ranges allowed us to directly measure compliance via accurate, continuous objective data replacing intermittent, subjective data. This not only allowed direct measurement of success or failure in achieving our targets but also served as a powerful tool in reinforcing principles and practice changes and in directing respiratory management. The continued use of this approach and incorporation of these data into our NICU culture has greatly assisted in sustaining this effort and, in our opinion, has improved overall care of this patient population.

CONCLUSIONS

Prolonged and repeated exposures to hyperoxia have been associated with BPD and ROP in the VLBW population. We conducted a quality improvement initiative aimed at limiting hyperoxia in our NICU. This included altering the SpO_2 target ranges, drafting comprehensive guidelines for oxygen management, implementing new technology and developing a comprehensive education program for all members of our NICU staff. Although our goal SpO_2 ranges did not change dramatically between periods, our approach to the use of oxygen did. We focused a great deal of our effort on educating staff as to the potential risks related to oxygen exposure in our patient population and involved all disciplines in the process to assure all viewpoints were represented. Through these efforts we were able to show a significant reduction in severe ROP and ROP requiring laser surgery without any perceived increased risks to our patient population.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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