Journal of Perinatology (2006) 26, 700–705

www.nature.com/jp

ORIGINAL ARTICLE

Avoiding hyperoxia in infants ⩽1250 g is associated with improved short- and long-term outcomes

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Objective: To determine the rate and severity of short- and long-term morbidity in very low birth weight infants treated before and after the implementation of a change in clinical practice designed to avoid hyperoxia.

Methods: Analysis of a prospectively collected database of all infants ⩽1250 g admitted to two Emory University NICU's from January 2000 to December 2004. A change in practice was instituted in January 2003 with the objective of avoiding hyperoxia in preterm infants with target O_2 saturation (SpO_2) at 93 to 85% (Period II). Before the change in practice, SpO_2 high alarms were set at 100% and low alarms at 92% (Period I). Statistical analysis included bivariate analyses and multivariate logistic regression comparing outcomes between the two periods.

Results: From January 2000 to December 2004, 502 infants met enrollment criteria and 202 (40%) were born in period II, after change in SpO_2 targets. Birth weight, gestational age and survival were similar between both periods. The rates for any retinopathy of prematurity, supplemental oxygen at 36 weeks post-conceptional age and the use of steroids for chronic lung disease were significantly lower in the infants born in Period II. There was no difference in the rates of necrotizing enterocolitis, intraventricular hemorrhage and periventricular leukomalacia. At 18 months corrected age (CA), the infants treated during Period II had a higher Mental Developmental Index (MDI) scores (80.2±18.3 vs 89.2±18.5; *P* 0.02) and similar Psychomotor Developmental Index (PDI) scores (83.9±18.6 vs 89.4±17.2; *P* 0.08) than those treated during Period I. The proportion of infants with an MDI or a PDI less than 70 was similar between the periods.

Conclusions: The change in practice to avoid hyperoxia is associated with a significant decrease in neonatal morbidity and does not have a detrimental effect on developmental outcomes at 18 months CA.
Journal of Perinatology (2006) **26,** 700–705. doi:10.1038/sj.jp.7211608; published online 12 October 2006

Keywords: hyperoxia; oxygen saturation; oxidative stress; very low birth weight infants; long term follow-up; clinical practice

Introduction

Improvements in perinatal care have increased the survival rates of premature infants. However, this improvement has resulted in a greater risk for significant short- and long-term morbidity among survivors.[1]

Several neonatal practices have been shown to impact the developing brain.[2,3] Therefore, it is becoming clear that the impact of changes in clinical practice should be carefully assessed to ensure that they do not have adverse short-term or long-term consequences. One such practice with potentially detrimental effects is the practice of monitoring oxygenation levels of very low birth weight (VLBW) infants who are receiving supplemental oxygen with pulse oximetry, especially when infants are exposed to persistent or alternating hyperoxia. VLBW frequently require oxygen therapy; the tenacity associated with monitoring oxygen saturation levels to avoid persistent or alternating hyperoxia may be critically important in the outcome of these infants.[4,5] This seems to be of particular significance if physiologic principles are not applied to clinical care and maintained continuously and if adequate monitoring equipment is not utilized.[6]

It is well supported in the literature that a significant part of the injury that occurs is likely to be secondary to the oxidative stress experienced by an immature infant who lacks appropriate anti-oxidant defense mechanisms.[7,8] Early work in the mid-1970s were already describing that the accumulated hypoxanthine during hypoxia could be responsible for the generation of oxygen radicals, especially during the reperfusion phase; thus explaining why the injury related to hypoxia occurs, to a large extent, in the reoxygenation period.[9] The poorly developed structure of many tissues results in limited ability to compensate physiologically in multiple organ systems, including the central nervous system,[2,3] respiratory system[10] and the hematological system.[11] Additionally, oxidative stress has been epidemiologically associated with detrimental effects on the maturation of the vascular and ophthalmologic organs involved in

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Received 23 May 2006; revised 15 August 2006; accepted 5 September 2006; published online 12 October 2006

development of retinopathy of prematurity (ROP),[4,5] the digestive system and the development of necrotizing enterocolitis (NEC).[12]

Animal models have more recently been used in relation to hyperoxic exposure, and the results are variable. Asphyxiated pigs treated with hyperoxia restored cerebral blood flow faster and more completely compared with room air-treated animals,[13] and higher levels of excitatory amino acids were found in the striatum of newborn asphyxiated piglets treated with room air compared hyperoxic treatment.[14] In contrast, reoxygenation with room air has been shown to induce less brain inflammation than reoxygenation with pure oxygen.[15] Finally, even when blood oxidative stress indicators and cerebral histopathology do not differ after reoxygenation with room air or with 100% O_2 after asphyxia, it may impair the early neurologic outcome of the newborn piglets treated with hyperoxia.[16] We recently reported that 90 min of breathing 96% oxygen markedly increases the presence of markers of oxidative stress, apoptosis and the proliferation of neural stem cells in the developing brain in a GFP.nestin transgenic mice model.[17]

In light of the irreversible nature of severe perinatal injury, its long-term consequences and the current knowledge of the role that free radicals play in the pathogenesis of multi-system injury; care should include choosing O_2 saturation (SpO_2) targets that avoid hyperoxia in infants breathing supplemental oxygen. However, there is concern that avoiding hyperoxia during early development using SpO_2 targets that prevent hyperoxia (i.e. 85 to 93%.) may be associated with greater mortality and/or short- and long-term detrimental neurological effects.

With the objective of avoiding hyperoxia in preterm infants starting at the time of birth, a new guideline of care was implemented in our institutions in January 2003. The high SpO_2 targets in the pulse-oximeter alarm aimed to avoid hyperoxia were set at 93% and the low SpO_2 target at 85%. Before the change in clinical practice, the SpO_2 high alarms were set at 100% and the low alarms at 92%. In order to elucidate the long-term impact on neurodevelopmental outcome of this practice guideline aimed to avoid hyperoxia, we sought to examine the relative changes in rates of survival and rates and severity of long-term outcome in VLBW infants treated before and after the implementation of the guidelines. We hypothesized that infants born during the period after the implementation of the new clinical practice would have similar rates of mortality, and that among those infants who survived, the rates of long-term morbidity would not be negatively affected.

Methods

We performed detailed analysis of a prospectively collected database of all inborn infants ⩽1250 g admitted to two Emory University neonatal intensive care units (NICU) (Grady Memorial Hospital and Emory Crawford Long Hospital) from January 2000 to December 2004. After obtaining approval by the Institutional Review Board of Emory University, all data were verified with chart review for accuracy. Infants with major congenital anomalies, outborns and infants deemed nonviable in the delivery room who received only comfort care measures until their demise were excluded from the analysis.

An educational program for all health care personnel was performed following a protocol described previously[4] during the last half of 2002, and a change in clinical practice was instituted in January 2003 with the objective of avoiding hyperoxia in preterm infants breathing supplemental oxygen. Before the change in practice, the SpO_2 high alarms were set at 100% and the low alarms at 92%, identified as Period I. The target SpO_2 aimed to avoid hyperoxia was selected in the range of 93 to 85%, identified as Period II. The evaluation of the results was as an intention to treat study, as no permanent records of saturation was obtained.

The predictor variable selected was the target SpO_2 as it was related to the outcome variables. Short-term outcome variables analyzed were: mortality, chronic lung disease (CLD), the use of steroids for CLD, severe intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), NEC, ROP and length of stay. Neurodevelopmental outcome at 18 months corrected age (CA) was assessed using the Bayley Scales of Infant Development-II R.[18–20] Infants received a Mental Developmental Index (MDI) and a Psychomotor Developmental Index (PDI) with a mean score of 100±15. Infants who received a score <70 (i.e. >2 s.d. below the mean) were considered significantly impaired. CLD was defined as the need for supplemental oxygen beyond 36 weeks post-conceptional age.[21] The rates of CLD were calculated using surviving infants at 36 weeks post-conceptional age as the denominator. ROP was diagnosed by pediatric ophthalmologists following the routine screening program of our institutions, the international classification[22] and the American Academy of Pediatrics guidelines.[23,24] The rates of ROP were calculated using as the numerator the number of cases of ROP diagnosed and as the denominator the total number of infants who received retinal examinations. IVH was defined as 1 week ultrasound evidence of grade III or IV intraventricular bleed based on Papile's classification,[25] and PVL was defined as ultrasound evidence of periventricular white matter injury at 1 month of age. Ultrasounds were obtained and read as routinely performed for clinical care. At the time that most of these ultrasounds were performed, this study had not been planned and no pediatric radiologist was aware of practice guideline changes in relation to SpO_2 targets. The rates of IVH and PVL reported in this study were calculated using the total number of cases of IVH and PVL diagnosed as the numerator and the total number of infants who received a head ultrasound at the specified times (1 week and 1 month, respectively) as the denominator. NEC was diagnosed based on modified Bell's classification[26] and those patients diagnosed with ⩾stage II disease were included in this analysis. Length of stay was calculated as the total number of days spent in the NICU divided by those

infants that survived to discharge. All these data and indicators were collected prospectively and entered into the database as such.

Demographic data are summarized as proportions, means with s.d.s and median with ranges. Differences between the two study periods were studied by two-tailed bivariate analyses using the χ^2 test for categorical data and with Fisher's exact test when appropriate. The Student's *t*-test was used for continuous data, including comparing the differences between the MDI and PDI scores. Multivariate logistic regression model was used to analyze the effect of potential confounding factors in the two periods (weigh, gestational age, use of steroids for bronchopulmonary dysplasia). Statistical analysis was done using the SPSS® software for windows (version 13.0). Statistical significance was considered if *P* was less than 0.05.

Results

Of the 692 infants with birth weight less than 1250 g admitted to the two NICU's between January 2000 and December 2004; 114 (16.4%) were outborn, 51 (7.4%) received comfort care in the delivery room, 25 (3.6%) had major congenital anomalies, all of which were excluded from the analysis. Of the 502 infants who met enrollment criteria, 202 (40%) were born after the change in practice guidelines during Period II (Figure 1).

The mean birth weight, gestational age and other recorded demographics were similar between the two periods (Table 1). Mortality rate was about 18% during both periods. The length of stay for the survivors was significantly lower in the infants born during Period II. In addition, among the infants who survived past 35 weeks post-conceptional age, the need for supplemental oxygen as well as the need to use steroids for CLD was significantly lower in those infants treated with the aim of avoiding hyperoxia (Table 2). For those infants who received ophthalmologic examination, the rate of ROP was significantly lower in the infants treated with the aim of avoiding hyperoxia (Table 3). There was a similar distribution of IVH and PVL among infants who had a head ultrasound performed in the two study periods (Table 4).

Based on the findings of this study, approximately six new cases of CLD, nine cases of ROP stage II and three cases of ROP stage III to IV can be prevented for every 100 infants with birth weight less

Table 1 Demographic and delivery characteristics of study infants with birth weight ⩽1250 g born in Period I and II

Parameter	*Period I* (n = *300*)	*Period II* (n = *202*)	P-*value*
Birth weight (g)	896 ± 211	886 ± 219	0.58
Gestational age (week)	26.8 ± 2.39	27.0 ± 2.44	0.54
Male sex	145 (48%)	101 (50%)	0.71
Small for gestational age	62 (21%)	48 (24%)	0.44
Black	266 (89%)	175 (87%)	0.49
White	13 (4%)	8 (4%)	0.83
Asian	0 (0%)	2 (1%)	0.31
Apgar score at 1 min	5 (0–9)	8 (0–8)	0.57
Apgar score at 5 min	5 (0–9)	7 (1–9)	0.67
Cesarean delivery	171 (57%)	111 (55%)	0.71
Antenatal steroids	209 (70%)	147 (73%)	0.48
Multiple gestation	52 (17%)	37 (18%)	0.81
Prenatal care	271 (90%)	187 (93%)	0.42

$P<0.05$ considered statistically significant.
Period I: January 2000 to December 2002. Target O_2 saturations (SpO_2) 100–92%.
Period II: January 2003 to December 2004. Target SpO_2 93–85%.
Discrete data presented as counts with percentage of cohort.
Continuous data presented as mean and s.d. or median with range.

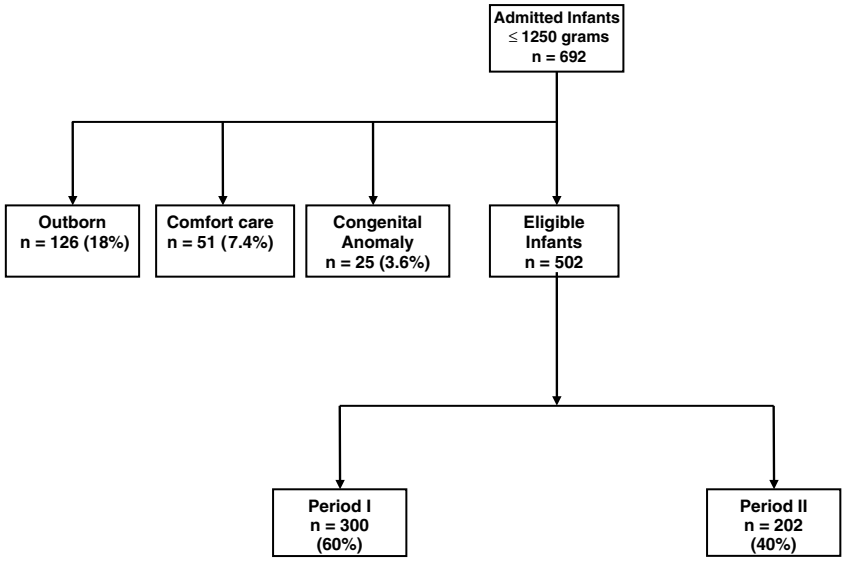

Figure 1 Cohort description. Period I: January 2000 to December 2002. Target O_2 saturations (SpO_2) 100 to 92%. Period II: January 2003 to December 2004. Target SpO_2 93 to 85%. Number in each box represents the sample size and percentage of infants for each group.

Table 2 Short-term morbidity in infants with birth weight ⩽1250 g born in Period I and II

Parameter	*Period I* (n = *300*)	*Period II* (n = *202*)	P-*value*
CLD (O_2 36 weeks)	153 (51%)	71 (35%)	0.00
Steroids for CLD	47 (16%)	18 (9%)	0.03
Length of stay	85.9±40.1	76.5±37.7	0.01
Surfactant in delivery room	208 (69%)	150 (74%)	0.26
NEC	28 (9%)	25 (12%)	0.30
Mortality	53 (18%)	38 (19%)	0.81

Abbreviations: CLD, chronic lung disease; NEC, necrotizing enterocolitis
$P<0.05$ considered statistically significant.
Period I: January 2000 to December 2002. Target O_2 saturations (SpO_2) 100–92%.
Period II: January 2003 to December 2004. Target SpO_2 93–85%.
Discrete data presented as counts with percentage of cohort.

Table 3 ROP in infants with birth weight ⩽1250 g born in Period I and II

Parameter	*Period I* (n = *300*)	*Period II* (n = *202*)	P-*value*
Eye exam	(*n* = 221)	(*n* = 152)	
Any ROP	130 (59%)	68 (45%)	0.00
Stage II ROP	47 (36%)	17 (25%)	0.01
Stage III and IV	16 (7%)	7 (4%)	0.27

Abbreviation: ROP, retinopathy of prematurity.
$P<0.05$ considered statistically significant.
Period I: January 2000 to December 2002. Target O_2 saturations (SpO_2) 100–92%.
Period II: January 2003 to December 2004. Target SpO_2 93–85%.
Discrete data presented as counts with percentage of cohort.

Table 4 Short-term neurological morbidity in infants with birth weight ⩽1250 g born in Period I and II

Parameter	*Period I* (n = *300*)	*Period II* (n = *202*)	P-*value*
Head ultrasound	(*n* = 275)	(*n* = 182)	
Any IVH	79 (29%)	53 (29%)	0.50
PVL	8 (3%)	7 (4%)	0.60

Abbreviations: IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia.
$P<0.05$ considered statistically significant.
Period I: January 2000 to December 2002. Target O_2 saturations (SpO_2) 100–92%.
Period II: January 2003 to December 2004. Target SpO_2 93–85%.
Discrete data presented as counts with percentage of cohort.

than 1250 g treated with lower SpO_2 limits aimed at avoiding hyperoxia.

A total of 247 infants survived to discharge in Period I, and 56% had an evaluation at 18 months CA. During Period II, 164 infants were discharged home, 54 were not yet eligible for developmental testing at the time of this study and 63% of those eligible had a developmental evaluation. The mean MDI scores were significantly

Table 5 Long-term neurological scores are better in infants with birth weight ⩽1250 treated with lower SpO_2 limits aimed at avoiding hyperoxia (Period II)

	Period I (n = *300*)	*Period II* (n = *202*)	P-*Value*
Death before discharge	*n* = 53	*n* = 38	
Age eligible for 18 month assessment	*n* = 247	*n* = 110	
Had 18-month follow-up, *n* (%)	138 (56%)	69 (63%)	
MDI (mean and s.d.)	80.2±18.3	89.2±18.5	0.02
PDI (mean and s.d.)	83.9±18.6	89.4±17.2	0.08
MDI⩽70 (*n* and %)	36 (26%)	12 (18%)	0.12
PDI⩽70	26 (19%)	12 (18%)	0.59

Abbreviations: MDI, Mental Developmental Index; PDI, Psychomotor Developmental Index.
$P<0.05$ considered statistically significant.
Period I: January 2000 to December 2002. Target O_2 saturations (SpO_2) 100–92%.
Period II: January 2003 to December 2004. Target SpO_2 93–95 to 85%.

higher in those infants treated with lower SpO_2 limits aimed at avoiding hyperoxia (80.2±18.3 vs 89.2±18.5; *P* 0.02) and the PDI scores were similar between the two periods (83.9±18.6 vs 89.4±17.2; *P* 0.08). Finally, the proportion of infants with MDI or PDI scores less than 70 was similar between the two study periods (Table 5).

Discussion

Studies have associated neonatal hyperoxia to injury to the developing brain,[2,3] lung[10] and retina.[4,5] In addition, there is an epidemiologic association with higher risk for childhood leukemia and cancer in neonates who are resuscitated with 100% O_2 at birth.[27,28] The deleterious effect of hyperoxia is not only relevant during the NICU stay but also in the first minutes of life. In the delivery room, hyperoxia may not only cause initial oxidative injury but it could trigger a cascade of events that may be impossible to stop despite excellent NICU care.[29] These deleterious effects of hyperoxemia may be also exacerbated by other interventions at birth like the addition of hypocapnia post asphyxia.[30] Unfortunately, many premature infants are still being exposed to unnecessary high levels of oxygen worldwide, despite the clear risk that hyperoxia represents to them.

Identifying the optimal SpO_2 range for VLBW infant has been challenging and controversial, and remains unknown. Despite this controversy over the ideal saturation range, it is well known that the arterial partial pressure of oxygen (PaO_2) cannot be reliably predicted when an infant is breathing supplemental oxygen if the SpO_2 is above 95%, as SpO_2 monitors are useful to detect hypoxemia but not hyperoxemia. Conversely, if the SpO_2 values are below 80% the infant is very likely to be hypoxemic. Following these physiologic principles and assuming an 'accepted PaO_2'

between 45 and 75 torr in the premature infant[6,31] breathing supplemental oxygen, the SpO_2 range should probably be not higher than 93% to consistently avoid high PaO_2 and not less than 85% to avoid potentially low PaO_2.

The findings of this study showed an improvement in CLD, ROP and length of stay without any increase in hospital mortality or short-term neurological adverse events when using lower targets for SpO_2 values. Even though the proportion of infants with severe ROP was statistically similar between the two periods (Table 3), a beneficial trend was observed in Period II from 7 to 4%, a relative risk reduction of 57%. The lack of statistical significance could be due to the fact that the number of infants with ROP III-IV was low. The significant reduction in the use of steroids for CLD may not be secondary to the decrease in rates of CLD but rather changes in practice following guidelines of the American Academy of Pediatrics.

In a recent summary, the effect of high and low saturations on morbidity is described.[32] Some of the studies summarized show that neonates with lower saturation targets presented with significantly lower occurrence of threshold ROP,[4] fewer days on oxygen, fewer days on artificial ventilation and fewer neonates with weights below the third percentile at discharge with no detrimental effect on survival or on the proportion of survivors who developed cerebral palsy.[33] In this study, when targeting high saturations, there was no apparent benefit in long-term development, while there was an increase in the duration of oxygen therapy in the high saturation group, an increase in the occurrence of home oxygen therapy and more frequent CLD in the high oxygen saturation group.[34] With regard to ROP, high oxygen saturation of 93% or more increased the risk for severe ROP, and also the risk for lung complications with no suggestion of increased mortality or poorer neurodevelopment.[35,36] Furthermore, it has been shown that changes in clinical guidelines and enforcement of clinical practices of O_2 management and monitoring were associated with a significant decrease in the rate of severe ROP in VLBW infants.[4] However, none of these studies have performed a detailed neurodevelopmental evaluation in the survivors at 18 months CA. To our knowledge, this study is the first one that provides detailed follow-up of premature infants treated with lower SpO_2 targets compared to those treated with higher SpO_2 targets at the same centers. The findings on this study show that there is no evidence of negative effects on long-term neurological outcome of lower SpO_2 targets. Actually, the MDI was statistically higher in the group of infants treated with the aim of avoiding hyperoxia. This finding is intriguing and needs further hypothesis-driven testing.

There are several weaknesses of this study. As a cohort study, not randomized prospectively, untested confounders could be partially associated with the findings that could be responsible for our findings. However, we have controlled for potential confounders in the analysis by means of a logistic regression analysis. In addition, no other clinical protocols or changes in nutritional guidelines that could affect the results were implemented during this study period. Another weakness is the inability to precisely determine the period of time in which the infants in Period II had saturation levels above 93%. It is well described that the aim of avoiding high SpO_2 and hyperoxia from the time of birth in infants breathing supplemental oxygen cannot be accomplished in all of the infants all of the time, just like using 'high' saturation target (i.e. 92 to 100%) does not avoid 'hypoxic' values. However, every study performed to date using lower SpO_2 targets shows a significant difference in the period of time spent with high saturation.[34,35] Additionally, the educational program and the intention to treat, accepting lower SpO_2 targets in these two centers, led to a different approach to oxygen therapy and increase awareness of health care personnel, aiming as best as possible to avoid periods of higher saturation. For this current study, we have only partial data available on actual levels of saturation after the educational process and implementation. In infants breathing supplemental oxygen in period 2, the oxygen saturation values were less than 96% during 84% of the time of the periods analyzed. In period 2, during 2004, there were audits done at random on the use of the high saturation alarm limits while infants were breathing supplemental oxygen. It was found to be in compliance in 96% of the cases audited.

Aiming to avoid hyperoxia was not associated with an increase in abnormal long-term outcome at follow-up and was associated with less CLD, as defined by oxygen prescription at 36 weeks, and with a reduced exposure to postnatal steroids. The latter may be related to the reduced oxidant exposure, the decrease in CLD, the knowledge gained over the years about the potential detrimental effects of postnatal steroids or all combined. Such reduced exposure may or may not be partially responsible for the observed improved long-term neurodevelopmental outcomes, but we cannot answer this question in this study.

Conclusions

An educational process and a change in clinical practice aimed at avoiding high SpO_2 and hyperoxia was associated with a significant decrease in neonatal rates of ROP and CLD and with a reduced length of stay, with no evidence of increased mortality or worse short-term neurological outcome (IVH and PVL). As important, aiming to avoid hyperoxia was not associated with an increase in abnormal outcome at 18 months follow-up. The higher MDI scores assessed by Bayley developmental testing suggest that avoiding hyperoxia may be associated with better long-term outcomes, but this needs to be determined.

Acknowledgments

This work was funded by Goddard Scholarship and ECRC from Emory University.

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