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Low Oxygen Saturation Target Range is Associated with Increased Incidence of Intermittent Hypoxemia

Juliann M. Di Fiore, BSEE¹, Michele Walsh, MD¹, Lisa Wrage, MPH², Wade Rich, RRT³, Neil Finer, MD³, Waldemar A. Carlo, MD⁴, Richard J. Martin, MD¹, and SUPPORT Study Group of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network^{*}

¹Division of Neonatology, Department of Pediatrics, Rainbow Babies and Children's Hospital, Case Western Reserve University, Cleveland, OH

²Statistics and Epidemiology Unit, RTI International, Research Triangle Park, NC

³Division of Neonatology, Department of Pediatrics, University of California, San Diego, CA

⁴Division of Neonatology, University of Alabama at Birmingham, Birmingham, AL

Abstract

Objective—To test the hypothesis that preterm infants randomized to a low vs high O₂ saturation target range have a higher incidence of intermittent hypoxemia.

Study design—A subcohort of 115 preterm infants with high resolution pulse oximetry enrolled in the Surfactant, Positive Pressure, and Oxygenation Randomized Trial were randomized to low (85%-89%) or high (91%-95%) O₂ saturation target ranges. Oxygen saturation was monitored until 36 weeks postmenstrual age or until the infant was breathing room air without respiratory support for 72 hours.

Results—The low target O₂ saturation group had a higher rate of intermittent hypoxemia (80% for 10 seconds and 3 minutes) prior to 12 days and beyond 57 days of life ($P < .05$). The duration shortened ($P < .0001$) and the severity increased ($P < .0001$) with increasing postnatal age with no differences between target saturation groups. The higher rate of intermittent hypoxemia events in the low target group was associated with a time interval between events of <1 minute.

Conclusion—A low O₂ saturation target was associated with an increased rate of intermittent hypoxemia events that was dependent on postnatal age. The duration and severity of events was comparable between target groups. Further investigation is needed to assess the role of intermittent hypoxemia and their timing on neonatal morbidity.

Intermittent hypoxemia may be associated with morbidity in preterm infants. In newborn animal models, administered intermittent hypoxemia paradigms have been shown to impair dopamine signaling,¹ contribute to neurological handicap,¹⁻³ and exacerbate retinal neovascularization.⁴ Although intermittent hypoxemia events are common in preterm infants, data relating to the prevalence of these events have been limited. Pulse oximetry

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Reprint requests: Juliann M. Di Fiore, BSEE, Division of Neonatology, Room 3100, Rainbow Babies and Children's Hospital, 11100 Euclid Ave, Cleveland, OH 44106. jmd3@case.edu.

^{*}List of members of the SUPPORT Study Group of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network is available at www.jpeds.com (Appendix).

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technology has enabled noninvasive recording of spontaneous intermittent hypoxemic events in preterm infants over prolonged periods of time. This has allowed for accurate documentation of the temporal changes in the incidence of intermittent hypoxemia events over the first few months of life. Recent data in a previous cohort of preterm infants of 24-28 weeks gestation have shown relatively few intermittent hypoxemia events over the first week of life, a progressive increase in events until approximately 5 weeks postnatal age followed by a decline thereafter.⁵

The multi-center Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) examined the role of high vs low O₂ saturation target ranges on retinopathy of prematurity (ROP). Following randomization to lower (85%-89%) or higher (91%-95%) O₂ saturation target ranges, infants in the lower target group were found to have a lower incidence of severe ROP. This was associated with an unexpected higher mortality in infants targeted to low baseline O₂ saturation in 2 separate clinical trials.^{6,7} The effect of these oxygenation target ranges on the occurrence of intermittent hypoxemia is unknown. As a lower baseline O₂ saturation target may increase hypoxic vulnerability and the likelihood of intermittent hypoxemia, we prospectively designed this study to test the hypothesis that infants randomized to a low compared with high O₂ saturation target range would have an increase in the incidence of intermittent hypoxemia.

Methods

The study population included a new subcohort of 115 preterm infants enrolled in the multi-center SUPPORT study from 2 sites: Rainbow Babies and Children's Hospital, Cleveland, and University of California San Diego. Enrollment criteria for the main trial included infants who were born between 24 weeks 0 days and 27 weeks 6 days of gestation for whom a decision had been made to provide full resuscitation. Infants born in other hospitals and those known to have major anomalies were excluded. Using a permutedblock randomization design, with stratification according to study center and gestational age (GA) (24 weeks 0 days-25 weeks 6 days or 26 weeks 0 days-27 weeks 6 days), infants were randomized to a low (85%-89%) or high (91%-95%) O₂ saturation target group within 2 hours of birth. Infants who were part of multiple births were randomly assigned to the same group.

Electronically altered pulse oximeters (Radical SET; Masimo, Irvine, California) were used to blind the staff to the randomization group. The nursing response was dictated by the individual caregiver and center. The clinical staff was blinded as to the randomization group and instructed to maintain infants in an O₂ saturation range of 88%-92%, with altered monitors showing target levels of 88%-92% with a maximum offset of 3%. For example, a displayed value of 90% corresponded to an actual O₂ saturation value of 87% in the low target group and 93% in the high target group.⁶ Actual values were displayed when the O₂ saturation values were <85% or >95% in both treatment groups. Limits of 85% and 95% that would trigger a monitor alarm were suggested, but they could be changed for individual patients. Centers received quarterly feedback for compliance in time spent in target range.

Due to the massive file sizes, storage, and analysis costs, only 2 centers from the main trial collected data with the highest resolution of 2 seconds averaging and 2 seconds sample rate needed for this data analysis (main SUPPORT study settings: 16 seconds averaging and 10 seconds sample rate). These files included up to 3.6 million O₂ saturation values per subject. Targeting of O₂ saturation and high resolution data collection began within 2 hours after birth and continued until 36 weeks postmenstrual age (PMA) or until the infant was breathing air without respiratory support for >72 hours, whichever came first. Respiratory support was defined as high frequency ventilation, conventional mechanical ventilation, nasal synchronized intermittent mandatory ventilation, continuous positive airway pressure,

nasal cannula, or hood. If the infant was off respiratory support for <72 hours and then support was re-administered, monitoring would have continued throughout that period. Infants weaned to room air for >72 hours but re-administered supplemental O₂ were returned to the original randomization group.

The study was approved by the Institutional Review Board at each site and by RTI International, which is the independent data coordinating center for the Neonatal Research Network. Written informed consent was obtained from the parent or guardian of each child before delivery.

Additional Institutional Review Board approval and waiver of consent was obtained to perform secondary analysis of de-identified data.

Respiration and apnea were not recorded for this study. We defined an intermittent hypoxemia event as a fall in O₂ saturation to 80% for 10 seconds and 3 minutes. To eliminate periods of fluctuations around the threshold point but include rapid cycles of hypoxia as can occur with periodic breathing, the minimal time interval between events was set to 4 seconds. Events were identified by custom software. The software output was verified by hand scoring of events in 4 1-hour segments in 5 randomly chosen infants. Events were then characterized by their duration and the time interval between each event (Figure 1). The time interval between each event was calculated as the time between the end of the intermittent hypoxemia event (designated by the return of O₂ saturation above 80%) and the beginning of the next intermittent hypoxemia event (designated by a fall below 80%). The severity, or nadir, of each event was also documented. For each postnatal day for each subject, a calculation was made of the total number, mean duration, and time interval between intermittent hypoxemia events. These values were then used in the model.

Demographic and clinical variables were compared between high and low arterial oxygen saturation (SaO₂) target groups using *t* tests or generalized estimating equation (GEE) regression models, adjusting for SUPPORT study stratification variables site and GA group, where appropriate. Due to sparse data a Fisher exact test was used to evaluate death. To model counts of intermittent hypoxemia events, a GEE regression model assuming a negative binomial distribution was used. The GEE model was prespecified to include SaO₂ target group and time variables and provided robust SE estimates, which take into account the correlations within multiple-birth clusters, including correlations between repeated measurements. Variables included in the final model for intermittent hypoxemia events were SaO₂ target group, linear and quadratic terms for postnatal age, interactions between SaO₂ target group and postnatal age variables, GA group, and respiratory support (yes or no, per day). An additional quadratic term that allowed the quadratic relationship of postnatal age and intermittent hypoxemia events to vary before and after 28 days was also included; this spline regression approach provided a better fit than simpler models.⁸ Also considered were interactions between GA group and postnatal age, between GA group and SaO₂ target group, and between the additional quadratic term and SaO₂ target group, as well as variables for sex, race, center, continuous positive airway pressure vs surfactant treatment group (an additional randomization of the main SUPPORT trial protocol), and caffeine use. Each of these additional terms considered were not significant and because of this and the small sample size, were not included in the final model. Similar models for the subsets of intermittent hypoxemia events that occurred with a time interval of <1 minute and 1-20 minute between events were run using the same final set of variables as the overall model. Additional models were run to model duration and severity of intermittent hypoxemia events. These models included variables for treatment group, linear and quadratic terms for age, GA group, and center.

Results

The population of 115 infants had a mean birth weight of 830 ± 181 g and GA of 25.8 ± 1.0 weeks. There were 50 infants in the GA range 24-25 weeks 6 days, and 65 infants in the GA range 26-27 weeks 6 days. Fifty-one percent of the infants were male and 35% were non-Hispanic white. Characteristics of infants randomized to the high ($n = 62$) and low ($n = 53$) target group are presented in the Table. There were no differences between groups in birth weight, GA, incidence of bronchopulmonary dysplasia, severe ROP, or death before discharge. In this small cohort, there was a trend towards a higher mortality at 36 weeks in the low target group ($P = .09$), mirroring the finding in the main trial, but this did not reach statistical significance. Caffeine use occurred on approximately 80% of days during the monitoring period in both infant groups. There were no differences between low and high target groups with respect to use of postnatal steroids (5.7% vs 4.8%), proportion discharged on diuretics (14.3% vs 14.0%), or inhaled bronchodilators (2% vs 3.5%). Infants in the low target group received respiratory support for 86% of the monitoring period compared with 92% in the high target group (relative rate [RR] low vs high target, 0.93, 95% CI 0.86-0.99, $P = .029$). The median baseline pulse oximetry oxygen saturation during days receiving O₂ supplementation was comparable with the main trial with a median pulse oximetry oxygen saturation of 92% (IQR: 91-94%) and 94% (IQR: 93-94%) in the low and high target groups, respectively.

The model-based estimates showed an increase in intermittent hypoxemia events over the first 3 weeks of life in both infant groups followed by a decrease in intermittent hypoxemia events in the high target group compared with a plateau in the low target group (Figure 2, A). The adjusted RR of intermittent hypoxemia events (the ratio of the adjusted mean number of intermittent hypoxemia events in the low target group/the adjusted mean number of intermittent hypoxemia events in the high target group, per day), revealed a significantly higher rate of intermittent hypoxemia events prior to 12 days, and beyond 57 days of age in the low target group ($P < .05$; Figure 2, B). Higher rates of intermittent hypoxemia events were associated with lower GA, (adjusted RR 1.24, 95% CI, 1.01-1.5, $P = .032$), and respiratory support, adjusted (RR 1.85, 95% CI 1.52-2.49, $P < .0001$).

The mean duration of intermittent hypoxemia events shortened ($P < .0001$) and the severity worsened ($P < .0001$) with increasing day of life (Figure 3). However, there were no differences in duration or severity between infant groups.

There was a wide range in the time interval between sequential intermittent hypoxemia events both within and between infants. To address the association between the timing of intermittent hypoxemia events and the O₂ saturation target group, the number of intermittent hypoxemia events was documented for 3 time interval ranges: (1) <1 minute; (2) 1-20 minutes; and (3) >20 minutes between intermittent hypoxemia events. The highest incidence of events occurred with a time interval between events of <1 minute, followed by a time interval of 1-20 minutes between events. There were relatively few intermittent hypoxemia events that occurred with a time interval of >20 minutes between events. Intermittent hypoxemia events occurring with a time interval between events of <1 minute were associated with a significantly higher relative rate of intermittent hypoxemia events in the low target group at <15 and >54 days of life ($P < .05$). After 65 days of life, there were a significantly higher number of intermittent hypoxemia events with a time interval of 1-20 minutes between events in the low target group ($P < .05$) with no differences between groups for intermittent hypoxemia events with a time interval of >20 minutes between events.

The above analysis examined the number and characteristics of intermittent hypoxemia events by increasing postnatal age. In addition, the effect of PMA on the occurrence of intermittent hypoxemia events was also assessed. The number of intermittent hypoxemia events was not significantly different by treatment group, at any PMA, indicating that postnatal rather than PMA is a major determinant of the relationship between intermittent hypoxemia and treatment group over time.

Discussion

This study showed an escalation in the incidence of intermittent hypoxemia events at <12 and >57 days of life in the low O₂ saturation target group. In both groups, events became shorter and more severe with increasing postnatal age with no differences between groups. Lastly, the higher incidence of intermittent hypoxemia in the low target group was predominantly associated with a time interval between events of <1 minute.

Intermittent hypoxemia events are ubiquitous in preterm infants.⁹⁻¹¹ Nonetheless, the precise incidence of these events is needed in order to address their potential pathophysiologic consequences. The higher incidence of intermittent hypoxemia in the low target group is consistent with McEvoy et al¹² showing a relationship between O₂ levels and intermittent hypoxemia in former preterm infants with chronic lung disease. Although these events are thought to be a consequence of immature respiratory control, this study and previous data in a similar infant cohort⁵ suggest that other developmentally-regulated pathologic mechanisms may be contributing. Relatively few events occurred during the first week of life with a significantly higher incidence of intermittent hypoxemia events in the low target group. This early time period may be a reflection of hypoxic depression compounded with peripheral chemoreceptor inhibition of breathing known to occur during the transition from fetal to neonatal life. The increased incidence in events in the low target group >57 days of age may be due to a low baseline alveolar PO₂ in the low target group which, in a model based analysis, has been shown to cause early onset of desaturation.¹³ It remains unclear why this low reserve did not consistently result in a higher number of intermittent hypoxemia events throughout the monitoring period. It is also possible that the higher incidence of events >57 days is due to relatively well infants coming off of monitors earlier, thus comparing ill infants in the low target group with relatively well infants in the high target group. However, there were no group differences in severity of illness variables such as caffeine use, postnatal steroids, incidence of bronchopulmonary dysplasia, and proportion discharged on diuretics or inhaled bronchodilators.

Caffeine use and respiratory support are main clinical therapies for apnea and accompanying desaturation. Although caffeine has been shown to decrease apnea,¹⁴ interestingly, it has been shown to have little effect on desaturation episodes.¹⁵ Both infant groups spent a comparable percentage of the monitoring period on caffeine therapy; therefore, it is unlikely that caffeine use affected the results of this study. Respiratory support was associated with a higher incidence of events within each treatment group. However, with the high target group having a higher percentage of time receiving respiratory support, this cannot explain the increased incidence of intermittent hypoxemia in the low target infants.

Both groups showed a comparable duration and severity of intermittent hypoxemia events. Previous data have suggested that preterm infants with increased apnea have an augmented ventilatory response to acute hypoxia.¹⁶ Thus, although more susceptible to initiation of a hypoxic event, low target group infants may have been able to rally a compensatory ventilatory response and recover as well as high target group infants.

The lower incidence of severe ROP in the main trial is in contrast to our previous findings of an association between intermittent hypoxemia and severe ROP.⁵ This may be due to an initial enhanced hyperoxia-induced inhibition of angiogenesis in the high O₂ target group. Animal models have suggested that the timing of patterns of intermittent hypoxemia events may also affect morbidity. During the recovery phase following acute hypoxic exposure, reactive O₂ species (ROS) has been shown to increase after a delayed response of several minutes.¹⁷ Current preterm infant data from our group suggest that ROP is associated with a time interval between events of 1-20 minutes, consistent with the ability to initiate an increase in ROS. In contrast, the higher number of events in the low target group occurred with a time interval between events of <1 minute, which may have limited the ROS response. The effect of the duration of recovery time between intermittent hypoxemia events on the resultant oxidative stress response has yet to be determined and merits further investigation.

Data are limited on the long-term consequences of intermittent hypoxemia events in preterm infants.¹⁸ Apnea of prematurity during hospitalization¹⁹ and cardiorespiratory events in the home²⁰ have been associated with neurodevelopmental impairment, with only 1 study showing mean O₂ saturation during apnea as a predictor of motor scores.²¹ Further analysis is ongoing to assess the relationship between intermittent hypoxemia events and neurodevelopmental outcome in this cohort.

As an intention to treat study design with 2 dichotomous groups, this study was limited by the challenge of keeping infants in the O₂ saturation target range.^{22,23} Similar to this study, the main SUPPORT trial revealed overlap in the median level of O₂ saturation between groups with median O₂ saturation levels slightly higher than targeted levels in both groups.⁶ Lowering the median saturation and increasing the time in the actual low target level may have resulted in an even higher incidence of events. Data used in this analysis were collected until 3 days after respiratory support was discontinued or until 36 weeks PMA. The GEE model assumption that data are missing completely at random may be violated because infants who dropped out due to a poor outcome (ie, death), or a favorable outcome (ie, discharged or on room air without support), are likely to differ from those who remained on respiratory support through 36 weeks PMA. Thus, the model results should be interpreted as applying only to the subset of infants who were alive and on respiratory support at that time. Lastly, enrollment for this study was limited because of memory storage and analysis costs with only 2 sites acquiring data at a high enough resolution to adequately detect intermittent hypoxemia events.

In conclusion, a low O₂ saturation target range is associated with an increased incidence of intermittent hypoxemia that is dependent on postnatal age. These events tend to occur <1 minute apart but are of comparable duration and severity regardless of level of O₂ exposure. Preliminary results from 3 clinical trials have supported an association between low O₂ targets and increased mortality.^{6,7} Although the etiology of such a mortality increase is unknown at this time, we speculate that the higher incidence of intermittent hypoxemia in the low target group might provide insight to unraveling underlying pathophysiology. Describing the dynamic changes in incidence and timing of events with increasing age is important as it may add insight into the contribution of multiple factors that influence both central and peripheral respiratory control during the transitional phase of fetal to neonatal respiration. Further studies are needed to assess the contribution of timing of events on neonatal morbidity. We speculate that to minimize episodes of intermittent hypoxemia, the optimal O₂ saturation target may need to be adjusted by postnatal age.

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Appendix

The following investigators, in addition to those listed as authors, are members of the SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network:

Dr Abhik Das (DCC Principal Investigator) and Dr Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

NRN Steering Committee Chairs: Alan H. Jobe, MD, PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-present).

Case Western Reserve University, Rainbow Babies and Children's Hospital (U10 HD21364, M01 RR80)—Avroy A. Fanaroff, MD; Nancy S. Newman, RN; Bonnie S. Siner, RN; Arlene Zadell, RN.

Eunice Kennedy Shriver National Institute of Child Health and Human Development—Rosemary D. Higgins, MD; Stephanie Wilson Archer, MA.

RTI International (U10 HD36790)—Abhik Das, PhD; W. Kenneth Poole, PhD; Marie G. Gantz, PhD; Margaret Cunningham, BS; Betty K. Hastings; Jeanette O'Donnell Auman, BS; Carolyn Petrie Huitema, MS; James W. Pickett II, BS; Dennis Wallace, PhD; Kristin M. Zaterka-Baxter, RN, BSN.

University of Alabama at Birmingham Health System and Children's Hospital of Alabama (U10 HD34216, M01 RR32)—Monica V. Collins, RN, BSN, MaEd; Shirley S. Cosby, RN, BSN. Vivien A. Phillips, RN, BSN.

University of California—San Diego Medical Center and Sharp Mary Birch Hospital for Women (U10 HD40461)—Maynard R. Rasmussen, MD; Paul R. Wozniak, MD; Kathy Arnell, RNC; Renee Bridge, RN; Clarence Demetrio, RN.

Glossary

GA	Gestational age
GEE	Generalized estimating equation
PMA	Postmenstrual age
RR	Relative rate
ROP	Retinopathy of prematurity
ROS	Reactive O ₂ species
SaO₂	Arterial O ₂ saturation

SUPPORT Surfactant, Positive Pressure, and Oxygenation Randomized Trial

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Figure 1.

A raw SaO₂ waveform with the duration of the event, denoted by *arrows* above, and the time interval between events, denoted by *arrows* below.

Figure 2.

A, The model based estimates showed an increase in intermittent hypoxemia events over the first 3 weeks of life in both infant groups followed by a decrease in intermittent hypoxemia events in the high target group compared with a plateau in the low target group. **B**, The RR of intermittent hypoxemia events (the ratio of the adjusted mean number of intermittent hypoxemia events in the low target group/the adjusted mean number of intermittent hypoxemia events in the high target group, per day) revealed a higher rate of intermittent hypoxemia events from <12 days, and >57 days of age in the low target group (* $P < .05$). *IH*, intermittent hypoxemia.

Figure 3. Intermittent hypoxemia event **A**, duration decreased and **B**, severity worsened with increasing postnatal age in both the low and high target groups with no differences between groups.

Table

Infant characteristics

	Low target (53)	High target (62)	P value [*]
Birth weight (g), mean (SD)	855 (191)	808 (171)	.16
GA (wk), mean (SD)	25.8 (1.1)	25.8 (1.0)	.75
BPD (O ₂ at 36 wk), n/N (%)	14/50 (28%)	24/62 (39%)	.45
Death before 36 wk PMA, n (%)	3 (6%)	0 (0%)	.09
Death before discharge, n (%)	4 (7.5%)	3 (4.8%)	.70
Severe ROP, n/N (%)	8/49 (16%)	13/58 (22%)	.41
Death or severe ROP, n/N (%)	12/53 (22.6%)	15/60 (25%)	.64
Caffeine, n/N (%) of monitored d	2245/2838 (79%)	2757/3417 (81%)	.87
Respiratory support [†] n/N (%) of monitored d	2451/2849 (86%)	3085/3369 (92%)	.03

BPD, bronchopulmonary dysplasia.

^{*} P-values from: t -tests for birth weight and GA; GEE models, adjusting for stratification factors (study center and GA age group), and familial clustering for BPD, ROP, death or ROP, caffeine, respiratory support; Fisher exact tests for death.

[†] High frequency jet ventilation, continuous positive airway pressure, conventional ventilation, nasal cannula, nasal synchronized intermittent mandatory ventilation, or hood.