Growth Outcomes of Preterm Infants Exposed to Different Oxygen Saturation Target Ranges from Birth

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Objective To test whether infants randomized to a lower oxygen saturation (peripheral capillary oxygen saturation [SpO_2]) target range while on supplemental oxygen from birth will have better growth velocity from birth to 36 weeks postmenstrual age (PMA) and less growth failure at 36 weeks PMA and 18-22 months corrected age.

Study design We evaluated a subgroup of 810 preterm infants from the Surfactant, Positive Pressure, and Oxygenation Randomized Trial, randomized at birth to lower (85%-89%, n = 402, PMA 26 ± 1 weeks, birth weight 839 ± 186 g) or higher (91%-95%, n = 408, PMA 26 ± 1 weeks, birth weight 840 ± 191 g) SpO_2 target ranges. Anthropometric measures were obtained at birth, postnatal days 7, 14, 21, and 28; then at 32 and 36 weeks PMA; and 18-22 months corrected age. Growth velocities were estimated with the exponential method and analyzed with linear mixed models. Poor growth outcome, defined as weight <10th percentile at 36 weeks PMA and 18-22 months corrected age, was compared across the 2 treatment groups by the use of robust Poisson regression.

Results Growth outcomes including growth at 36 weeks PMA and 18-22 months corrected age, as well as growth velocity were similar in the lower and higher SpO_2 target groups.

Conclusion Targeting different oxygen saturation ranges between 85% and 95% from birth did not impact growth velocity or reduce growth failure in preterm infants. *(J Pediatr 2016;176:62-8)*.

The improved survival of extremely low gestational age infants highlights the significant incidence of growth restriction seen around the age of term equivalence,[1] which persists into later childhood.[2] The incidence of postnatal growth restriction (weight less than the 10th percentile for postmenstrual age [PMA] at the time of hospital discharge) ranges anywhere from 79% to 99%[1,3] when fetal-infant growth curves are used.[4] Poor postnatal growth is associated with poor neurodevelopmental outcome,[2,5] as well as increased risks in adulthood for metabolic syndrome and type 2 diabetes if there is subsequent catch-up growth.[6]

The recent emphasis on early and improved nutritional support recognizes the association between nutrition and growth[7-9]; however, a prospective study, by Embleton et al[10] was only able to attribute 45% of variance in weight gain to energy intake deficits, suggesting that postnatal growth is influenced by factors beyond caloric intake. Tissue oxygenation has been postulated to be among these factors.[11-16] Studies in animals that have investigated this possibility have shown species-specific outcomes, with rat pups raised in hypoxic conditions after birth

BPD	Bronchopulmonary dysplasia
FiO_2	Fraction of inspired oxygen
PMA	Postmenstrual age
ROP	Retinopathy of prematurity
RR	Relative risk
SpO_2	Peripheral capillary oxygen saturation
SUPPORT	Surfactant, Positive Pressure and Pulse Oximetry Randomized Trial

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showing reduced body mass and hamster pups raised in similar conditions having unaffected growth.[11]

In humans, the relationship between oxygenation and postnatal growth is not well understood. Infants with bronchopulmonary dysplasia (BPD) have slower growth velocities when weaned from supplemental oxygen before discharge,[12,13] whereas those discharged on home oxygen have either better growth[14,15] or no difference in growth.[16] For preterm infants without BPD, assignment to different saturation targets starting several weeks after birth did not impact later growth[17,18]; however, a retrospective study of neonatal units in the UK with differing oxygen saturation targeting policies showed that infants cared for in units with lower saturation targets incidentally also had better in-hospital growth.[19] The design of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network Surfactant, Positive Pressure and Pulse Oximetry Randomized Trial (SUPPORT) offered an opportunity to investigate this possibility in a randomized and controlled fashion from the time of birth.[20,21] On the basis of the UK data, we hypothesized that infants enrolled in SUPPORT assigned to the lower saturation target group would have better growth velocity and less growth failure in-hospital and at 18-22 months corrected age.

Methods

Our sample is composed of a subgroup of infants enrolled in SUPPORT. This subgroup of infants was enrolled sequentially in participating centers after the secondary study was approved by individual-center Institutional Review Boards and enrollment in the main trial was underway. SUPPORT was a 2 × 2 factorial, randomized trial, in which the oxygen saturation targeting arm was designed to determine whether exposure to a lower saturation target soon after birth, within the accepted normal range at the time, 85%-95%, was associated with a lower incidence of severe retinopathy of prematurity (ROP) or death before discharge from the hospital; the continuous positive airway pressure arm was designed to determine whether early continuous positive airway pressure use with limited ventilation was associated with increased survival without BPD at 36 weeks PMA compared with surfactant and conventional ventilator strategy. Between February 2005 and February 2009, women at risk for delivering between 24 weeks 0 days and 27 weeks 6 days of gestation were asked to enroll in the study at participating centers. Infants were randomized to either lower (85%-89%) or higher (91%-95%) saturation targets within the accepted oxygen saturation range in the first 2 hours after birth. Pulse oximeters (Masimo Corp, Irvine, California), electronically altered for masking, were used for both groups until 36 weeks PMA or until the infant was breathing ambient air and off positive pressure support for more than 72 hours.

The protocol for the growth secondary study was approved by the Institutional Review Boards of all the participating centers, and written informed consent was obtained from each infant's parent or guardian before any measurements were acquired for the study. In addition to the patient descriptors collected in the main trial,[20] selected anthropometric measurements and nutrition snapshots were periodically collected by research nurses at each institution. Measurements were obtained at birth, weekly for the first 4 weeks, then at 32 and 36 weeks PMA and 18-22 months corrected age. If an infant was deemed stable, weight was obtained with a bedside scale, length was measured with the Preemie Length Board (Ellard Instrumentation, Ltd, Monroe, Washington), and head circumference was measured with a tape measure. Each measurement was obtained twice and then averaged. Detailed 24-hour nutritional data were collected weekly for the first 4 weeks and then at 32 and 36 weeks PMA by chart review. Type and volume of intravenous solutions, including composition of parenteral nutrition, and type and volume of enteral feedings, including modular additives, were recorded. Composition of milk formula and breast milk (mother's own or donor) was based on the assumed average composition of breast milk and the manufacturer's product information for the various milk formulas. Research nurses used standardized study forms while collecting information, and all data subsequently were transmitted to the central Neonatal Research Network data-coordinating center at RTI International.

The primary outcome measures were growth failure, defined as weight less than 10th percentile, for survivors to 36 weeks PMA and at 18-22 months corrected age, and in-hospital growth velocities. The reference growth standards used were the sex-specific intrauterine growth curves of Olsen et al[22] for in-hospital growth and the World Health Organization Growth Curves[23] for growth at 18-22 months corrected age.

Clinical characteristics and outcomes for infants in the higher and lower oxygen saturation target groups were compared by the use of linear mixed models for continuous variables and robust Poisson regression for binary outcomes, with adjustment for multiple birth clustering and trial stratification variables: gestational age (24-25 and 26-27 weeks) and center. An unadjusted Wilcoxon rank sum test was used for skewed continuous variables. In-hospital growth velocity was calculated by the exponential method.[24] In a post-hoc analysis, mortality and select primary growth outcomes were analyzed by identifying the quartile of actual median saturations while on supplemental oxygen. Adjusted results for these analyses were obtained with robust Poisson regression and expressed as relative risks (RRs) and 95% CIs. The proportion of infants with severe illness (defined as the fraction of inspired oxygen [FiO_2] >0.4 and mechanical ventilation for more than 8 hours in the first 14 days) was analyzed by quartile of actual median saturation by use of the Mantel-Haenszel χ^2 test. All analyses were performed at RTI International with SAS version 9.3 (SAS, Cary, North Carolina).

Results

A total of 1316 infants were enrolled in SUPPORT; of these, the parents or caregivers of 810 infants provided consent for