Resuscitation of Preterm Infants with Different Inspired Oxygen Fractions

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Objective To test the hypothesis that an initial fraction of inspired oxygen (FiO_2) of 30% during resuscitation of preterm infants results in less oxidative stress and is associated with improved clinical outcomes compared with an FiO_2 of 65%.

Study design Preterm infants of gestational age <32 weeks (n = 193) were randomized to start resuscitation with either 30% oxygen (low-oxygen group) or 65% oxygen (high-oxygen group), after which the FiO_2 was adjusted based on oxygen saturation values. The primary outcome was bronchopulmonary dysplasia (BPD) assessed at 36 weeks postmenstrual age. Secondary outcomes included major neonatal illnesses and markers of oxidative stress.

Results The median gestational age of included infants was $28^6/_7$ weeks (IQR, $26^5/_7$-$30^3/_7$ weeks). The incidence of BPD was not significantly different between the low-oxygen and high-oxygen groups (24% vs 17%; $P = .15$). The FiO_2 in both groups was adjusted to a mean of 40% by 7 minutes in the low-oxygen group and by 11 minutes in the high-oxygen group. No differences in markers of oxidative stress were noted between groups.

Conclusion Initial supplementation of preterm infants with 30% oxygen during the fetal-to-neonatal transition is as safe as 65% oxygen, with no differences in oxidative stress markers or BPD. *(J Pediatr 2014;164:1322-6).*

Resuscitation of infants at birth with 100% oxygen is associated with increased morbidity and mortality[1,2]; thus, current resuscitation guidelines advise starting the resuscitation of term infants with air or blended oxygen.[3,4] The optimal fraction of inspired oxygen (FiO_2) at which to start resuscitation of preterm infants remains unknown. The latest International Liaison Committee on Resuscitation guidelines state that both hyperoxemia and hypoxemia should be avoided in the absence of information on the initial FiO_2.[4]

Small studies on FiO_2 for the resuscitation of preterm infants have compared low and high initial FiO_2.[5-7] In those studies, FiO_2 was increased in the low-oxygen groups according to oxygen saturation (SpO_2) targets, suggesting that starting resuscitation of preterm infants with room air might provide insufficient oxygen. FiO_2 was decreased in the high-oxygen groups based on the SpO_2 targets. Furthermore, Vento et al[7] reported that resuscitation of preterm infants of gestational age (GA) ≤28 weeks with an initial FiO_2 of 30% (n = 37) resulted in decreased oxidative stress markers and a decreased risk of bronchopulmonary dysplasia (BPD) compared with such infants with an initial FiO_2 of 90% (n = 41).

Based on these data, it seems that starting the resuscitation of preterm infants with room air is too low and starting at 90% FiO_2 is too high, and that the optimum level is most likely between these extremes. Thus, we aimed to assess the safety and efficacy of starting the resuscitation of preterm infants with an intermediate FiO_2. We hypothesized that starting the resuscitation of preterm infants (GA <32 weeks) with an initial FiO_2 of 30% would decrease the incidence of BPD compared with an initial FiO_2 of 65%.

Methods

This double-blind, randomized controlled trial was performed on the neonatal intensive care unit (NICU) of the Erasmus Medical Center–Sophia Children's Hospital, Rotterdam, The Netherlands, a level III NICU. The study protocol was approved by the Erasmus Medical Center's Medical Ethics Committee.

Inborn preterm infants of GA <32 weeks were eligible for this study. Determination of GA was based on early fetal ultrasonography or on the date of the last men-

BPD	Bronchopulmonary dysplasia
FiO_2	Fraction of inspired oxygen
GA	Gestational age
NICU	Neonatal intensive care unit
SpO_2	Oxygen saturation

strual period. Written informed consent was obtained from all parents antenatally, because the intervention was performed directly after birth. Mothers at risk for preterm delivery before 32 weeks of gestation were approached for participation. Exclusion criteria included major congenital malformations, chromosome defects, and metabolic or endocrine disorders.

The study design and resuscitation procedures have been described in detail previously.[8] In short, the resuscitation units with an oxygen blender (Bird Ultrablender; Cardinal Health, Dublin, Ohio) as standard equipment were modified for this study by adding an additional oxygen blender (PM5200; Precision Medical, Northampton, Pennsylvania). This study blender was randomized to either 30% or 65% oxygen via a computer-generated list by an individual not involved in the resuscitation. Before the start of each resuscitation, the study blender was activated by a switch on the resuscitation unit. From that moment, either 30% oxygen (low-oxygen group) or 65% oxygen (high-oxygen group) was provided. The physician remained blinded to group assignment.

Resuscitation

All resuscitations of preterm infants were performed by a neonatologist or fellow. Delayed cord clamping was not practiced in our center during the study period. Immediately after cord clamping, the infant was placed on the resuscitation unit and resuscitated according to standard guidelines, with stimulation and prevention of heat loss. A disposable SpO_2 sensor (Nellcor Max-N; Covidien, Dublin, Ireland) was applied to the infant's right hand or wrist before the pulse oximeter (Nellcor OxiMax N-600x; Covidien) was activated. Infants were resuscitated with either a flow inflating bag (Jackson Rees modification T-piece breathing system; Intersurgical, Wokingham, United Kingdom) or a T-piece resuscitator (Neopuff; Fisher & Paykel Healthcare, Auckland, New Zealand), according to the physician's preference.

The objective of the resuscitation was to keep the pulse rate stable and >100 bpm and to achieve a target SpO_2 of 88%-94% at 10 minutes after birth. FiO_2 was adjusted before 10 minutes of age when SpO_2 was >94% (FiO_2 was reduced), heart rate was <100 bpm (FiO_2 was increased), or SpO_2 and/or heart rate dropped. To adjust the FiO_2, the physician deactivated the research switch, which deactivated the study blender. Subsequently, FiO_2 was supplied via the regular oxygen blender, which by default was set to 21% oxygen and could be manually adjusted to the desired FiO_2 without knowledge of the initial FiO_2 to which the infant had been randomized earlier.

Outcome Variables

The primary study outcome was the incidence of BPD at 36 weeks postmenstrual age, diagnosed according to the physiological criteria of Walsh et al,[9] including a room air challenge test at 36 weeks postmenstrual age. Secondary outcomes included resuscitation variables, mortality, survival without BPD, incidence of major neonatal diseases, and markers of oxidative stress. Clinical definitions have been reported previously.[8]

Oxidative Stress

Glutathione concentration and synthesis rates were determined on postnatal day 2 using a stable isotope study as described previously.[10,11] Non–protein-bound iron concentration was assessed in blood samples collected within 24 hours after birth and on day 6 of life. Samples were collected in heparinized microtainers and immediately placed on melting ice. After centrifugation at $3500 \times g$ for 10 minutes, the plasma fraction was removed from the lower layer and stored at $-80°C$ until further analysis. Plasma samples were shipped on dry ice to the University of Siena, Siena, Italy, where the non–protein-bound iron was determined as described previously.[12]

Urinary oxidative stress markers were determined within 24 hours after birth and on day 6 of life. Urine was collected by placing gauze in the infant's diaper. After centrifugation at $2800 \times g$ for 5 minutes, the urine was stored at $-20°C$ until analysis. Urine samples were shipped on dry ice to La Fe University & Polytechnic Hospital, Valencia, Spain, where the urinary 8-hydroxy-2′-deoxyguanosine/2-deoxyguanosine ratio (a marker of oxidative damage to DNA), ortho-tyrosine/phenylalanine ratio (a marker of oxidative damage to protein), 3-nitro-tyrosine (a marker of nitrosative damage to protein), and 3-chlor-tyrosine (a marker of inflammation caused by free radicals) were determined by high-performance liquid chromatography coupled to mass spectrometry,[13] which was modified for 3-nitro-tyrosine and 3-chlor-tyrosine based on the study of Orhan et al.[14]

Statistical Analyses

Cohort studies reported an incidence of BPD of 30% in preterm infants at GA <32 weeks.[9,15] For a reduction of 15%, 100 infants per group were required to provide a power level of 80% with a 1-sided type I error of 0.05. Differences between groups were assessed using the Mann-Whitney test for continuous measurements and the χ^2 test for categorical measurements ($P < .05$). All analyses were performed according to an intention-to-treat principle. Data are presented as mean ± SD or median (IQR) unless stated otherwise. All analyses were performed using SPSS version 20 (IBM, Armonk, New York).

Results

Out of 781 eligible preterm infants born between August 2008 and February 2012, 193 were analyzed in this study (Figure 1; available at www.jpeds.com). The main reason for missed inclusion was imminent preterm delivery, which left no time to obtain informed consent before birth. Owing to the acute nature of the resuscitation of preterm infants, 67 infants were missed despite consent because the attending neonatologist neglected to include them. The 583 infants not included in the study had a median GA of $29^2/_7$ weeks (IQR, $27^2/_7$-$30^6/_7$ weeks) and a median birth weight of 1150 g (IQR, 900-1425 g). After randomization, 5 infants were excluded owing to a postnatally diagnosed major congenital abnormality. General demographic and obstetric characteristics are presented in Table I.