Environmental or Nasal Cannula Supplemental Oxygen for Preterm Infants: A Randomized Cross-Over Trial

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Objective To test the hypothesis that environmental compared with nasal cannula oxygen decreases episodes of intermittent hypoxemia (oxygen saturations <85% for ≥10 seconds) in preterm infants on supplemental oxygen by providing a more stable hypopharyngeal oxygen concentration.

Study design This was a single center randomized crossover trial with a 1:1 parallel allocation to order of testing. Preterm infants on supplemental oxygen via oxygen environment maintained by a servo-controlled system or nasal cannula with flow rates ≤1.0 L per kg per minute were crossed over every 24 hours for 96 hours. Data were collected electronically to capture real time numeric and waveform data from patient monitors.

Results Twenty-five infants with gestational age of 27 ± 2 weeks (mean ± SD) and a birth weight of 933 ± 328 g were studied at postnatal day 36 ± 26. The number of episodes of intermittent hypoxemia per 24 hours was 117 ± 77 (median, 98; range, 4-335) with oxygen environment vs 130 ± 63 (median, 136; range, 16-252) with nasal cannula ($P = .002$). Infants on oxygen environment compared with nasal cannula also had decreased episodes of severe intermittent hypoxemia ($P = .005$). Infants on oxygen environment compared with nasal cannula had a lower proportion of time with oxygen saturations <85% (.05 ± .03 vs .06 ± .03, $P < .001$), and a lower coefficient of variation of oxygen saturation ($P = .02$).

Conclusions In preterm infants receiving supplemental oxygen, servo-controlled oxygen environment decreases hypoxemia compared with nasal cannula. *(J Pediatr 2018;■■:■■-■■).*

Trial registration ClinicalTrials.gov: NCT02794662.

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Preterm infants have immature control of breathing that results in frequent intermittent hypoxemia episodes that make it challenging to target oxygen saturations (SpO_2) in a desired range.[1] As a consequence, preterm infants spend a considerable proportion of time outside their targeted range.[2] The goal of oxygen supplementation is to maintain adequate oxygenation while minimizing episodes of hypoxemia and hyperoxemia.[2-4]

Intermittent hypoxemia in preterm infants is associated with episodic spontaneous respiratory insufficiency, which may be due to transient hypoventilation.[5] Intermittent hypoxemia is also associated with adverse short- and long-term outcomes including retinopathy of prematurity and neurodevelopmental impairment.[6,7] Hyperoxemia carries a different set of health concerns, including the potential to lead to oxidative stress and injury.[8] Hyperoxemia can occur when oxygen treatment is used to avoid or treat episodes of hypoxemia.[2] In addition, repeated episodes of intermittent hypoxemia/hyperoxemia is associated with alterations in vascular tone in preterm infants that may injure the vascular bed of various organs including the eyes and brain.[6,7,9,10] There is evidence that oxygen delivery at flows ≤1 L per kg per minute through nasal cannulae, although in common use, may lead to unstable oxygen delivery[11] as they allow entrainment of air with infant breaths.[12]

In infants treated with oxygen via nasal cannula, the approximate effective hypopharyngeal fraction of inspired oxygen (FiO_2) can be calculated using formulae incorporating FiO_2, cannula flow, and minute ventilation.[11,13] Standardized charts based on infant weight, set FiO_2, and cannula flow have been validated

FiO_2	Fraction of inspired oxygen
SpO_2	Oxygen saturations

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to determine a relatively accurate estimation of the effective FiO_2.[14] However, effective oxygen concentration can be affected by nasal vs mouth breathing as well as breathing rate, volume, and inspiratory time which fluctuate over time.[15] At the University of Alabama at Birmingham Regional Neonatal Intensive Care Unit, the Giraffe Incubators (GE Healthcare, Chicago, Illinois) and C2000E Isolette Incubators (Draeger Inc, Telford, Pennsylvania) are fitted with a servo-oxygen control system for oxygen administration. This servo-oxygen control system maintains a digitally set oxygen environment inside the incubator that can be set at 21% (ambient oxygen) or from 22% to 65% oxygen. This oxygen environment avoids the need to calculate effective oxygen concentrations because the set oxygen concentration is equal to the hypopharyngeal oxygen concentration during inspiration. Oxygen hoods (oxyhood or headbox) that are commonly used also maintain a set oxygen environment, but are not servo-controlled. An oxygen environment may provide more stable oxygenation and decrease episodes of intermittent hypoxemia in preterm infants that are receiving oxygen therapy compared with nasal cannula, but this has not been assessed. The aim of our study was to test the hypothesis that in preterm infants (<37 weeks of gestation at birth) receiving oxygen supplementation but not positive pressure (ventilator/continuous positive airway pressure) support, the use of oxygen environment would decrease episodes of intermittent hypoxemia when compared with nasal cannulae.

Methods

This study included preterm infants <37 weeks of gestation admitted to the level 4 Regional Neonatal Intensive Care Unit at the University of Alabama at Birmingham. Infants were enrolled from April to September 2016. Infants receiving oxygen therapy via nasal cannula with flow rates ≤1.0 L per kg per minute or oxygen environment were eligible for inclusion if they met the following criteria: off ventilator and/or continuous positive airway pressure support for more than 48 hours prior to study entry, in an incubator for thermoregulation, and parents/legal guardians had provided consent for enrollment.

Infants were excluded from this study if they had any of the following: a major malformation, a neuromuscular condition that affected respiration, a terminal illness, or a decision to withhold or limit support. This study was approved by the Institutional Review Board at the University of Alabama at Birmingham. This study is registered with www.clinicaltrials.gov (NCT02794662).

The primary outcome was the number of episodes of intermittent hypoxemia (defined as SpO_2 less than 85% for ≥10 seconds) per 24 hours. Secondary outcomes included the proportion of time with oxygen saturations below 85%, the proportion of time with oxygen saturation below 91%, the proportion of time with oxygen saturations in the target range from 91% to 95%, the proportion of time with oxygen saturations above 95%, the number of episodes of severe intermittent hypoxemia (defined as SpO_2 less than 80% for ≥10 seconds) per 24 hours, the number of episodes of bradycardia (defined as heart rate less than 100 beats per minute for ≥10 seconds) per 24 hours, and the coefficient of variation of oxygen saturation to assess oxygen stability. These data were collected prospectively using ixTrend (iexcellence, Wildau, Germany) software to electronically capture real time numeric data sampled each second and waveform data sampled at 500 hertz for electrocardiogram and 125 hertz for nonelectrocardiogram signals from patient monitors. Data imputation was not used. Other secondary outcomes included episodes of bedside intervention including tactile stimulation, additional oxygen supplementation, continuous positive airway pressure or bag and mask ventilation, and the number of changes in FiO_2. These outcomes were abstracted from the electronic medical record. The mean effective FiO_2 was determined by the average of the effective FiO_2 concentration for each study hour over the total number of hours studied.

This was a single center randomized crossover pilot study with a 1:1 parallel allocation of infants to the order of testing each of the 2 interventions (oxygen environment or nasal cannula oxygen) using a stratified permuted block design. The random allocation sequence was generated by the Pediatric Research Office at the University of Alabama at Birmingham and Children's of Alabama. Randomization was performed using sequentially numbered sealed opaque envelopes after informed consent was obtained. The effective FiO_2 for infants on nasal cannula was calculated using standardized charts based on infant weight, set FiO_2, and cannula flow[14] and was used to swap from nasal cannula to oxygen environment. The effective FiO_2 was maintained when swapping from oxygen environment to nasal cannula by using the aforementioned standardized charts. The set oxygen concentration while on oxygen environment was the effective FiO_2. All infants enrolled in the study had routine monitoring with oxygen saturation averaging times of 7 seconds and uniform target saturation ranges of 91%-95% for the duration of the study. Following a 24-hour period on the first intervention, the infants were crossed over to a 24-hour period using the alternate mode. Then, the infants were crossed over to a 24-hour period using the initial intervention before being crossed over to another 24-hour period on the alternate intervention. The infants had a 15- to 30-minute washout period to allow stabilization between each crossover. Data from the washout period were not recorded. Infants who no longer required oxygen therapy after the end of at least the second 24-hour recording period completed the trial without further crossovers. It was not possible to blind staff to the study intervention, but the computer recording was not viewable by staff caring for the infants.

A sample size of 25 infants was required to determine if oxygen environment decreased the number of intermittent hypoxemia episodes by 20% in the 48-hour crossover period on either intervention, with a power of 80%, a 2-tailed type I error rate of .05, assuming a SD of 0.5 of the mean. All analyses were performed using intention to treat. Numeric data were analyzed using MATLAB (MathWorks, Natick, Massachusetts). Results were analyzed by generalized mixed model using both random effects (intercept) and fixed effects (treatment group and time), assuming gamma distribution for continuous out-

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