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

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Abstract

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 cross-over 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 liter per kilogram 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 $\pm$ standard deviation) and a birth weight of 933 ± 328 grams 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 versus 130 ± 63 (median, 136; range, 16–252) with nasal cannula ($p=0.002$). 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% (0.05 ± 0.03 vs 0.06 ± 0.03 , $p<0.001$), and a lower coefficient of variation of oxygen saturation ($p=0.02$).

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Conclusion—In preterm infants receiving supplemental oxygen, servo-controlled oxygen environment decreases hypoxemia compared with nasal cannula. Trial registration ClinicalTrials.gov NCT02794662

Keywords

Intermittent hypoxemia; respiratory distress syndrome; bronchopulmonary dysplasia; servo-controlled; incubator; supplemental; infant; newborn; neonate; neonatal

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 which 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 liter per kilogram per minute through nasal cannulae, although in common use, may lead to unstable oxygen delivery¹¹ 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 to determine a relatively accurate estimation of the effective FiO_2 .¹⁴ However, effective oxygen concentration can be affected by nasal versus 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, IL) and C2000E Isolette Incubators (Dräger Inc, Telford, PA) 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' 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' 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 liter per kilogram 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 SpO₂ 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 91–95%, the proportion of time with oxygen saturations above 95%, the number of episodes of severe intermittent hypoxemia (defined as SpO₂ 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 non- electrocardiogram 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 FiO₂. These outcomes were abstracted from the electronic medical record. The mean effective FiO₂ was determined by the average of the effective FiO₂ concentration for each study hour over the total number of hours studied.

This was a single center randomized cross-over pilot study with a 1:1 parallel allocation of infants to the order of testing each of the two 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 FiO₂ for infants on nasal cannula was calculated using standardized charts based on infant weight, set FiO₂, and cannula flow¹⁴ and was used to swap from nasal cannula to oxygen environment. The effective FiO₂ 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 cross-over. 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 cross-overs. 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 two tailed type I error rate of 0.05, assuming a standard deviation 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 outcomes and Poisson for count data using log link function, to consider the correlation associated with repeated observations from the same subject. To test for evidence of carryover effects, we fit the model with treatment and time by treatment interaction and the model with treatment and time (no interaction). There were no significant treatment by time interaction effects or time effects in any of the outcomes so there was no evidence of carry-over effects. Therefore, we fit the model with only treatment to test for treatment differences. No adjustment for multiple testing was done as there is a single primary outcome. There are several secondary outcomes which were pre-specified. SAS 9.4 was used for all statistical analyses. A p value of <0.05 was considered statistically significant.

Results

Twenty-seven infants were randomly assigned to the order of intervention (Figure 1). Two infants were excluded from the analysis. One infant was excluded because the parents withdrew consent due to concerns of nasal irritation on nasal cannula. One infant was excluded as the infant was weaned to room air before completing the first 24 hour period on oxygen environment. Twenty-five infants with a gestational age of 27 ± 2 weeks (mean $\pm$ standard deviation) and a birth weight of 933 ± 328 grams were analyzed in this study (Table I). Eighteen of the infants completed 96 hours of the study, and 4 infants completed 72 hours and 3 infants completed 48 hours of the study as they were no longer on supplemental oxygen at 48 hours. Infants were studied at a postmenstrual age of 32 ± 3 weeks and had a weight of 1268 ± 333 grams at study entry. On average, infants included in this study had been ventilated for a mean of 10 days (range 0–47) before study entry and were on respiratory support or oxygen supplementation for 64 days (range 6–153) during their hospitalization.

There were 117 ± 77 (median, 98; range 4–335) episodes of intermittent hypoxemia per 24 hours in the oxygen environment group compared with 130 ± 63 (median, 136; range, 16–252) in the nasal cannula group ($p=0.002$). There were 47 ± 47 (median, 28; range 0–175) episodes of severe intermittent hypoxemia per 24 hours in the oxygen environment group compared with 48 ± 36 (median, 39; range, 3–145) in the nasal cannula group ($p=0.005$). Infants on oxygen environment had a lower proportion of time with $\text{SpO}_2 < 85\%$ compared with infants on nasal cannula [$5 \pm 3\%$ (median, 4%; range, 0–14%) versus $6 \pm 3\%$ (median, 6%; range, 1–13%); $p<0.001$, Figure 2). The proportion of time with $\text{SpO}_2 < 91\%$, 91 to 95%, and $> 95\%$ did not show significant difference between groups (all $p>0.05$) (Table 2). There was no statistically significant difference in the number of episodes of bradycardia per 24 hours [6 ± 5 (median, 5; range, 1–9) on oxygen environment versus 6 ± 7 (median, 3; range, 2–10) on nasal cannula; $p=0.90$] between the two treatments.

The coefficient of variation of SpO_2 was significantly lower while on oxygen environment [0.05 ± 0.02 (median, 0.04; range, 0.02–0.09)] compared with nasal cannula [0.05 ± 0.01 (median, 0.05; range, 0.03–0.09); $p=0.02$]. Infants had a decreased number of adjustments in FiO_2 while on oxygen environment compared with nasal cannula (5 ± 3 per 24 hours on oxygen environment versus 6 ± 3 per 24 hours on nasal cannula; $p=0.002$). The effective FiO_2 concentration did not differ significantly between groups in this study (0.25 ± 1.4 on oxygen environment versus 0.26 ± 0.04 on nasal cannula; $p=0.11$). There was no difference in the composite number of recorded bedside interventions while on oxygen environment compared with nasal cannula (5 [range, 0–22] per 24 hours on oxygen environment versus 5 [range, 0–33] per 24 hours on nasal cannula; $p=0.24$).

Discussion

The results of this cross-over trial support the hypothesis that a servo-controlled oxygen environment reduces episodes of intermittent hypoxemia and hypoxemia compared with a nasal cannula in preterm infants on supplemental oxygen therapy. Infants had a lower proportion of time with oxygen saturations less than 85% while on oxygen environment compared with nasal cannula. It is possible that oxygen environment provides a more stable hypopharyngeal oxygen concentration compared with nasal cannula.

This study is generalizable to preterm infants cared for in neonatal intensive care units that can provide a servo-controlled oxygen environment (either in an incubator or oxygen hood). Although this study included only 25 preterm infants, the power of the study was increased by the cross-over design and the allocation to two separate 24 hour periods on each intervention. This study was not blinded and caregivers were aware of how infants were receiving oxygen but were not aware of the hypothesis and outcomes of the trial. Nonetheless, knowledge of the treatment allocation may have resulted in information bias from infants in one group being treated differently by staff. Data collected from the electronic medical record including the number and direction of changes of oxygen concentration may have been subject to bias on the part of the staff recording these interventions. However, a major strength of the study is that the primary analysis and most secondary analyses were based on electronically collected data not affected by biases or inaccuracies in manual recording of events. The real time recording of high-resolution

numeric and waveform data from patient monitors resulted in the collection of a large amount of accurate and precise individual patient data that could be analyzed quantitatively using mathematical algorithms for objective measurements of the outcomes.

Previous randomized controlled trials have attempted to improve oxygen saturation targeting and reduce intermittent hypoxemia. One randomized controlled trial that included 16 preterm infants compared routine care with an algorithm-based control using the Breathsavers quality improvement initiative algorithm of the Vermont Oxford Network.¹⁶ The frequency of desaturations, the severity of desaturations, and the percentage of time spent in the target range were not different between groups. Randomized controlled trials of closed loop systems showed that these systems may be more effective at maintaining oxygen saturation targets compared with a caregiver dedicated to FiO₂ titration.² Closed loop systems may decrease the number of episodes of severe intermittent hypoxemia^{2,17} and have been shown in cross-over studies to increase the proportion of time within oxygen saturation target ranges.^{17–19} However, closed loop systems are currently available only on selected ventilators. In the current study, the proportion of time spent with oxygen saturation targets within the target range did not differ between the two treatment groups but there was a decrease in the number of episodes of intermittent hypoxemia and the proportion of time with oxygen saturations less than 85% among infants on oxygen environment compared with infants on nasal cannula.

The current study supports the findings of a randomized controlled crossover study comparing low flow oxygen [FiO₂ = 1.0] or low flow air through nasal cannula in 14 preterm infants.²⁰ As expected, low flow oxygen at 0.1 liters per minute was more effective in decreasing episodes of desaturation in preterm infants compared with low flow air at 0.1 liters per minute or sham treatment. This study found that there was no difference in episodes of hypoxemia between low flow air and sham treatment suggesting that low flow air at 0.1 liters per minute did not assist breathing. In the current study, there was no difference in the number of episodes of bradycardia between oxygen environment and nasal cannula at flows of 1 liter per kilogram per minute suggesting that low flow nasal cannula may not stimulate breathing.

All the infants enrolled in the current study were on effective FiO₂ higher than 0.21 at study entry, and there were no significant differences in the effective FiO₂ while on oxygen environment compared with nasal cannula. There is evidence from the National Institute of Child Health and Human Development Neonatal Research Network that some infants on nasal cannula are managed with effective FiO₂ concentrations < 0.23.¹⁴ Many infants prescribed an effective oxygen concentration < 0.23 are able to pass the 30 minute room air challenge test.¹⁴ Oxygen environment avoids the difficulty of needing to calculate effective oxygen concentrations because the hypopharyngeal oxygen concentration is the same as the set oxygen concentration, and it is not affected by mouth breathing or irregular breathing patterns among preterm infants. The oxygen concentration with the oxygen environment system may be affected by the opening of incubator doors and port holes which allows mixing with room air although the servo-control function rapidly adjusts for changes in oxygen concentration so that the set oxygen environment is generally maintained during

infant care. During parental holding infants on oxygen environment require blow by oxygen to maintain oxygenation, which could affect parent-infant interaction.

In our study, infants spent a decreased proportion of time with oxygen saturations less than 85% while on oxygen environment compared with nasal cannula. Previous studies have suggested that oxygen delivery modes may affect SpO₂ targeting. A prospective quality improvement study aimed at improving oxygen saturation targeting followed 71 infants <1500 grams receiving oxygen supplementation, and showed that infants on nasal cannula spent a higher proportion of time above the target range compared with infants on non-invasive positive pressure ventilation/continuous positive airway pressure.²¹ In another quality improvement study aimed at improving oxygen saturation targeting, infants receiving oxygen therapy via nasal cannula spent less time within the target range compared with infants on continuous positive airway pressure or mechanical ventilation²² even though presumably infants on nasal cannula were less ill.

The current study is consistent with, and extends the findings of the study by Di Fiore et al, which found that hypoxemic episodes are common (50–100 per day) among infants at the lowest gestations.⁶ Infants in the current study who were all off ventilator support and continuous positive airway pressure had a mean of 117–130 episodes of intermittent hypoxemia per 24 hours. Another study using data from a subset of preterm infants enrolled in the SUPPORT trial found that hypoxemic episodes became shorter in duration but increased in severity with increasing postmenstrual age but these data were biased as only infants in worse health remained in the study at later postmenstrual ages.⁵

In conclusion, the current trial demonstrates that in preterm infants on supplemental oxygen therapy, use of servo-controlled oxygen environment reduces episodes of intermittent hypoxemia compared with low flow nasal cannula, likely by providing a more stable effective hypopharyngeal FiO₂ concentration. Further studies comparing oxygen environment with nasal cannula focused on outcomes associated with oxygen therapy among preterm infants are warranted to determine the clinical significance of these findings.

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Abbreviations

SpO ₂	oxygen saturations
FiO ₂	fraction of inspired oxygen
OE	Oxygen environment

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Figure 1.

Flow diagram showing screening, randomization, and the number of infants included in the final data analysis. OE = oxygen environment; NC = nasal cannula

Figure 2.

Box plot with whiskers showing the proportion of time with oxygen saturations less than 85% on oxygen environment (OE) versus nasal cannula (NC). Infants on oxygen environment had oxygen saturations < 85% for a lower proportion of time compared with infants on nasal cannula oxygen therapy.

Table 1

Baseline and clinical characteristics of the study participants.

Male gender, no. (%)	14 (56)
Race	
White, no. (%)	18 (72)
Black, no. (%)	5 (20)
Hispanic, no. (%)	2 (8)
Gestational age, weeks and days $\pm$ SD (weeks)	27 0/7 $\pm$ 2
Birth weight, grams $\pm$ SD	933 $\pm$ 328
Days after birth at study entry, days $\pm$ SD	36 $\pm$ 26
Weight at study entry, grams $\pm$ SD	1268 $\pm$ 333
Antenatal steroids, no. (%)	22 (88)
Histological chorioamnionitis, no. (%)	14 (56)
Cesarean section delivery, no. (%)	15 (60)
Surfactant, no. (%)	17 (68)
Postnatal steroids, no. (%)	4 (16)
Days ventilated before study entry, days (range)	10 (0–47)
Days on respiratory support, days (range)	64 (6–153)
Bronchopulmonary dysplasia at 36 weeks', no. (%)	10 (40)
Retinopathy of prematurity stage 3, no. (%)	4 (16)
Necrotizing enterocolitis stage 2, no. (%)	2 (8)

Table 2

Outcomes by mode of supplemental oxygen therapy

	Oxygen Environment	Nasal Cannula	p value
No. of episodes of IH* per 24 hours, mean $\pm$ SD (median, range)	117 $\pm$ 77 (98, 4–335)	130 $\pm$ 63 (136, 16–252)	0.002
Proportion of time SpO ₂ less than 85%, mean $\pm$ SD (median, range)	0.05 $\pm$ 0.03 (0.04, 0.00–0.14)	0.06 $\pm$ 0.03 (0.06, 0.01–0.13)	< 0.001
Proportion of time SpO ₂ less than 91%, mean $\pm$ SD (median, range)	0.28 $\pm$ 0.09 (0.28, 0.12–0.44)	0.29 $\pm$ 0.09 (0.27, 0.11–0.49)	0.27
Proportion of time SpO ₂ from 91 to 95%, mean $\pm$ SD (median, range)	0.50 $\pm$ 0.09 (0.51, 0.24–0.69)	0.49 $\pm$ 0.10 (0.48, 0.21–0.67)	0.13
Proportion of time SpO ₂ more than 95%, mean $\pm$ SD (median, range)	0.22 $\pm$ 0.14 (0.18, 2–55)	0.22 $\pm$ 0.12 (0.20, 0.04–0.61)	0.52
No. of episodes of severe IH per 24 hours, mean $\pm$ SD (median, range)	47 $\pm$ 47 (28, 0–175)	48 $\pm$ 36 (39, 3–145)	0.005
No. of episodes of bradycardia per 24 hours, mean $\pm$ SD (median, range)	6 $\pm$ 5 (5, 1–9)	6 $\pm$ 7 (3, 2–10)	0.90
Coefficient of variation of SpO ₂ , mean $\pm$ SD (median, range)	0.05 $\pm$ 0.02 (0.04, 0.02–0.09)	0.05 $\pm$ 0.01 (0.05, 0.03–0.09)	0.02
Effective FiO ₂ during study, mean $\pm$ SD (median, range)	0.25 $\pm$ 0.04 (0.24, 0.21–0.38)	0.26 $\pm$ 0.04 (0.25, 0.21–0.43)	0.11
No. of FiO ₂ adjustments per 24 hours, mean $\pm$ SD (median, range)	5 $\pm$ 3 (5, 0–11)	6 $\pm$ 3 (7, 0–11)	0.002
No. of recorded interventions per 24 hours, mean $\pm$ SD (median, range)	5 $\pm$ 3 (3, 0–22)	5 $\pm$ 3 (3, 0–33)	0.24

* IH = intermittent hypoxemia