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Nasal Continuous Positive Airway Pressure With Heliox in Preterm Infants With Respiratory Distress Syndrome

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KEY WORDS

preterm infants, nasal CPAP, heliox, respiratory distress syndrome

ABBREVIATIONS

CI—confidence interval
FiO_2—fraction of inspired oxygen
NCPAP—nasal continuous positive airway pressure
PcO_2—partial pressure of carbon dioxide
PO_2—partial pressure of oxygen
RDS—respiratory distress syndrome
RR—relative risk

Drs Colnaghi and Pierro contributed equally to this work.

Drs Colnaghi, Perro, Migliori, Ciralli, Matassa, Vendettuoli, Mercadante, Consonni, and Mosca substantially contributed to the conception and design of the study as well as the acquisition, analysis, and interpretation of the data. In addition, they all contributed to the draft, critically revised the article, and gave the final approval for publication.

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WHAT'S KNOWN ON THIS SUBJECT: Nasal continuous positive airway pressure (NCPAP) is a noninvasive ventilatory support that may reduce the need for mechanical ventilation in preterm infants with respiratory distress syndrome. Heliox, a helium-oxygen mixture, has shown positive effects, especially in obstructive diseases.

WHAT THIS STUDY ADDS: NCPAP with heliox reduces the need for mechanical ventilation in preterm infants with respiratory distress syndrome in comparison with NCPAP with medical air.

abstract

OBJECTIVE: To assess the therapeutic effects of breathing a low-density helium and oxygen mixture (heliox, 80% helium and 20% oxygen) in premature infants with respiratory distress syndrome (RDS) treated with nasal continuous positive airway pressure (NCPAP).

METHODS: Infants born between 28 and 32 weeks of gestational age with radiologic findings and clinical symptoms of RDS and requiring respiratory support with NCPAP within the first hour of life were included. These infants were randomly assigned to receive either standard medical air (control group) or a 4:1 helium and oxygen mixture (heliox group) during the first 12 hours of enrollment, followed by medical air until NCPAP was no longer needed.

RESULTS: From February 2008 to September 2010, 51 newborn infants were randomly assigned to two groups, 24 in the control group and 27 in the heliox group. NCPAP with heliox significantly decreased the risk of mechanical ventilation in comparison with NCPAP with medical air (14.8% vs 45.8%).

CONCLUSIONS: Heliox increases the effectiveness of NCPAP in the treatment of RDS in premature infants. *Pediatrics* 2012;129:e333–e338

Preterm birth is frequently complicated by respiratory distress syndrome (RDS). Mechanical ventilation and exogenous surfactant replacement therapy are cornerstones in RDS treatment.[1] Mechanical ventilation may lead to lung injury, which is considered an important risk factor for the development of bronchopulmonary dysplasia, a major complication of prematurity.[2–4] To avoid invasive ventilation, the use of early NCPAP has been proposed as an effective strategy.[5–8] However, NCPAP fails in up to 40% of infants born between 27 and 31 weeks of gestation, which is defined as the need for mechanical ventilation.[8]

Since 1935, the use of heliox, usually with a 4:1 ratio, has been proposed as a medical therapy for pulmonary obstructive diseases.[9] Studies in adult and pediatric patients have reported the beneficial effects of heliox, such as reduction of the resistive work of breathing and ventilatory support as well as the improvement of gas exchange.[10,11]

These effects have been attributed to the physical characteristics of helium. Because helium has approximately one-seventh the density of air, it can reduce turbulent flow in the airways, reducing the resistance to flow, as predicted by the Pouseille law. Consequently, helium decreases the pressure required to move gases to the periphery of the lung and enhances gas exchange in the distal airways because of a higher carbon dioxide (CO_2) diffusion coefficient.[12–14]

Until recently, very few articles about heliox ventilation in neonates, particularly preterm infants, were published. Existing data for adult and pediatric patients suggest that heliox may improve the effectiveness of noninvasive ventilation.[15–21]

The aim of our pilot study was to test the efficacy, safety, and feasibility of using heliox to reduce the need for mechanical ventilation in preterm infants with RDS and NCPAP treatment.

METHODS

Study Design

Between February 2008 and September 2010, we conducted a randomized pilot study in the NICU of Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico, University of Milan and the Department of Neonatology and Neonatal Intensive Care, Spedali Civili Hospital, Brescia, Italy.

Inborn infants with a gestational age of 28 to 32 weeks with a Silverman score $\geq$5, RDS radiologic findings and a required fraction of inspired oxygen (Fi_{O_2}) $>$0.25 to maintain an oxygen saturation of 88% to 95% within the first hour of life were enrolled. Exclusion criteria were major congenital malformations, grade 2 or higher intraventricular hemorrhage, intubation in the delivery room and requiring Fi_{O_2} $>$0.4 to maintain oxygen saturation between 88% and 95% before randomization.

The study protocol was approved by the ethics committee of Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico of Milan and Spedali Civili Hospital of Brescia, Italy. For all eligible infants, written informed consent was obtained from the parents before birth.

Randomization

Eligible infants were randomly assigned within 1 hour of life by block randomization (block size of 4), using a closed-envelope method. Randomization was stratified at each center by gestational age into the following two strata: 28^{+0} to 29^{+6} weeks and 30^{+0} to 32^{+6} weeks. The list of randomization was not visible to the clinicians.

Study Intervention

All infants were treated with NCPAP by using the Infant Flow SiPAP (VIASYS Healthcare Palm Springs, CA). The control group received NCPAP with standard medical air. The patients assigned to the heliox group were treated for 12 hours after randomization with NCPAP plus Heliox21 (BOC Medical, The Linde Group, Munich, Germany), a mixture of 80% helium and 20% oxygen, stored in 10-L cylinders. Seven to eight cylinders were required for each patient. Each heliox cylinder cost 90 €, which results in a mean cost of ~750 € for a 12-hour treatment.

After 12 hours, all patients still requiring NCPAP were treated with medical air. The NCPAP device was not modified for heliox treatment. To exchange standard air with heliox, we designed a switching device for the air line that was connectable to the heliox cylinders. We adjusted the flow to maintain a stable pressure level during heliox administration because when using a flowmeter calibrated for oxygen or air, a correction factor (based on the helium concentration) must be applied to correct the flow rate difference. The heliox was warm and humidified using a standard device (MR 730, Fisher & Paykel, Auckland, New Zealand). In both groups, the starting NCPAP level was set at 4 to 6 cm H_2O and Fi_{O_2} adjusted to maintain oxygen saturation levels between 88% and 95%.

Maternal pregnancy diseases, prenatal corticosteroid treatment, type of delivery, gestational age, birth weight, Apgar score, and gender were recorded for each infant. We also recorded hourly oxygen saturation, Fi_{O_2}, blood gases, blood pressure, heart rate, and body temperature during the first 12 hours after randomization. The Silverman score, a systematic assessment of neonatal respiratory status, was calculated at the beginning of treatment, after 6 hours, and at the end of treatment. This score consists of 5 parameters (chest movements, intercostal retractions, xiphoid retractions, nasal

flaring, and expiratory grunt) that are each rated on a scale from 0 to 2. The sum of the 5 parameters gives a total score, where 0 indicates no respiratory distress, 1 to 4 indicates mild distress, 4 to 6 indicates moderated distress, and 7 to 10 indicates severe distress.[22] Silverman scoring was recorded only in patients being treated by NCPAP and was discontinued if a patient required mechanical ventilation. The clinician in charge of assessing the score was not aware of the treatment type (gas, biochemical properties, expected effect) or study design.

Primary Outcome

The main outcome was the requirement of mechanical ventilation within the first 7 days of life.

Mechanical ventilation began when one of the following criteria was present: Fio_2 >0.4 to maintain an oxygen saturation 88% to 95% for at least 30 minutes or less if rapid clinical deterioration occurred, apnea (defined as more than 4 episodes of apnea per hour or more than 2 episodes of apnea per hour requiring ventilation with a bag and mask), or respiratory acidosis (defined as a partial pressure of carbon dioxide [Pco_2] >65 mm Hg, 8.5 kPa, and pH <7.2 on an arterial or capillary blood gas sample).

Secondary Outcomes

The secondary outcomes were treatment with surfactant, duration of ventilatory support (both mechanical ventilation and NCPAP), number of surfactant doses, length of stay, mortality, and incidence of major complications of prematurity (pneumothorax, necrotizing enterocolitis, patent ductus arteriosus, retinopathy of prematurity, bronchopulmonary dysplasia, intraventricular hemorrhage, and periventricular leukomalacia).

The intubated infants that required a Fio_2 of >0.40 to maintain an oxygen saturation of 88% to 95% were treated with surfactant (Curosurf–Chiesi Farmaceutici, Parma, Italy; 200 mg/kg).

To stop mechanical ventilation, the following criteria had to be present: effective respiratory drive, Fio_2 <0.4 to maintain an oxygen saturation of 88% to 95%, mean airway pressure <7 cm H_2O, pH >7.25, and Pco_2 < 60 mm Hg. NCPAP was stopped when the Fio_2 was <0.3, the Silverman score was <4 in the absence of apnea for at least 24 hours, and the CPAP level gradually decreased to 2 cm H_2O.

Statistical Analysis

Based on the data from participating centers (years, 2006–2007), we estimated that 65% of infants born between 28 and 32 weeks of gestation would require mechanical ventilation. We calculated the sample size expecting a 50% reduction. With 80% power and a 2-sided significance level of 0.05, 27 infants would be needed in each group.

For the primary outcomes, we used the Cochran-Mantel-Haenszel test. Risk ratios (RRs), 95% confidence intervals (CIs), and *P* values were reported. A log-binomial regression analysis was performed on the primary outcomes by using a number of covariates, including treatment, gestational age, gender, and center of birth. For the secondary outcomes, proportional data were analyzed by using the Cochran-Mantel-Haenszel test and continuous data by using an analysis of covariance. Overall differences between treatment groups and associated 95% CIs were reported. An analysis of normality of data was also performed; a suitable transformation was performed for data not normally distributed. When there were no suitable transformations, data were analyzed by using the Wilcoxon rank sum test, and the median difference between treatments and an associated *P* value were reported. To test the impact of time (baseline, 6 h, and 12 h) and treatment on the Silverman score, we performed a 2-way analysis of variance with repeated measures. Continuous variables were reported as a mean ± SD.

The Silverman score was reported as a median and range.

All statistical analysis was performed in SAS 9.1.3 (SAS Institute, Inc, Cary, NC).

RESULTS

A total of 51 patients were enrolled (24 in the control group and 27 in the heliox group). There were no differences in clinical characteristics at birth and prenatal conditions between the 2 groups (Table 1). At baseline, the Silverman score was similar between the groups (median 6, range 5–10 vs 6, range 5–8, $P = .52$) and improved over the first 12 hours in both groups (heliox group versus control group at 6 hours: median 3, range 1–8 vs 4, range 1–8, $P = .32$; at 12 hours median 3, range 0–5 vs 4, range 1–5, $P = .07$). Although the trend showed a greater improvement in the heliox group, significance was not observed. Heliox treatment significantly decreased the risk of intubation for mechanical ventilation (14.8% vs 45.8%; $P = .029$, RR 0.32, 95% CI 0.12–0.88) and decreased the surfactant need (11.1% vs 43.5%; $P = .021$, RR 0.26, 95% CI 0.08–0.82) (Table 2). After adjusting the primary outcome for a number of covariates, including treatment, gestational age, gender, and center by using a log-binomial regression analysis, the effect of heliox was still significant (mechanical ventilation: RR 0.32, 95% CI 0.2–0.9; surfactant: RR 0.27, 95% CI 0.12–0.90).

Although there were no significant differences in the Fio_2, oxygen saturation, and blood pressure between groups, a positive trend was found in the heliox group. The total duration of NCPAP was 26 ± 37 days in the heliox group

TABLE 1 Main Clinical Features at Birth and Maternal Diseases

	Heliox Group (n = 27)	Control Group (n = 24)
Gestational age mean ± SD, wk	30.6 ± 1.4	30.6 ± 1.2
Birth weight mean ± SD, g	1454.0 ± 332.2	1430.3 ± 327.4
Apgar 1 min, median (range)	7 (4–9)	7 (4–9)
Apgar 5 min, median (range)	8 (8–10)	8 (7–9)
Male gender, n (%)	18 (66.7)	15 (62.5)
White, n (%)	17 (63)	13 (54.2)
Cesarean delivery, n (%)	22 (81.5)	21 (87.5)
Antenatal corticosteroids, n (%)	23 (85)	23 (95.8)
Incomplete course	4 (14.8)	3 (12.5)
Complete course	19 (70.4)	20 (83.3)
Diabetes, n (%)	2 (7.4)	2 (8.3)
Chorionamionitis, n (%)	5 (18.5)	5 (20.8)
PROM >24 h, n (%)	2 (7.4)	4 (16.7)
Gestosis, n (%)	4 (14.8)	4 (16.7)
Birth weight <10°, n (%)	5 (18.5)	2 (8.3)

All data were not statistically different between groups. PROM, premature rupture of membranes.

TABLE 2 Primary and Secondary Outcomes

	Heliox Group (n = 27)	Control Group (n = 24)	RR (95% CI)	P
Mechanical ventilation, n (%)	4 (14.8)	11 (45.8)	0.32 (0.12–0.88)	.029
Need of surfactant, n (%)	3 (11.1)	10 (43.5)	0.26 (0.08–0.82)	.021
Patent ductus arteriosus, n (%)	12 (44.4)	10 (41.7)	1.06 (0.56–2)	.998
Air leak, n (%)	0	3 (12.5)		.103
Retinopathy of prematurity, n (%)	1 (3.8)	1 (4.5)	0.85 (0.56–13)	.999
Oxygen at 28 d of life, n (%)	3 (12)	2 (8.3)	2.88 (0.32–25)	.609
Oxygen at 36 wk PMA, n (%)	2 (8)	1 (4.5)	1.92 (0.18–19.8)	.997
Necrotizing enterocolitis, n (%)	0	1 (4.2)		.490
Periventricular leukomalacia, n (%)	0	0		.998
Intraventricular hemorrhage, n (%)	0	0		.999
Sepsis, n (%)	1 (3.8)	3 (12.5)	0.3 (0.34–2.7)	.340

PMA, postmestrual age.

versus 33 ± 6 days in the control group (P = .681). Six patients (22.2%) in the heliox group and 8 (33.3%) in the control group started NCPAP at 4 cm H_2O; 15 patients (55.6%) in the heliox group and 10 (41.6%) in the control group started NCPAP at 5 cm H_2O; 6 patients (22.2%) in the heliox group and 6 (25.1%) in the control group started NCPAP at 6 cm H_2O. The starting CPAP levels did not differ between the 2 groups, and the levels did not influence the need for mechanical ventilation. Nineteen patients (70%) in the heliox group were treated with caffeine and 16 (67%) in the control group (P = .49). Respiratory distress was the main reason for NCPAP failure (3 in the heliox group and 7 in the control group); 2 infants were intubated for apnea (1 in the heliox group and 1 in the control group); 3 infants in the control group were intubated for pneumothorax. Mechanical ventilation was started at 4 ± 2 hours in the heliox group versus 10 ± 11 hours in the control group (P = .347). The duration of mechanical ventilation was 8.6 ± 3.36 vs 5.17 ± 4.48 days (P = .144). The number of surfactant doses was 1.65 ± 0.5 vs 1.78 ± 0.9 (P = .744). The length of stay was 52 ± 30 days in the heliox group vs 47 ± 33 days in the control group (P = .627). There were no differences in complications of prematurity (Table 2), and no side effects were reported.

DISCUSSION

Our study shows that exposing premature infants with respiratory distress to heliox and NCPAP significantly decreased the need for mechanical ventilation.

We showed that heliox therapy is feasible and safe during respiratory support with NCPAP. No adverse effects related to the treatment were seen in any patients, and the technique was well tolerated in all patients. To our knowledge, this is the first study of heliox delivery with noninvasive ventilation in newborn infants.

Over the past decade, heliox delivered by both invasive and noninvasive ventilation has been used in a variety of obstructive respiratory disorders in adults and children.[10,11,23,24] In children with bronchiolitis, heliox and NCPAP improved clinical score and CO_2 elimination, and reduced accessory muscle use and expiratory wheezing; however, no reduction in intubation rate was seen.[15–21] A recent Cochrane meta-analysis concluded that heliox may significantly improve the respiratory status of infants with acute bronchiolitis. The meta-analysis failed to show a reduction in the rate of mechanical ventilation or the length of intensive care stay in patients with bronchiolitis.[25] The Cochrane review reported 4 trials (84 patients in total), but only 2 (Liet et al[19] and Cambonie et al[20]) could be analyzed in terms of need for intubation (58 patients total). In those studies, the rate of intubation varied from 10% to 20%. These 2 aspects and the use of different methods to deliver heliox reduced the chances of detecting significance.

To date, the use of heliox in preterm infants has been sporadic and restricted. In the 1980s, heliox treatment was shown to decrease the work of breathing and airway resistance, and to improve thoracoabdominal synchronicity

in premature infants with bronchopulmonary dysplasia.[26] In a randomized controlled trial of infants with RDS in the presurfactant era, Elleau et al[27] proved that infants required a shorter duration of ventilation when ventilated with heliox and experienced fewer deaths as well as fewer cases of bronchopulmonary dysplasia. This study proved the efficacy of heliox in premature infants with RDS in clinical outcomes, such as days of ventilation and bronchopulmonary dysplasia. The patients in the heliox group required lower levels of Fio_2 and had a lower mean airway pressure. In 2009, Migliori et al[13] showed that heliox reduces the resistive work of breathing and ventilatory support requirement while improving gas exchange in mechanically ventilated preterm infants. All these studies focused on ventilated infants.

Nevertheless, recent clinical trials have demonstrated that NCPAP can reduce the need for mechanical ventilation and intubation to administer surfactant and can be used as the first-line treatment in preterm infants with RDS.[5–8]

In an animal model of adult respiratory distress syndrome, Nawab et al[28] showed that heliox did better than nitrox in improving the distribution of inhaled gas, reducing mechanical ventilation and oxygen requirements, and attenuating lung inflammation. RDS in preterm infants is due to a surfactant deficiency that leads to lung injury, leakage of fluid into the lung, and inflammatory cellular infiltrates that cause diffusion abnormalities and a ventilation-perfusion mismatch. An increased dead-space ventilation and reduced lung compliance determine the increased work of breathing, resembling features of adult respiratory distress syndrome.[29] Edema obstructs and narrows the smaller airways, which results in turbulent flow and increased airway resistance; the physical properties of heliox can provide relief from these symptoms. Our data confirm the theoretical benefits of heliox in RDS.

Williams et al[30] conducted an observational study in very few preterm infants spontaneously breathing heliox through a nasal cannula. The authors reported rapid improvement in respiratory parameters when heliox was administered. In our study, both NCPAP with medical air and NCPAP with heliox improved the Silverman score in nonintubated patients. Heliox seemed to be more effective, but no statistical significance was found at any point in time. We also found a similar pattern in Fio_2, Pao_2/Fio_2, Pco_2, and pH that did not reach statistical significance. This may be due to the small sample size of our study and the parameters that were not recorded after initiating mechanical ventilation, which resulted in a more decreased sample size. A randomized controlled trial may demonstrate significance in those outcomes.

Most of our patients were intubated within the first 10 hours. Moreover, none of the patients in the heliox group required intubation after heliox was discontinued. This may clinically justify a short course of heliox therapy. Heliox therapy is expensive, and the daily consumption may be elevated because this gas flows faster through devices[31]; thus, it would be demanding to administer heliox throughout the whole NCPAP treatment. An important finding of this study is that a short course of heliox during the first phase of RDS can reduce the requirement for mechanical ventilation in preterm infants with RDS.

There were no significant differences between groups for any secondary outcomes; however, the study was not designed to detect a difference in those outcomes.

The major limitations were the small sample size and the lack of blinding in the study. Because we delivered heliox via cylinders and standard air via the central wall supply, blinding the clinicians was nearly impossible. This is an important bias that should be taken into account. This problem can be overcome in additional studies by using the same mode of delivery for both mixtures.

Given these important limitations, future trials are needed before changing routine practice.

CONCLUSIONS

In summary, heliox delivered with NCPAP is safe and effective in reducing the need of intubation in the first week of life in premature infants with RDS. However, this was a pilot study, and no definitive conclusions can be drawn on the basis of our results.

Additional studies are needed to confirm our data and verify whether heliox therapy is able to reduce the incidence of complications of prematurity, such as bronchopulmonary dysplasia.

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