Noninvasive Inhaled Nitric Oxide Does Not Prevent Bronchopulmonary Dysplasia in Premature Newborns

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Objective To assess the efficacy and safety of early, noninvasive inhaled nitric oxide (iNO) therapy in premature newborns who do not require mechanical ventilation.

Study design We performed a multicenter randomized trial including 124 premature newborns who required noninvasive supplemental oxygen within the first 72 hours after birth. Newborns were stratified into 3 different groups by birth weight (500-749, 750-999, 1000-1250 g) prior to randomization to iNO (10 ppm) or placebo gas (controls) until 30 weeks postmenstrual age. The primary outcome was a composite of death or bronchopulmonary dysplasia (BPD) at 36 weeks postmenstrual age. Secondary outcomes included the need for and duration of mechanical ventilation, severity of BPD, and safety outcomes.

Results There was no difference in the incidence of death or BPD in the iNO and placebo groups (42% vs 40%, $P = .86$, relative risk = 1.06, 0.7-1.6). BPD severity was not different between the treatment groups. There were no differences between the groups in the need for mechanical ventilation (22% vs 23%; $P = .89$), duration of mechanical ventilation (9.7 vs 8.4 days; $P = .27$), or safety outcomes including severe intracranial hemorrhage (3.4% vs 6.2%, $P = .68$).

Conclusions We found that iNO delivered noninvasively to premature infants who have not progressed to early respiratory failure is a safe treatment, but does not decrease the incidence or severity of BPD, reduce the need for mechanical ventilation, or alter the clinical course. *(J Pediatr 2014;165:1104-8)*.

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Inhaled nitric oxide (iNO) is a safe and effective treatment for near-term and term newborns with acute hypoxemic respiratory failure and persistent pulmonary hypertension (PH) of the newborn.[1,2] However, whether iNO therapy is useful for the management of preterm infants remains controversial.

Bronchopulmonary dysplasia (BPD) is a major sequela of prematurity, occurring in 10 000-15 000 cases per year in the US and leading to significant morbidities such as prolonged ventilation and hospitalization, and recurrent respiratory exacerbations with rehospitalizations during infancy.[3] Endotracheal intubation and mechanical ventilation are associated with lung injury and promote lung inflammation, which increases the risk and severity of BPD in preterm infants.[4] Early initiation of nasal continuous positive airway pressure (CPAP) might decrease the need for intubation and mechanical ventilation, thereby decreasing the risk of ventilator-induced lung injury and BPD, although the evidence is controversial.[5-7]

iNO can improve gas exchange and reduce PH in premature infants, but clinical trials of iNO in premature newborns with hypoxemic respiratory failure have yielded conflicting results to date.[8] However, improvement in pulmonary morbidity and neuroprotection in subsets of this population have been reported.[9,10] Whether iNO delivered noninvasively in infants who have not progressed to respiratory failure will alter the clinical course and decrease the incidence and severity of (BPD) has not been studied.

Therefore, we hypothesized that early and prolonged treatment with noninvasive iNO with nasal CPAP or nasal cannula would reduce the need for endotracheal intubation and mechanical ventilation and the risk for BPD. To test this hypothesis, we performed a multicenter randomized controlled trial to determine whether early noninvasive iNO would reduce the combined endpoint of mortality or BPD in premature newborns (500-1250 g) who required oxygen

BPD	Bronchopulmonary dysplasia
CPAP	Continuous positive airway pressure
iNO	Inhaled nitric oxide
NO	Nitric oxide
PH	Pulmonary hypertension
PMA	Postmenstrual age

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by nasal cannula or CPAP at the time of randomization in the first 72 hours after delivery.

Methods

Five clinical centers with tertiary care neonatal intensive care units and a study coordinating center participated in the trial. The study was approved by individual Institutional Review Boards and the Food and Drug Administration under an Investigational New Drug Exemption and monitored by an independent data and safety monitoring board appointed by the National Heart, Lung, and Blood Institute. Criteria for enrollment included gestational age at or less than 34 weeks, birth weight between 500 and 1250 g, postnatal age less than 72 hours, and on supplemental oxygen by nasal cannula or CPAP. Exclusion criteria were lethal congenital anomalies or congenital heart disease (including an atrial septal defect larger than 1 cm and ventricular septal defect larger than 2 mm). Patients were enrolled after written informed consent was obtained from parents.

Randomization was stratified by center and birth weight into one of 3 groups (500-749; 750-999; 1000-1250 g) balanced in blocks of 2 or 4 within strata based upon a planned enrollment of 124 patients. Randomization numbers were linked to masked iNO or placebo study gas cylinders identified only by sequence numbers.

After randomization, the noninvasive oxygen delivery circuit was configured to allow delivery of iNO at 10 ppm or nitrogen placebo through a shielded iNOVent device (INO Therapeutics, Inc, Clinton, New Jersey). This shielding allowed visualization of the set nitric oxide (NO) dose, but not the read-out of the NO/NO_2 analyzers. Study gas was delivered until 30 weeks postmenstrual age (PMA) (minimum of 2 weeks).

The primary outcome measure was the combined endpoint of death or BPD at 36 weeks PMA. BPD was defined according to the National Institutes of Health criteria by the need for supplemental oxygen or the use of respiratory support for positive airway pressure at 36 weeks PMA.[11] Tests were performed by respiratory therapists who were blinded to treatment group.

Secondary outcomes included assessment of the severity of BPD as defined by the oxygen reduction test,[11] the subsequent need for and duration of endotracheal intubation, and mechanical ventilation. Safety outcomes were severe intracranial hemorrhage as assessed by cranial ultrasound at 7 and 28 days, necrotizing enterocolitis, the need for treatment of a patent ductus arteriosus, and retinopathy of prematurity requiring treatment.

Treatment Strategies

iNO was initiated noninvasively at 10 ppm to yield a minimum of 5 ppm to the posterior pharynx.[12] Study gas was delivered through CPAP devices or nasal cannula using configurations designed to consistently deliver the set, blinded dose with proximal dose monitoring, and integrated alarms. Study gas was delivered for a minimum of 2 weeks and until 30 weeks PMA. The dose was decreased to 5 ppm if intubation was required. To assure consistent iNO delivery through nasal cannula, the minimum blended gas flow rate was set at 0.75 L/min. NO delivery was discontinued if the flow rate was reduced below this level as weaning progressed.

Nasal cannula and CPAP strategies were individualized to allow for local practices. CPAP was typically initiated at 5-8 cm H_2O and high flow nasal cannula was delivered using flow rates of 2-8 L/min. Indications for intubation and mechanical ventilation were at the discretion of each participating center. In general, centers participating in this trial used refractory apnea (requiring bag-mask ventilation) or progressive respiratory failure with PCO_2 greater than 70 torr and pH less than 7.2 as criteria for intubation.

Sample Size and Analyses

The planned sample size for this trial was 124 infants, which was based upon the estimate that a 2-group χ^2 test would have 91% power to detect the difference between the placebo group proportion of 0.60 for the incidence of BPD and mortality and the iNO group proportion of 0.35 when the sample size in each group was 62. Safety analyses were conducted by the data and safety monitoring board and through routine monitoring of all serious adverse events and a formal interim analysis midway through the trial. Preplanned subgroup analyses were performed according to birth weight stratum prior to randomization.

Binomial data were analyzed using χ^2/Fisher exact test, where appropriate. Continuous data were compared using the Student *t*-test, or the Wilcoxon test for data that were not normally distributed. Analyses controlling for birth weight strata, site, and other covariates were conducted using generalized estimating equations (PROC GENMOD in SAS; SAS Institute, Cary, North Carolina). The analysis plan adjusted for study site and randomization strata using Cochran-Mantel-Haenszel testing. Generalized estimating equations were used to provide parametric model adjustment for these design effects. The level of statistical significance was set at *P* value of $<.05$.

Results

Between July, 2007 and February, 2012, 1749 newborns who met the birth weight criterion were screened at 5 clinical sites (**Figure**; available at www.jpeds.com); 432 infants met eligibility criteria and 124 newborns were randomized for this study. The most common reasons for ineligibility included the lack of an early need for supplemental oxygen (40%) and endotracheal intubation with mechanical ventilation (20%) during the first 72 hours after birth. For the 124 randomized patients, 59 (48%) were in the iNO group and 65 (52%) in the control group, including 19 newborns in the 500-749 g stratum, 38 newborns in the 750-999 g stratum, and 67 newborns in the 1000-1250 g