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One-Year Respiratory Outcomes of Preterm Infants Enrolled in the Nitric Oxide_[H1] (to Prevent) Chronic Lung Disease Trial of Inhaled Nitric Oxide

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Abstract

Objective—To identify whether inhaled nitric oxide treatment decreased indicators of long-term pulmonary morbidities after discharge from the NICU.

Study design—The NO CLD trial enrolled preterm infants (<1250g) between 7–21 days of age who were ventilated and at high risk for BPD. Follow-up occurred at 12 ± 3 months of age adjusted for prematurity; long-term pulmonary morbidities and other outcomes were reported by parents during structured blinded interviews.

Results—456 infants (85%) were seen at 1 yr. Compared with control infants, infants randomized to inhaled nitric oxide received significantly less bronchodilators [odds ratio (OR) 0.53 (95% confidence interval 0.36–0.78)], inhaled steroids [OR 0.50 (0.32–0.77)], systemic steroids [OR 0.56 (0.32–0.97)], diuretics [OR 0.54 (0.34–0.85)], and supplemental oxygen [OR 0.65 (0.44–0.95)] after discharge from neonatal intensive care. There were no significant differences between parental report of re-hospitalizations [OR 0.83 (0.57–1.21)] or wheezing or whistling in the chest [OR 0.70 (0.48–1.03)].

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Conclusions—Infants treated with inhaled nitric oxide received fewer outpatient respiratory medications than the control group. However, any decision to institute routine use of this dosing regimen should also take into account the results of the 24 month neurodevelopmental assessment.

Keywords

inhaled nitric oxide (iNO); preterm; bronchodilators; oxygen; diuretics; hospitalization; outcome; bronchopulmonary dysplasia (BPD)

Lung disease remains one of the most common sequelae of premature birth.(1–7) Many very low birth weight infants with and without a history of bronchopulmonary dysplasia (BPD) continue to have symptomatic pulmonary disease in the first years after discharge from neonatal intensive care, often manifesting as wheezing, a dependence on pulmonary medications, and episodic re-hospitalization for respiratory disease.(8–11) For example, Greenough et al showed that at 12 months of age, 42% of very premature infants experienced wheezing, 36% used bronchodilators, and 17% used inhaled steroids.(2)

In the NO CLD randomized clinical trial, inhaled nitric oxide (iNO) treatment increased survival without BPD at 36 weeks corrected gestational age in a group of very low birth weight infants at high risk for pulmonary morbidity.(12,13) In addition, infants randomized to iNO had fewer days of supplemental oxygen and assisted ventilation, and were less likely to be discharged home on supplemental oxygen.(12–14)

Although BPD is a standard measure of pulmonary outcome in neonatology, the importance of measuring clinically relevant long-term outcomes of neonatal care has also been emphasized.(15) For instance, Davis et al found that bronchopulmonary dysplasia was a poor surrogate endpoint for pulmonary morbidities in the first year of life. (16) They concluded that important pulmonary outcomes after discharge from the neonatal intensive care unit (NICU) should be measured directly. Given the high prevalence of post-discharge pulmonary morbidities in very low birth weight infants, we aimed to identify whether iNO treatment had a lasting impact on infants' pulmonary health beyond the initial neonatal hospitalization. We hypothesized that infants randomized iNO would have less pulmonary medication use, fewer respiratory re-hospitalizations, and less parental report of wheezing than infants randomized to placebo.

Methods

Primary Study

As previously reported, the NO CLD study was a multi-center, randomized, double-blind, placebo-controlled trial of inhaled nitric oxide (iNO) treatment.(13) The study population consisted of preterm infants (500–1250g birth weight) at high risk for BPD who required ventilation or continuous positive airway pressure between 7–21 days of age.

Randomization was stratified according to both birth weight (500 to 799 g and 800 to 1250 g) and site with the use of permuted blocks. The study design included cluster randomization of siblings; if more than one infant from a multiple gestation was entered into the trial, only the first sibling enrolled underwent randomization; any additional infants from that pregnancy who met entry criteria were assigned to the same blinded treatment as the randomized sibling. Study gas was started at a concentration of 20 ppm and was subsequently weaned by a set protocol over at least 24 days (median 25 days). The physiological definition of BPD was used,(7,17) which included a room air challenge test, and the primary endpoint of the study was survival without BPD, assessed at 36 weeks postmenstrual age. The trial was approved by institutional

review boards and consent was obtained at each site at the time of enrollment in the primary study.

12-Month Follow-Up

Infants who had survived and been discharged to home were assessed in neonatal follow-up clinics at 12 ± 3 months of age, adjusted for prematurity. Medical care between NICU discharge and follow-up was not standardized and was at the discretion of the treating physicians; however, original treatment allocation was randomized by site to account for regional differences in care. In the standardized follow-up interviews at 12 months, parents were asked about their children's health since discharge from the initial neonatal hospitalization. Examiners and families remained masked to study gas allocation. Specifically, interviewers documented any history since discharge of the use of bronchodilators, inhaled steroids, systemic steroids, home oxygen, or diuretics, or the occurrence of "wheezing or whistling in the chest." Parents also reported any re-hospitalizations after discharge from neonatal intensive care.

Statistical Analysis

Chi-squared and t-tests were used to test for differences between groups in discrete and continuous demographic variables respectively. Odds ratios for 12-month outcome variables were calculated using generalized estimating equations (GEE) to account for the non-independence of twins and triplets in this cluster randomized trial. Number needed to treat (NNT) and 95% confidence interval (95% CI) were calculated by taking the inverse of the risk difference and 95% CI calculated under the GEE model. The standard error of the risk difference was calculated from the robust covariance matrix provided by the GEE regression coefficients using the delta method, or first order Taylor series expansion.

Post-hoc exploratory stratified analyses were conducted on the whole follow-up cohort to assess whether infants with selected characteristics had different responses to iNO. Variables included race and sex because these are known risk factors for wheezing after discharge from the NICU. (2,8,10,18) Age at study entry (7–14 days versus 15–21 days postnatal age) was also selected due to evidence of interaction of these factors with treatment outcome in the primary trial. (13) Birth weight (500–799g vs 800–1200g) was tested because infants were randomized according to birth-weight strata, eligibility criteria required a higher minimum degree of respiratory illness in the higher birth weight group, and other studies of iNO have suggested a better response in larger infants. (19) The most commonly reported marker of pulmonary disease, bronchodilator use, was used as the outcome for these unadjusted stratified analyses. In addition, five GEE models -- adjusting for race, sex, BPD status, age at entry, and birth weight respectively -- were used to test for confounding. Interaction terms were added to these models to test for any significant interactions. Statistical analyses were performed using Stata version 9 (College Station, Texas).

Results

Infants (n=455) born to 418 mothers, representing 85% of infants surviving to discharge from neonatal intensive care, were seen at follow-up (Figure). Four infants died after discharge to home (two had received iNO, two placebo). In addition, three infants (one iNO, two placebo) were ineligible for assessment of post-discharge respiratory morbidities because they were still inpatients and had never been discharged home. Among the infants who survived to discharge, there were no statistically significant differences between the 77 infants lost to follow-up and the 455 infants who were assessed at 12 mo with regards to: birth weight (mean 763 g vs. 766 g, $p=0.875$), gestational age (mean 25.8 wks vs. 25.7 wks, $p=0.686$), race (white: 44.2% vs. 57.6%, $p=0.177$), sex (male: 49.4% vs. 55.4%, $p=0.325$), diagnosis of BPD (55.8% vs. 56.3%, $p=0.945$), or respiratory severity score (mean airway pressure $\times$ FiO₂) (13,20) at enrollment

(mean 3.87 vs. 3.89, $p=0.970$). Among infants lost to follow-up, a higher percentage had been enrolled at 7–14 days of age (48.1% of those lost vs. 36.3% of those seen, $p=0.049$).

Among subjects seen in follow-up, 230 infants (born to 208 mothers) had received iNO and 225 infants (born to 210 mothers) had received placebo. There were no statistically significant demographic differences between the groups (Table I). As expected from the results of the main trial, fewer infants seen in follow-up had BPD in the iNO group than in the placebo group, although the difference did not reach statistical significance.

There was wide variation in the prevalence of outpatient pulmonary medications among infants discharged from the different NICU sites, with the number of infants prescribed bronchodilators ranging from 18–100%, home oxygen use from 11–72%, and diuretics from 0–50%. Nevertheless, significant differences were seen in the history of pulmonary medication use between the iNO and placebo groups (Table II).

We conducted post-hoc exploratory analyses to assess for differences in the effect of iNO in different demographic subgroups. We used the most frequently reported type of medication, bronchodilators, as the outcome for this exploratory analysis. In separate GEE models adjusting for race, sex, age at entry, birth weight, and BPD status, the adjusted odds ratios were all within 4% of the unadjusted OR, suggesting a lack of confounding. When interaction terms between iNO and these selected variables were added to these regression models, none of the interactions were statistically significant. Similarly, in stratified unadjusted analyses, we found no evidence of heterogeneity in the effect of iNO on bronchodilator use by demographic characteristics at enrollment; all subgroups tested had similar estimated odds ratios (Table III).

Discussion

At the 12 month follow-up of infants in the NO CLD trial, fewer infants treated with iNO than placebo had received medications for wheezing. In addition, fewer infants in the iNO group had received diuretics or home oxygen, and fewer were still on supplemental oxygen at the time of follow-up. Reduction in medication use in the iNO group suggests improved post-discharge pulmonary health. However, there were no significant differences in re-hospitalizations or parental report of wheezing.

The odds ratios were similar for all of the medications studied; this is more consistent with a true effect of iNO than with a spurious finding. For bronchodilator use, post-hoc exploratory analyses showed no evidence of confounding or interaction for the variables tested (race, sex, age at study entry, birth weight, and BPD status). There was a similar reduction for infants enrolled at both 7–14 days of age and 15–21 days, despite the fact that infants enrolled earlier had more improvement in survival without BPD.⁽¹³⁾ The non-significance of the effect of iNO in some of the demographic subgroups tested in the underpowered exploratory analysis should be interpreted cautiously. The similarity of the point-estimates for the odds ratios and the tests for interaction do not identify differences in response to iNO. Of note, the statistically significant decrease in bronchodilator use in the smaller birth weight group differs from the results for BPD in the study by Kinsella et al, in which infants <1000g did not seem to benefit from iNO in post-hoc analysis.⁽¹⁹⁾ However, this study used different eligibility criteria, age at treatment, iNO dosing, and duration of therapy than the NO CLD study. Post-hoc analyses in both studies should be interpreted with caution.

Animal models suggest several possible biological mechanisms.^(21–25) iNO may decrease baseline airway resistance by inhibiting abnormal elastin deposition or smooth muscle proliferation.^(22,24,26) Increased alveolarization could improve pulmonary compliance and oxygenation^(21–24). Stimulation of angiogenesis and/or inhibition of vascular smooth muscle proliferation could also improve oxygenation.⁽²³⁾ Improved surfactant function could limit

overall lung injury.(21) There could also be alterations in dynamic respiratory responses, such as bronchoconstriction or inflammation in response to allergens or infection.

INO did not decrease respiratory re-hospitalizations. One explanation is that hospitalization is a good marker of respiratory severity, and iNO did not prevent severe disease. Alternatively, re-hospitalization may act as a poor marker of severity of illness; non-biological factors such as holidays, insurance status, socioeconomic status, and provider-patient interactions may influence the decision to hospitalize a child.(27–34)

Similarly, there was no significant difference in parental report of “wheezing or whistling in the chest.” Although a true lack of drug effect is possible, another explanation is that parents did not accurately identify wheezing. Parents of infants with a history of prolonged ventilation may be sensitized to respiratory symptoms and prone to over-identify wheezing. Such non-differential misclassification of wheezing in the iNO and placebo groups would tend to bias results towards an odds ratio of 1, thereby decreasing the ability to detect an effect of iNO.

Compared with other trials of iNO for the prevention of BPD,(19,35,36) the NO CLD protocol was notable for later postnatal age of initiation, a higher initial concentration (20 ppm), and a longer duration of treatment (median 25 days).(13) Although this approach seems to improve survival without BPD and the need for pulmonary medications in infancy, pending results from the 24-month neurodevelopmental assessments should be included in any risk-benefit analysis. The greater exposure to iNO in this study than in other trials precludes extrapolation of data about neurological outcome from other studies.

The strengths of this study include the large sample size and the randomized blinded design. Families and physicians remained blinded to treatment allocation before and after NICU discharge. Stratified randomization by site should balance both known and unknown social and biologic confounders associated with medication use and rehospitalization – including regional variations in patient populations and medical practice -- between the iNO and placebo groups.

The primary limitation of this study is the extent to which differences in reported medication use reflect actual differences in health. Although there may be some misclassification due to misreported medication histories, or non-ideal prescription practices by providers, it is unlikely that such misclassification would be differential with regard to iNO exposure because parents and physicians remained blinded. Similarly, although some of the individual pulmonary morbidities reported may be unrelated to prematurity, we would expect this number to be relatively small and non-differential with respect to study drug. In addition, the NO CLD sample size was chosen to detect a 12.5% absolute increase in survival without BPD. Among the smaller group of infants who survived and presented to follow-up, we are likely under-powered to detect clinically important differences in some secondary outcomes. Finally, medication use may not capture nuances of pulmonary health as well as more detailed validated measures of quality of life, symptoms, and pulmonary mechanics.

We cannot exclude the possibility that, despite randomization, unmeasured differences between the iNO and placebo groups biased the results towards a larger or smaller apparent effect. In addition, although we found no significant differences in the demographic variables tested between the infants who were followed-up and those who were lost, the groups could be different in other unmeasured ways. Previous studies have shown that children who are difficult to follow may have more neurodevelopmental disability and socioeconomic disadvantage than children who are easily followed.(37,38) It is reasonable to hypothesize then that a higher rate of pulmonary disability would have been seen in both the iNO and placebo groups if all infants had been followed-up. However, it is uncertain whether loss to follow-up was a source of bias in this study.

Another important limitation of all trials is generalizability. The infants in this study met criteria that placed them at high risk for death or BPD; however, iNO was used as a preventative strategy and not as a rescue treatment. If iNO use becomes prevalent in a more general population at higher or lower risk for death or BPD, the benefit from iNO may be different.

In conclusion, very low birth weight infants randomized to iNO were significantly less likely to use bronchodilators, steroids, diuretics, or oxygen after NICU discharge. Although the pulmonary benefit seems promising, any decision to institute routine use of this dosing regimen should also take into account the results of the 24 month neurodevelopmental assessment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Follow-Up Status of Infants Enrolled in the NO CLD Trial
Overall eligibility and enrollment data previously reported.¹³

Table 1
Demographics of the 12-Month Follow-Up Population.

	INO n= 230	Placebo n=225
Birth Weight (g), mean $\pm$ SD	769 $\pm$ 163	762 $\pm$ 150
Gestational Age (wks), mean $\pm$ SD	25.8 $\pm$ 1.4	25.7 $\pm$ 1.5
Race, n(%)		
White	141 (61.3)	121 (53.8)
Black	56 (24.2)	64 (28.4)
Hispanic	22 (9.5)	31 (13.8)
Other	11 (4.8)	9 (4.0)
Female, n(%)	108 (47.0)	95 (42.2)
Entry at 7–14 days, n(%)	84 (36.5)	81 (36.0)
BPD, n(%)	123 (53.5)	133 (59.1)
Discharge October-March	102 (44.3)	100 (44.4)
First Degree Relative with Asthma	44 (19.1)	48 (21.3)

There were no statistically significant differences between the iNO and placebo groups for the variables listed. Data are means $\pm$ standard deviation or number of infants (percent).

Table 2
Markers of Pulmonary Morbidity after Discharge from the NICU

	INO (%)	Placebo (%)	OR* (95%CI)	NNT** (95% CI)
Wheezing or whistling in the chest	49.6	56.4	0.70 (0.48–1.03)	---
Bronchodilator Use	40.1	54.1	0.53 (0.36–0.78)	6.3 (4.0–15.6)
Inhaled Steroid Use	19.8	32.4	0.50 (0.32–0.77)	7.5 (4.6, 19.6)
Systemic Steroid Use	11.0	17.7	0.56 (0.32–0.97)	14.1 (7.3, 250.0)
Diuretic Use	18.6	28.4	0.54 (0.34–0.85)	9.0 (5.2–33.3)
Any Home O₂ Use	38.4	49.5	0.65 (0.44–0.95)	9.4 (5.0, 76.9)
Persistent O₂ Use at Time of Follow-Up	3.0	9.4	0.30 (0.13–0.73)	15.9 (9.4–52.6)
Any Hospitalization	46.5	50.4	0.83 (0.57–1.21)	---
Respiratory Hospitalization	22.6	21.9	1.03 (0.65–1.62)	---

* Odds Ratio

** Number needed to treat were calculated by GEE. NNT represents the number of patients that would need to be treated with a therapy in order to improve one patient's outcome. Respiratory hospitalizations included admissions for wheezing and/or respiratory infection.

Table 3

Bronchodilator Use by Subgroup.

	INO (%)	Placebo (%)	Odds Ratio[*] (95% CI)
White	37.7	49.6	0.54 (0.32–0.91)
Minority	43.8	59.4	0.54 (0.31–0.96)
Female	31.4	48.4	0.49 (0.27–0.88)
Male	47.5	58.3	0.56 (0.34–0.94)
Study Entry: 7–14 days old	34.5	50.0	0.51 (0.27–0.96)
Study Entry: 15–21 days old	43.4	56.4	0.54 (0.33–0.88)
Birth Weight 500–799g	38.1	51.6	0.53 (0.33–0.87)
Birth Weight 800–1250g	43.8	58.2	0.54 (0.29–1.01)

^{*} Odds Ratio, calculated by GEE.