Published in final edited form as:

Am J Perinatol. 2009 April ; 26(4): 317–322. doi:10.1055/s-0028-1104743.

Inhaled Nitric Oxide for Preterm Premature Rupture of Membranes, Oligohydramnios, and Pulmonary Hypoplasia

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Abstract

We sought to determine if inhaled nitric oxide (iNO) administered to preterm infants with premature rupture of membranes (PPROM), oligohydramnios, and pulmonary hypoplasia improved oxygenation, survival, or other clinical outcomes. Data were analyzed from infants with suspected pulmonary hypoplasia, oligohydramnios, and PPRM enrolled in the National Institute of Child Health and Development Neonatal Research Network Preemie Inhaled Nitric Oxide (PiNO) trial, where patients were randomized to receive placebo (oxygen) or iNO at 5 to 10 ppm. Outcome variables assessed were PaO₂ response, mortality, bronchopulmonary dysplasia (BPD), and severe intraventricular hemorrhage (IVH) or periventricular leukomalacia (PVL). Twelve of 449 infants in the PiNO trial met criteria. Six infants received iNO and six received placebo. The iNO group had a mean increase in PaO₂ of 39±50 mm Hg versus a mean decrease of 11±15 mm Hg in the control group. Mortality was 33% versus 67%, BPD (2/5) 40% versus (2/2) 100%, and severe IVH or PVL (1/5) 20% versus (1/2) 50% in the iNO and control groups, respectively. None of these changes were statistically significant. Review of a limited number of cases from a large multicenter trial suggests that iNO use in the setting of PPRM, oligohydramnios, and suspected pulmonary hypoplasia improves oxygenation and may decrease the rate of BPD and death without increasing severe IVH or PVL. However, the small sample size precludes definitive conclusions. Further studies are required to determine if iNO is of benefit in this specific patient population.

Keywords

Nitric oxide; pulmonary hypoplasia; oligohydramnios; PPRM; bronchopulmonary dysplasia

Premature rupture of membranes is a complication occurring in over 30% of preterm deliveries.¹ Neonates with a history of preterm premature rupture of membranes (PPROM) and subsequent oligohydramnios are at high risk for lethal pulmonary hypoplasia.² In a prospective study, PPRM occurring before 25 weeks' gestation with severe oligohydramnios for >14 days had a predicted mortality rate >90%.³ Possible treatment options for this high-risk group of infants include inhaled nitric oxide (iNO). These infants may benefit from the pulmonary vasodilatory effects of iNO due to their suspected

pulmonary hypoplasia and associated pulmonary hypertension. A retrospective analysis found that PPRM, oligohydramnios, and pulmonary hypoplasia in preterm infants were independent predictors of pulmonary hypertension.⁴ Several case reports have also shown that these infants may be responsive to iNO with a decrease in oxygenation index (OI), but a possibly higher risk of intraventricular hemorrhage (IVH).^{5,6}

The National Institute of Child Health and Development Neonatal Research Network Premie Inhaled Nitric Oxide (PiNO) trial found that the use of iNO in premature infants with severe respiratory failure unresponsive to surfactant did not decrease the rate of death or bronchopulmonary dysplasia (BPD).⁷ From this multicenter randomized trial and a small pilot study in larger premature infants,⁸ we identified a subset of infants with PPRM, oligohydramnios, and suspected pulmonary hypoplasia and evaluated the effect of iNO exposure in this subgroup for the present analysis.

METHODS

A retrospective subset analysis of short-term outcomes among infants enrolled in the PiNO trial and the Larger Premie Pilot was performed. Enrollment in the PiNO trial was limited to infants <34 weeks' gestation and 401 to 1500 g birth weights, requiring assisted ventilation with respiratory failure 4 hours following surfactant.⁷ The Larger Premie Pilot enrolled infants using identical criteria except infants had birth weights >1500 g.⁸ Infants were enrolled from January 4, 2001 to September 26, 2003 from 16 centers. The trial was approved by the institutional review board of each participating center, and each center provided clinical care according to its own management style. Written informed consent was obtained from a parent or guardian of each infant.

Study gas (iNO or oxygen placebo) was initiated at 5 ppm and was increased to 10 ppm of iNO or simulated flow if PaO₂ did not increase by >20 mm Hg within 30 minutes. Study gas was discontinued for infants with no response at this flow level or for clinical deterioration. Weaning of study gas followed criteria as defined by the study protocol.⁷ Maximum gas exposure time was 14 days. All clinical providers were blinded to treatment assignment. Primary outcomes included mortality (death prior to discharge home or within 365 days in hospitalized infants) and/or BPD (oxygen use at 36 weeks' postmenstrual age). Secondary outcomes included severe IVH (grade 3 or 4 IVH by head ultrasound at 28 days of life) or periventricular leukomalacia (PVL). Other secondary outcomes were days on mechanical ventilation, days on oxygen, and change in PaO₂ from baseline. Neurodevelopmental status was assessed at 18 to 22 months corrected age using Bayley Scales of Infant Development II–R.

To be included in the current retrospective subset analysis, infants had (1) suspected pulmonary hypoplasia based on clinician interpretation of a chest radiograph with small and hypoplastic-appearing lungs; (2) premature rupture of membranes and/or oligohydramnios documented on antenatal ultrasound 5 or more days prior to delivery.

There was one protocol violation requiring reclassification of study gas exposure in the subgroup. One infant randomized to placebo received iNO in violation of protocol and for the purposes of this analysis was categorized as exposed to iNO.

Results of statistical analyses for this present study were limited due to small sample size. Fisher exact tests and *t* tests were used for analyses of the primary and secondary outcomes, as well as for testing differences between study groups in baseline characteristics, status at randomization and response to study gas.

RESULTS

Baseline Characteristics and Status at Randomization

Twelve of the 449 enrolled infants met the criteria for suspected pulmonary hypoplasia associated with PPRM and/or oligohydramnios. Of these infants, six were exposed to inhaled nitric oxide and six were unexposed control subjects. Baseline characteristics for each group are shown in Table 1. Two infants (one in each group) came from the Larger Preemie Pilot, whereas the remainders were infants <1500 g from the PiNO trial. The average gestational age of the iNO group was 2 weeks younger than the control group.

At the time of randomization, the treatment groups were similar in clinical status (Table 2), with the exception of higher use of inotropic support and higher OI in the control group. All infants were managed with high-frequency ventilation and none received postnatal corticosteroids. Pulmonary hemorrhages or seizures prior to initiation of the study gas were not reported. One infant in the iNO group and two in the control group developed an air leak prior to the start of the study gas. Baseline OI ranged from 10 to 100, with the suggestion of a higher mean OI in the control group (44 ± 30) compared with the iNO group (27 ± 20). However, this difference is attributed to a single patient with a baseline OI of 100 in the control group. All *p* values were nonsignificant in Table 1 and Table 2.

Primary and Secondary Outcomes

Mortality was 33% ($n = 2/6$) in the iNO group compared with 67% ($n = 4/6$) in the control group (Table 3). Death occurred at a median of 1 day of age. Of the seven infants who survived to 36 weeks' postmenstrual age, four developed BPD. BPD was diagnosed in 40% ($n=2/5$) of the iNO group and 100% ($2/2$) in the control group. One infant in the iNO group with BPD subsequently died after 36 weeks' postmenstrual age. The relative risk for death or BPD in this subset of patients favored the iNO group, although not significantly (relative risk=0.50; 95% confidence interval 0.22 to 1.11).

A head ultrasound was obtained on all surviving infants at 28 days of life. Out of five surviving infants in the iNO group, one developed grade 3 IVH. In comparison, the control group had two survivors at 28 days of life. Of these, one developed grade 4 IVH. Infants in both groups who died prior to 28 days either did not have a head ultrasound done or had no evidence of severe IVH or PVL by an earlier head ultrasound.

As conclusions from a statistical analysis with this small cohort are limited, Table 4 provides individual patient clinical variables of interest. As shown, both study groups had suspected pulmonary hypoplasia with rupture of membranes occurring in the early second trimester for at least 4 weeks prior to delivery (mean of 18 ± 3 versus 19 ± 3 weeks gestation). Although only five infants out of the subset had an echocardiogram prior to randomization, four out of five of these infants were diagnosed with pulmonary hypertension with echocardiographic findings of tricuspid regurgitation, a flattened interventricular septum, decreased right ventricular function, and/or right-to-left shunting across the ductus arteriosus or foramen ovale. The response to study gas was greater in the iNO group compared with the control group as evidenced by change in PaO_2 (39 ± 50 versus -11 ± 15 , $p=0.09$). For survivors in the iNO group compared with the control group, there was a suggestion of decreased time on oxygen (61 ± 38 days versus 90 ± 6 days) and decreased time on the ventilator (19 ± 15 days versus 39 ± 30 days).

DISCUSSION

In the subset of premature infants enrolled in the randomized, placebo-controlled PiNO trial with the diagnosis of PPRM, oligohydramnios, and suspected pulmonary hypoplasia,

administration of iNO may be associated with lower mortality and BPD. However, no definitive conclusions can be made about the use of iNO in this specific diagnostic group without larger randomized studies. Data suggest that infants receiving iNO had an acute improvement in oxygenation as well as shorter duration on supplemental oxygen and mechanical ventilation without an increase in severe IVH or PVL in survivors. To our knowledge, this is the first report to characterize iNO treatment-based outcomes among this high-risk patient group within a randomized, controlled trial. All other studies of this population are case series of iNO treatment. Despite the small sample size, this study may still provide useful information to the intensivist considering use of iNO in specific clinical scenarios.

We chose to analyze the outcomes of the subset of patients with suspected pulmonary hypoplasia because of earlier studies suggesting improved oxygenation and survival after iNO in this patient population.^{4–6,9,10} There are several potential mechanisms by which iNO may benefit this group of infants. iNO acts as a selective pulmonary vasodilator to reduce the pulmonary hypertension associated with lung hypoplasia. iNO has also been shown to improve ventilation-perfusion matching in both adults and term infants with persistent pulmonary hypertension.^{11–13} Furthermore, iNO may improve airway structure, decrease pulmonary vasculature remodeling, and decrease lung inflammation, especially in the preterm infant vulnerable to developmental disruptions and inflammation after PPROM. Increased radial alveolar counts and decreased smooth muscle are reported in terminal bronchioles of preterm lambs ventilated with iNO.¹⁴ Animal studies have also shown reduced vascular remodeling after iNO exposure.¹⁵ In a lamb model of severe respiratory distress syndrome, Kinsella and colleagues found that iNO decreased lung neutrophil accumulation.¹⁶ iNO may also replete endogenous NO stores because proinflammatory cytokines and elevated C-reactive protein levels attenuate endogenous NO production.^{17,18}

The PiNO trial of all preterm infants with respiratory failure from which our data set was extracted found that iNO administration did not reduce the incidence of death or BPD. However, post hoc analyses found that infants treated with iNO with birth weight >1000 g had decreased mortality and BPD, whereas those <1000 g had increased rates of death and severe IVH or PVL.⁷ Subgroup analysis of another randomized trial also suggested a reduction in BPD for those premature infants 1000 to 1250 g receiving iNO.¹⁹ Similarly, a retrospective analysis of preterm infants with pulmonary hypertension found that infants >1000 g were more likely to respond to iNO.⁴ In our subpopulation, the average size of infants was slightly over 1000 g in both study groups. The suggestion of decreased death and BPD without any increase in the rate of severe IVH from our analysis may thus apply to iNO use in larger premature infants.

Three small case series describe preterm infants with oligohydramnios and PPROM who demonstrated improved oxygenation, decreased ventilatory support, and improved survival after treatment with iNO.^{5,6,9} A retrospective study also found that eight very low-birth-weight infants with oligohydramnios and presumed pulmonary hypoplasia had improved arterial oxygenation and increased survival compared with matched controls and no increase in IVH.¹⁰ All studies included infants similar to those reported here with rupture of membranes at <25 weeks' gestation and most for >14 days. The case series found that two out of three iNO-exposed infants developed subsequent chronic lung disease,^{5,9} but no comparison group was available. Three of eight infants in one series developed severe IVH after iNO.⁶

The main difference in results between this sub-group analysis and the previous literature is the additional suggestion of decreased BPD and severe IVH after iNO exposure in this population of infants. The study by Uga et al¹⁰ showed no difference in BPD rate between

iNO and control groups. However, that study utilized iNO at a starting dose of 30 to 40 ppm compared with the 5 to 10 ppm used in the PiNO trial, with a higher BPD rate in their iNO group (six out of eight infants). The higher dose could have resulted in increased peroxynitrite production and subsequent oxidative injury associated with the pathogenesis of BPD. The concern for increased risk of IVH after iNO exposure was not substantiated by our study. Theoretically, there is an increased risk of hemorrhage due to inhibition of platelet aggregation by iNO. Only one iNO-exposed infant in our study developed severe IVH. No infants from the iNO or control group of Uga et al's retrospective study developed severe IVH.¹⁰

The major limitation of this study is the small sample size of the subgroup. As a retrospective analysis of prospectively collected data, this study was not powered for the analysis. The potential significance of decreased mortality and BPD after iNO exposure must be tempered with this knowledge. However, unlike other published case series, the 12 subjects from this study were within a randomized, controlled trial. A potential limitation is that an intention-to-treat analysis was not used, and infants were classified according to actual iNO exposure. However, this decision only affected classification of one infant. Another study limitation may be the existence of concealed differences between the two study groups. The apparent trend toward worse outcome among control patients may be due in part to group differences in severity of illness, especially given the increased use of inotropes and higher OI in the control group. In addition, the PiNO trial strategy adjusted the iNO dose from 5 to 10 ppm based upon clinical response. Although the majority of iNO-exposed subjects (4/6) had a complete response to only 5 ppm iNO, the different doses of iNO in study subjects may potentially further confound interpretation. Unmeasured variability in the degree of pulmonary hypoplasia among subjects could also influence the effectiveness of therapy as well as outcomes. Unfortunately, echocardiograms were not required of every subject to document pulmonary hypertension. It is very important to emphasize that the suggested potential benefit of iNO is speculative, and based on small numbers of infants.

CONCLUSIONS

In an analysis of a small subset of patients with PPROM, oligohydramnios, and suspected pulmonary hypoplasia, the data demonstrate an increased PaO₂ and suggest a decreased rate of death or BPD among those exposed to iNO compared with controls. However, the small sample size limits definitive conclusions. Although iNO use cannot be recommended in preterm infants outside of clinical trials,^{7,20,21} the subgroup of infants with PPROM and oligohydramnios may theoretically derive greater benefit from the drug due to nitric oxide-sensitive pulmonary hypertension and beneficial effects of iNO on the parenchyma, conducting airways, and pulmonary vasculature. Use of iNO in this subgroup of premature patients requires prospective study to delineate the potential positive and negative effects of treatment.

Acknowledgments

The Preemie Inhaled Nitric Oxide Study and Larger Preemie Pilot were funded by the National Institute of Child Health and Development (NICHD) and Department of Health and Human Services (DHHS) U10 HD34216, U10 HD27853, U10 HD27871, U10 HD40461, U10 HD40689, U10 HD27856, U10 HD27904, U10 HD40498, U10 HD40521, U10 HD36790, U10 HD21385, U10 HD27880, U10 HD27851, U10 HD21373, and GGRCs: M01 RR 08084, M01 RR 06022, M01 RR 00750, M01 RR 00070, M01 RR 00039, M01 RR 00044. NO Therapeutics (Clinton, NJ) provided study gas, gas delivery systems, and site monitoring for all hospitals, as well as capitation funding for the hospitals that were not members of the NICHD.

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Table 1

Baseline Characteristics

Characteristic	Inhaled Nitric Oxide (<i>n</i> =6)	Placebo (<i>n</i> =6)
Birth weight (g)	1039±355	1179±369
Gestational age (wk)	27±2	29±3
Gestational age at ROM (wk)	18±3	19±3
Male <i>n</i> (%)	4 (67)	2 (33)
Mother's ethnic group, <i>n</i> (%)		
White	2 (33)	4 (67)
Black	1 (17)	1 (17)
Hispanic	2 (33)	0 (0)
Other	1 (17)	1 (17)
Prenatal corticosteroids, <i>n</i> (%)	6 (100)	5 (83)
Delivery by cesarean section, <i>n</i> (%)	4 (67)	3 (50)
Apgar scores < 4 at 1 min, <i>n</i> (%)	2 (33)	4 (67)
Apgar scores < 4 at 5 min, <i>n</i> (%)	0 (0)	1 (17)
Inborn	6 (100)	6 (100)

Plus-minus values are means±standard deviations. ROM, rupture of membranes.

Table 2

Status of Infants at Randomization

Status	Inhaled Nitric Oxide (<i>n</i> =6)	Placebo (<i>n</i> =6)
Age (h)	12±8	11±4
Oxygenation index, median (range)	19 (11±64)	39 (10–100)
Surfactant (No. of doses given)	2±1	2±1
High frequency ventilation, <i>n</i> (%)	6 (100)	6 (100)
Inotropic support, <i>n</i> (%)	2 (33)	6 (100)
Sedation or analgesia, <i>n</i> (%)	6 (100)	5 (83)
Paralytic agents, <i>n</i> (%)	3 (50)	2 (33)
Air leaks, <i>n</i> (%)	1 (17)	2 (33)

Plus-minus values are means±standard deviations.

Table 3

Primary and Secondary Outcomes

Outcome, <i>n</i> (%)	Inhaled Nitric Oxide (<i>n</i> =6)	Placebo (<i>n</i> =6)	<i>p</i> Value
Death or BPD	3/6 (50)	6/6 (100)	0.18
Death	2/6 (33)	4/6 (67)	0.57
BPD [*]	2/5 (40)	2/2 (100)	0.43
Grade 3 or 4 IVH or PVL [†]	1/5 (20)	1/2 (50)	0.46

^{*} This outcome is for infants who survived to 36 weeks' post-menstrual age (five in iNO group and two in control group).

[†] This outcome is for infants who survived to 28 days of life (five in iNO group and two in control group).

Table 4

Summary of Individual Subjects

	Birth weight (g)	GA (wk)	GA at ROM (wk)	PPHN by ECHO	Initial OI	Time on Study Gas (h)	Change in paO ₂ (mm Hg)	Time on O ₂ (d) [§]	Time on Vent (d) [§]	Death (age in d)	BPD	Severe IVH/PVL	NDI //
iNO group													
1	1380	28	18	*	20	90	22	40	8	N	N	Y	N
2	780	27	22	Y	17	60	60			Y (119)	Y	N	
3	856	27	21	*	17	69	116	116	21	N	Y	N	N
4	800	26	18	Y	64	19	5			Y (1)			
5	1595	31	14	*	11	72	7	34	8	N	N	N	N
6	820	24	16	*	36	1	-7	53	39	N	N	N	N
Mean±SD or n (%)	1039±355	27±2	18±3	2 (100)	27±20	52±34	39±50	61±38	19±15	2 (33)	2 (40)	1 (20)	0 (0)
Placebo group													
7	1820	32	18	*	42	1	-13			Y (1)			
8	1108	28	20	*	46	7	7			Y (1)			
9	1369	31	18	N	10	1	-20			Y (11)			
10	930	28	18	*	100	1	12	86	60	N	Y	N	//
11	1064	28	24	Y	28	1	-9	94	18	N	Y	Y	//
12	785	25	17	Y	36	1	-26			Y (1)			
Mean±SD or n (%)	1179±369	29±3	19±3	2 (67)	44±30	1±0.2	-11±15	90±6	39±30	4 (67)	2 (100)	1 (50)	

* ECHO not done prior to start of treatment.

[†] Infant randomized to placebo and switched to open label iNO (protocol violation). paO₂ data unavailable.

[‡] Infant randomized to placebo but study gas never started. Gas exposure data unavailable.

[§] Comparisons of time on oxygen and time on the ventilator are among survivors only.

// NDI defined as moderate to severe cerebral palsy, blindness, or deafness at 18 to 22 months of age. Surviving infants in placebo group were lost to follow-up.

GA, gestational age; ROM, rupture of membranes; PPHN, pulmonary hypertension; ECHO, echocardiogram; OI, oxygenation index; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; NDI, neurodevelopmental impairment; SD, standard deviation; iNO, inhaled nitric oxide.