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NEURODEVELOPMENTAL OUTCOMES OF PREMATURE INFANTS WITH SEVERE RESPIRATORY FAILURE enrolled in a RANDOMIZED CONTROLLED TRIAL OF INHALED NITRIC OXIDE

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Abstract

Objectives—We hypothesized that inhaled nitric oxide (iNO) would not decrease death or neurodevelopmental impairment (NDI) in infants enrolled in the NICHD Preemie iNO Trial (PiNO) trial, nor improve neurodevelopmental outcomes among the follow-up group.

Study design—Infants <34 weeks, <1500 g with severe respiratory failure were enrolled in the multicenter, randomized, controlled trial. NDI at 18–22 months corrected age was defined as: moderate to severe cerebral palsy (CP), MDI or PDI score<70, blindness, or deafness.

Results—Of 420 patients enrolled, 109 receiving iNO (52%) and 98 receiving placebo (47%) died. The follow-up rate among survivors was 90%. iNO did not reduce death or NDI (78% vs. 73%; [RR (95% CI) 1.07 (0.95–1.19)], or NDI or MDI<70 among the follow-up group. Moderate-severe CP was slightly higher with iNO [2.41 (1.01–5.75)], as was death or CP among infants ≤1000 g BW [1.22 (1.05–1.43)].

Conclusions—In this extremely ill cohort, iNO did not reduce death or NDI, or improve neurodevelopmental outcomes. Routine iNO use among premature infants should be limited to research settings until further data are available.

Keywords

premature; nitric oxide; cerebral palsy; Bayley Scales of Infant Development; extremely low birth weight (ELBW); very low birth weight (VLBW); neurodevelopmental

The prognosis for survival of the most vulnerable preterm infants has improved dramatically due to advances in perinatal and neonatal care (1,2), but their neurodevelopmental outcomes do not appear to have benefited similarly. Cerebral palsy (CP) rates among extremely preterm and extremely low birth weight (ELBW) infants have been unchanged over time (3,4). Cognitive outcomes at 18–22 months corrected age have been variably reported to be

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worsening (5–7), unchanged (8), or mildly improved (4). Therefore, there is a substantial impetus to find interventions that improve neurodevelopmental outcomes.

Results of a single-center, randomized controlled trial among premature infants found that treatment with inhaled nitric oxide (iNO) significantly reduced death or chronic lung disease (9), and disability or developmental delay at 2-years of age (10). A recent multicenter study of moderately ill, preterm infants treated with iNO beginning at <48 hours showed a reduced rate of death or bronchopulmonary (BPD) only in subgroup analysis of infants with birth weight 1000–1250 grams (11). Another multicenter study of preterm infants with more established lung disease treated with iNO beginning after 7 days of age showed an increased rate of survival without BPD (12). In the NICHD Neonatal Research Network, we conducted a multicenter trial (PiNO trial) of a more severely ill preterm cohort and found no overall reduction in death or BPD with iNO, but post-hoc analysis demonstrated benefit for infants >1000 grams birth weight (13). Prior to the trial, we hypothesized that iNO would not reduce death or neurodevelopmental impairment at 18–22 months adjusted age; we now report those results, and the overall neurodevelopmental outcomes of the PiNO trial cohort.

METHODS

NICHD PiNO TRIAL AND DEFINITIONS

Enrollment in the multicenter, randomized, double-masked, placebo-controlled trial occurred 1/4/2001–9/26/2003, as previously published by Van Meurs, et. al. (13). The primary outcome for that analysis was death or BPD, with BPD defined as treatment with oxygen at 36 weeks gestation. The institutional review boards of all participating centers approved the study including neurodevelopmental follow-up. Informed consent was obtained from parents or legal guardians. Infants were eligible if they were less than 34 weeks of gestation, 401–1500 grams BW, mechanically ventilated, and had severe respiratory failure defined by specific criteria. Eligible infants must have received at least one dose of surfactant at least 4 hours prior to meeting oxygenation index (OI) criterion for entry, which was defined as an OI of 10 or more on two consecutive measurements of arterial blood gases between 30 minutes and 12 hours apart. OI entry criteria were modified at the request of the Data Safety and Monitoring Committee during the trial due to higher than expected mortality rates in both treatment groups, revising the respiratory criteria for entry to an OI of at least 5 followed by an OI of at least 7.5 within 30 minutes to 24 hours. Hence, for the purposes of analysis, the study design was considered to have two strata based on the OI entry criterion. Randomization to iNO (iNO Therapeutics) or placebo was stratified according to center and birth weight category (401–750 g, 751–1000 g, 1001–1500 g). Research nurses collected demographic, perinatal and infant data including morbidities and treatments at each center using common definitions developed by investigators of the PiNO Study (13), and as previously described (13–15). Mode of ventilation was not dictated by the study protocol, nor was it a randomization factor. Study gas was initiated at 5 ppm and could be increased to 10 ppm, with escalation and weaning criteria defined by the study protocol. The maximum study gas exposure was 14 days; the duration of study gas exposure for the iNO group was 76 ± 73 hours (based on N=210 iNO subjects), and for the placebo group was 39 ± 65 hours (based on N=208 placebo subjects). After a planned interim analysis by the data safety and monitoring committee indicated that the incidence of grade 3 or 4 intraventricular hemorrhage (IVH) (14) or periventricular leukomalacia (PVL) was higher in the iNO group, recruitment was terminated with 95% of targeted enrollment completed, after a total of 210 infants had been randomized to iNO and 210 to placebo. Final data analysis demonstrated no significant overall difference in the rate of severe IVH or PVL, or in the rate of death or BPD between iNO and placebo groups. However, post-hoc subgroup analyses suggested that iNO was associated with a reduced rate of death or BPD for infants

with BW>1000 grams, and an increased rate of severe IVH or PVL for infants with BW ≤1000 grams (13).

NEURODEVELOPMENTAL FOLLOW-UP

Our primary outcome for the follow-up component of the PiNO trial was death or neurodevelopmental impairment at 18–22 months of age corrected for prematurity; we believed it was crucial to encompass patient outcomes from the time of randomization rather than focus solely on those patients who survived to hospital discharge. Neurodevelopmental impairment (NDI) was defined as moderate to severe CP, bilateral blindness (no useful vision in either eye) or deafness (requiring hearing aids in both ears), Bayley Scales of Infant Development (BSID) II Mental Developmental Index (MDI) or Psychomotor Developmental Index (PDI) less than 70. Death was defined as death during or after initial hospitalization up to the time of the 18–22 month neurodevelopmental follow-up visit. Secondary outcomes included: death or moderate to severe CP; NDI and its components among the follow-up group; “isolated delay” among the follow-up group defined as MDI or PDI<70 in the absence of moderate to severe CP, blindness or deafness; and “unimpaired status” among the follow-up group defined as MDI and PDI≥85, and no moderate to severe CP, blindness or deafness.

The elements of the follow-up visit were based on the NICHD NRN Follow-up Study of ELBW infants, previously described in detail (4,16). All neurologic assessments were performed by certified, masked examiners who had been trained in the assessment procedure in an annual 2-day workshop. The neurologic examination was based on those of Amiel-Tison (17), Russell (18), and Palisano (19). Cerebral palsy was defined as a nonprogressive central nervous system disorder characterized by abnormal muscle tone in at least one extremity and abnormal control of movement and posture, which interfered with or prevented age-appropriate motor activities. CP was classified as “moderate” if the child could sit independently or with support, but not independently ambulate, and “severe” if the child was unable to sit or walk even with support. Certified examiners administered the BSID-II MDI and PDI (20). Scores were adjusted for prematurity. Scores of <70 are two standard deviations (SD) below the mean. Scores of 49 were assigned to infants whose extremely severe neurologic or neurodevelopmental impairment prevented examination.

Head circumference and weight percentiles were based on age corrected for prematurity (21). Visual and hearing impairment were assessed by parent interview, physical examination, and best available medical record. Research personnel administered standardized questionnaires regarding socioeconomic status information, including highest level of education attained by primary caregiver, and other factors.

STATISTICAL ANALYSIS

Clinical characteristics and unadjusted outcomes of iNO and placebo groups were compared using chi-square test or Fisher’s Exact test for categorical variables, t-tests for means of continuous variables, and Wilcoxon tests for medians and interquartile ranges. Differences between treatment groups with respect to primary and secondary outcomes were analyzed by relative risk (RR) and 95% confidence intervals (CI). Adjusted relative risks and 95% CI were calculated using two Poisson regression models (22). “Model #1” included BW category, center, OI entry criterion stratum, sex, and treatment group as covariates. “Model #2” included those covariates as well as length of iNO exposure, IVH grade 3 or 4 or PVL, BPD, and postnatal steroids. Only Model #1 could be applied to composite outcomes that included death due to the fact that patients may have died before factors such as BPD, postnatal steroids, or even IVH/PVL could be determined or diagnosed. Interaction terms were tested where relevant. Modeling was not possible for some outcomes due to small numbers. For post-hoc analyses

of outcomes substratified by birth weight category, Cochran-Mantel-Haenszel test controlling for OI strata was used.

RESULTS

PATIENT DISPOSITION

Of the 420 patients enrolled, 109 receiving iNO (52%) and 98 receiving placebo (47%) died before 18–22 months adjusted age (adjusted $p=0.27$) (Figure; available at www.jpeds.com). In each treatment group, 10 patients were lost to follow-up; 5 declined to return, one moved out of state, 6 could not be contacted, and the reason for loss to follow-up was not reported for 8. The follow-up rate among survivors was 90% (91/101) for the iNO group and 91% (102/112) for the placebo group. The primary outcome for this analysis was able to be determined for 198 patients receiving iNO (95%) and 200 receiving placebo (95%); 2 patients in the iNO group could not be assigned a NDI status due to incomplete follow-up (one missing PDI, another missing MDI and PDI). The lost to follow-up group was more likely to be black than the group that returned for neurodevelopmental follow-up (11/20 (55%) vs. 62/193 (32%); $p=0.0109$).

CHARACTERISTICS OF THE OVERALL COHORT AND FOLLOW-UP GROUP

Among all patients for whom the primary outcome of death or neurodevelopmental outcome could be determined (“trial cohort”), there were no significant differences between treatment groups in major demographic and perinatal characteristics (Table I). There were also no significant differences between treatment groups in important later clinical characteristics known to be associated with adverse neurodevelopmental outcome (4,16,23,24) among the follow-up cohort (Table II).

PRIMARY AND SECONDARY OUTCOMES

The rates of death or NDI were high for both iNO and placebo groups (78% vs. 73%, respectively), and there was no significant difference between them (adjusted RR, 1.06; 95% CI, 0.95–1.17; $p=0.30$) (Table III). The rates of death or moderate to severe CP were also not significantly different between the treatment groups. Among the follow-up group, there were no significant differences between treatment groups in the risk for NDI, MDI<70, PDI<70, deafness, blindness, isolated delay or unimpaired status (Table III). The adjusted RR (95% CI) for moderate to severe CP was 2.41 (95% CI, 1.01–5.75; $p=0.048$). Somatic measures did not differ between treatment groups (Table III).

We performed post hoc analyses to explore the potential effects of BW and mode of ventilation at randomization (HFV vs. conventional) on outcomes (Table IV). Infants with BW ≤ 1000 g given iNO had a significantly higher risk for death, and for death or moderate to severe cerebral palsy. The interaction between BW and treatment group on death was significant ($p=0.02$) but on death or moderate to severe cerebral palsy was not significant ($p=0.12$). Infants given iNO by conventional ventilation had a significantly higher risk for death ($p=0.02$), and for death or moderate to severe cerebral palsy than infants given placebo ($p=0.02$). The interaction between mode of ventilation and treatment group on death was significant ($p=0.04$), but on death or moderate to severe cerebral palsy, or on moderate to severe cerebral palsy in the follow-up cohort were not significant ($p=0.22$ and $p=0.35$, respectively). There was no significant association of birth weight group with mode of ventilation for the entire cohort ($p=0.79$), or for the follow-up group only ($p=0.39$). We further substratified results based on birth weight category (Table V). Among 401–750 gram infants, 73% (69/94) of the iNO group died compared with 56% (55/99) of the placebo group ($p=0.01$); 81% of the iNO group died or had moderate-severe cerebral palsy compared with 62% of the placebo group ($p=0.0039$).

DISCUSSION

In this follow-up analysis of the multicenter, randomized, controlled trial of iNO for premature infants with severe respiratory failure, we found that iNO was not associated with a reduction in death or NDI, or with improved neurodevelopmental outcomes among survivors at 18–22 months of age corrected for prematurity. Indeed, we found a slightly increased risk of moderate to severe CP among survivors given iNO, and post hoc analyses suggested a higher risk of death or CP with iNO treatment among infants <1000 grams.

In follow-up to the single-center, double-masked, randomized, placebo-controlled trial by Schreiber, et. al. (9), Mestan, et. al. (10) found a significant reduction in neurodevelopmental impairment in the iNO group (24%) compared with the placebo group (46%). Although our findings may appear to be inconsistent with these results, the NICHD trial differed substantially from the previous study. Eligibility for the Schreiber trial (9) was open to infants <34 weeks gestation and <72 hours of age who had received surfactant, and were mechanically ventilated; there were no OI eligibility criteria. This likely contributed not only to the earlier age at study entry for patients in the Schreiber trial, but also to a significantly lower median OI at randomization in the follow-up cohort (6.94 in the Schreiber trial vs. 17 in the PiNO trial). The early, more “routine” approach to intervention with iNO for mechanically ventilated preterm infants (25) and a potentially longer period of exposure in a less severely ill population may have played roles in the observed reduction in severe morbidities and adverse neurodevelopmental outcomes. In fact, subgroup analysis in the Schreiber trial (9) demonstrated that only those infants with OI less than 6.94 (median) benefited from the treatment. These observations underscore the differences between the trials: indeed, in our present analysis, only 11 of 193 survivors to follow-up had an OI at randomization of less than 7. Of note, the Mestan study (10) demonstrated that iNO was significantly associated with improved neurodevelopmental outcomes, even after adjustment for treatment group differences in intermediate variables such as severe IVH and BPD. This finding may implicate previously reported nitric oxide mechanisms involving tolerance to cerebral ischemia (26), and inhibition of cytokines (27). Such protective processes could attenuate subtle brain injury not easily demonstrated by cranial US, suggesting the need for more advanced neuroimaging such as magnetic resonance imaging (MRI) to be included in future trial designs.

The short-term results of two further multicenter, double-masked, randomized, placebo-controlled trials have also been published (11,12). Long-term neurodevelopmental outcome results from these trials are yet to come, but these study designs should be contrasted to the NICHD trial. The trial by Kinsella, et. al. (11) had no OI entry criteria, and subsequently enrolled mildly to moderately ill preterm infants (iNO mean OI=5.4; placebo mean OI=5.8). Similar to the NICHD trial, there was no significant difference in death or BPD between treatment groups, but subgroup analysis showed that iNO was beneficial in infants 1000–1250 g. The Ballard trial (12) targeted preterm infants with more established lung disease. In both the Ballard and Kinsella trials, exposure to iNO was longer than that in the PiNO trial; this prolonged exposure may be needed for NO-associated lung growth and functional changes to occur (28,29). Overall, the NICHD PiNO trial sought to “rescue” a vastly more ill cohort than any of the other recent trials, and iNO exposure was relatively brief. Thus, it is not surprising that our cohort did not appear to benefit from the purported pulmonary or neuroprotective mechanisms of iNO treatment.

Our finding of an increased adjusted RR for moderate to severe CP with iNO is concerning, although it is only one of several secondary outcomes examined, and patient numbers are quite small. But our findings indicate that iNO use, as administered to this critically ill study cohort, certainly does not reduce the risk for moderate to severe CP. The results of our post-hoc analysis are also intriguing, but should be approached with considerable caution. Infants of ≤ 1000 g

BW given iNO appear to be at increased risk for death and death or CP. The results of our sub-stratified birth weight analysis (Table V) suggest that this finding may be primarily explained by the outcomes of the very smallest preterm infants (401–750 g BW), which could prompt the need for circumspection in future trial designs. Infants given iNO on conventional ventilation at randomization also appear to be at increased risk. However, it is important to remember that mode of ventilation was not randomized in this trial, and indications for conventional ventilation or HFV may have varied substantially among centers. Therefore, discussion regarding the potential mechanism for this post-hoc finding would be purely speculative.

In conclusion, our findings demonstrate no benefit from iNO exposure on death or neurodevelopmental impairment, or neurodevelopmental outcomes in early childhood among the severely ill premature infants in this trial. In light of previous analyses (10) suggesting a reduction in adverse neurodevelopmental outcomes when iNO is administered earlier to a less severely ill preterm patient cohort, we await the follow-up studies of recently completed trials (11,12) to determine the appropriate premature population, optimal timing for initiation of iNO, and length of treatment exposure. Until further data are available, routine iNO use among premature infants should be limited to research settings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Hack M, Friedman H, Fanaroff AA. Outcomes of extremely low birth weight infants. *Pediatrics* 1996;98:931–937. [PubMed: 8909488]
2. Lemons JA, Bauer CR, Oh W, et al. Very low birth weight outcomes of the National Institute of Child Health and Human Development Neonatal Research Network, January 1995 through December 1996. *Pediatrics* 2001;107:e1–e8. [PubMed: 11134465]
3. Lorenz JM, Wooliever DE, Jetton JR, Paneth N. A quantitative review of mortality and developmental disability in extremely premature newborns. *Arch Pediatr Adolesc Med* 1998;152:425–435. [PubMed: 9605024]
4. Vohr BR, Wright LL, Poole WK, McDonald SA. Neurodevelopmental outcomes of extremely low birth weight infants <32 weeks' gestation between 1993 and 1998. *Pediatrics* 2005;116:635–643. [PubMed: 16143580]
5. Emsley HCA, Wardle SP, Sims DG, Chiswick ML, D'Souza SWD. Increased survival and deteriorating developmental outcome in 23–25 week old gestation infants, 1990–1994 compared with 1984–1989. *Arch Dis Child Fetal Neonatal Ed* 1998;78:F99–F104. [PubMed: 9577278]
6. Hack M, Fanaroff AA. Outcomes of infants of extremely low birth weight and gestational age in the 1990's. *Early Hum Devel* 1999;53:193–218. [PubMed: 10088988]
7. Hintz SR, Kendrick DE, Vohr BR, Poole WK, Higgins R. Changes in neurodevelopmental outcomes at 18–22 months corrected age among infants born at less than 25 weeks gestation 1993–1999. *Pediatrics* 2005;115:1645–1651. [PubMed: 15930228]
8. Jacobs SE, O'Brien K, Inwood S, Kelly EN, Whyte HE. Outcome of infants 23–26 weeks' gestation pre and post surfactant. *Acta Paediatr* 2000;89:959–965. [PubMed: 10976839]

9. Schreiber MD, Gin-Mestan K, Marks JD, Huo D, Lee G, Srisuparp P. Inhaled nitric oxide in premature infants with respiratory distress syndrome. *NEJM* 2003;349:2099–2107. [PubMed: 14645637]
10. Mestan KKL, Marks JD, Hecox K, Huo D, Schreiber MD. Neurodevelopmental outcomes of premature infants treated with inhaled nitric oxide. *NEJM* 2005;353:23–32. [PubMed: 16000353]
11. Kinsella JP, Cutter GR, Walsh WF, et al. Early inhaled nitric oxide therapy in premature newborns with respiratory failure. *NEJM* 2006;355:354–364. [PubMed: 16870914]
12. Ballard RA, Truog WE, Martin RJ, et al. Improved outcome with inhaled nitric oxide in preterm infants mechanically ventilated at 7–21 days of age. *NEJM* 2006;355:343–353. [PubMed: 16870913]
13. Van Meurs KP, Wright LL, Ehrenkranz RA, et al. Inhaled nitric oxide for premature infants with severe respiratory failure. *NEJM* 2005;353:13–22. [PubMed: 16000352]
14. Papile L, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a case study of infants with birth weights less than 1500. *J Pediatr* 1978;92:529–534. [PubMed: 305471]
15. Walsh MC, Kliegman RM. Necrotizing enterocolitis: treatment based on staging criteria. *Pediatr Clin N Am* 1986;33:179–201.
16. Vohr BR, Wright LL, Dusick AM, et al. Neurodevelopmental and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993–1994. *Pediatrics* 2000;105:1216–1226. [PubMed: 10835060]
17. Amiel-Tison, C. Neuromotor status. In: Taeusch, HW.; Yogman, MW., editors. *Follow-up Management of the High-Risk Infant*. Boston MA: Little, Brown and Company; 1987. p. 115-126.
18. Russell DJ, Rosenbaum PL, Cadman DT, Gowland C, Hardy S, Jarvis S. The gross motor function measure: a means to evaluate the effects of physical therapy. *Dev Med Child Neurol* 1989;31:341–352. [PubMed: 2753238]
19. Palisano R, Rosenbaum P, Walter S, et al. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol* 1997;39:214–223. [PubMed: 9183258]
20. Bayley, N. *Bayley Scales of Infant Development-II*. San Antonio, TX: Psychological Corporation; 1993.
21. Kuczmarski, RJ.; Ogden, CL.; Grummer-Strawn, LM., et al. *Advance data from vital and health statistics*. Hyattsville, Maryland: National Center for Health Statistics; 2000. CDC growth charts: United States. <http://www/cdc.gov/growthcharts>
22. Zou G. A modified Poisson regression approach to prospective studies with binary data. *Am J Epidemiol* 2004;159:702–706. [PubMed: 15033648]
23. Stoll BJ, Hansen N, Adams-Chapman I, et al. Neurodevelopmental and growth impairment among extremely-low-birth-weight infants with neonatal infection. *JAMA* 2004;292:2357–2365. [PubMed: 15547163]
24. Hintz SR, Kendrick DE, Stoll BJ, et al. Neurodevelopmental outcomes of extremely low birth weight infants after NEC. *Pediatrics* 2005;115:696–703. [PubMed: 15741374]
25. Barrington KJ, Finer NN. Inhaled nitric oxide for respiratory failure in preterm infants. *The Cochrane Database of Systematic Reviews*. 2006;(Issue 1)CD000509.pub2
26. Gidday JM, Shah AR, Maceren RG, et al. Nitric oxide mediates cerebral ischemic tolerance in a neonatal rat model of hypoxic preconditioning. *J Cereb Blood Flow Metab* 1999;19:331–340. [PubMed: 10078885]
27. Kourembanas S, Mc Quillan LP, Leung GK, Faller DV. Nitric oxide regulates the expression of vasoconstrictors and growth factors by vascular endothelium under both normoxia and hypoxia. *J Clin Invest* 1993;92:99–104. [PubMed: 8326022]
28. McCurnin DC, Pierce RA, Chang LY, et al. Inhaled NO improves early pulmonary function and modifies lung growth and elastin deposition in a baboon model of neonatal chronic lung disease. *Am J Physiol Lung Cell Mol Physiol* 2005;288:L450–L459. [PubMed: 15591412]
29. Bland RD, Albertine KH, Carlton DP, MacRitchie AJ. Inhaled nitric oxide effects on lung structure and function in chronically ventilated preterm lambs. *Am J Respir Crit Care Med* 2005;172:899–906. [PubMed: 15976381]

Figure 1.
Patient disposition and attrition to neurodevelopmental follow-up at 18–22 months of age corrected for prematurity

Table 1

Perinatal and early neonatal characteristics of trial cohort and follow-up group*.

	Trial cohort [†]			Follow-up group		
	iNO	Placebo	P value	iNO	Placebo	P value
N	198	200		91	102	
Birth weight	835 ± 265	830 ± 261	0.84	958 ± 276	864 ± 271	0.02
Gestational age	25.9 ± 2.3	25.9 ± 2.2	0.67	26.8 ± 2.3	26.2 ± 2.2	0.07
Male	123 (62%)	122 (61%)	0.90	62 (68%)	59 (58%)	0.18
Race [‡]			0.77			0.76
White	91 (46%)	93 (47%)		43 (47%)	46 (45%)	
Black	64 (32%)	71 (36%)		27 (30%)	35 (34%)	
Hispanic	35 (18%)	32 (16%)		17 (19%)	18 (18%)	
Asian/Pacific	4 (2%)	2 (1%)		4 (4%)	2 (2%)	
Other	4 (2%)	2 (1%)		0	1 (1%)	
Antenatal steroids ^{**}	116/169 (69%)	114/167 (68%)	1.00	56/73 (77%)	58/88 (66%)	0.18
Born at study hospital ^{**}	156 (79%)	153/199 (77%)	0.74	78 (86%)	87 (85%)	1.00
Cesarean section	138 (70%)	133 (67%)	0.56	69 (76%)	66 (65%)	0.13
Apgar<4 at 5 minutes	27/166 (16%)	22/164 (13%)	0.57	7/74 (9%)	11/87 (13%)	0.70
OI at randomization (median, interquartile range)	17.2 (12.0 – 27.4)	16.1 (11.0 – 27.4)	0.28	16.3 (12.0 – 24.0)	14.9 (10.5 – 21.6)	0.23
OI at randomization	23.2 ± 17.0	22.1 ± 16.8	0.54	20.0 ± 12.9	18.1 ± 11.3	0.27
HFV at randomization	115 (58%)	119 (60%)	0.85	61 (67%)	57 (56%)	0.15
Number surfactant doses at randomization	2.1 ± 0.8	2.2 ± 0.9	0.23	2.0 ± 0.9	2.2 ± 1.0	0.10
Hours of gas exposure (median, interquartile range)	65 (19–98)	2 (1–71)	<0.0001	72 (42–115)	2 (1–75)	<0.0001

* Data presented as N (%) or mean ± S.D. unless otherwise noted

[†] Trial cohort includes all patients for whom a primary outcome was determined; follow-up group includes patients surviving to neurodevelopmental follow-up

[‡] Race or ethnic group was self-reported by the mother of the baby

** Data were not available for all infants

Table 2

Later clinical characteristics of the follow-up cohort*.

	iNO	Placebo	P value
N	91	102	
Sepsis/pneumonia [†]	45 (49%)	47 (46%)	0.75
Proven necrotizing enterocolitis [‡]	8/90 (9%)	8/101 (8%)	1.0
BPD ^{**}	52 (57%)	67/101 (66%)	0.19
Postnatal steroids	46 (51%)	59 (58%)	0.38
Grade 3 or 4 IVH or PVL [‡]	25 (27%)	22/99 (22%)	0.29
Threshold ROP [‡]	27/88 (31%)	29/98 (30%)	1.0
Corrected age at follow-up (mo)	20.4 ± 3.5	20.6 ± 3.9	0.68
Maternal education less than high school [‡]	21/87 (24%)	24/96 (25%)	1.0

* Data presented as N (%) or mean ± S.D. unless otherwise noted

[†] Sepsis/pneumonia after 72 hours of age[‡] Necrotizing enterocolitis stage IIA or greater (15)^{**} BPD defined as treatment with oxygen at 36 weeks gestation[‡] Data were not available for all infants

Table 3

Primary and secondary outcomes: Unadjusted and adjusted relative risks (RR) and 95% confidence intervals (95% CI)

	iNO n (%)	Placebo n (%)	RR (95% CI) Unadjusted	p value	MODEL #1 p value	MODEL #2* p value	p value
N=died or had follow-up	200	200					
Death or NDI [†]	154/198 (78%)	146 (73%)	1.07 (0.95–1.19)	0.32	1.06 (0.95–1.17)	0.30	N/A
Death or moderate to severe CP	127/199 (64%)	109 (54%)	1.17 (0.99–1.38)	0.07	1.15 (0.99–1.34)	0.07	N/A
N=follow-up group only	91	102					
NDI [†]	45/89 (51%)	48 (47%)	1.07 (0.80–1.44)	0.74	1.04 (0.79–1.36)	0.78	1.19 (0.81–1.73) 0.37
Moderate to severe CP	18/90 (20%)	11 (11%)	1.85 (0.93–3.71)	0.11	2.01 (1.01–3.98)	0.045	3.24 (1.01–5.75) 0.048
MDI<70	37/86 (43%)	35/98 (36%)	1.20 (0.84–1.73)	0.39	1.15 (0.83–1.60)	0.40	1.38 (0.86–2.22) 0.19
PDI<70	29/85 (34%)	32/99 (32%)	1.06 (0.70–1.59)	0.92	1.07 (0.73–1.56)	0.74	1.04 (0.60–1.79) 0.89
Deaf	5/90 (6%)	5 (5%)	1.13 (0.34–3.79)	1.00	Too few to model	Too few to model	
Blind	2/90 (2%)	1 (1%)	2.27 (0.21–24.58)	0.60	Too few to model	Too few to model	
Isolated delay [‡]	24/88 (27%)	35 (34%)	0.79 (0.51–1.23)	0.37	0.72 (0.48–1.07)	0.10	0.79 (0.44–1.42) 0.43
Unimpaired	21/90 (23%)	26 (25%)	0.92 (0.56–1.51)	0.86	0.85 (0.54–1.35)	0.50	0.91 (0.46–1.81) 0.79
Head circumference (cm)	46.8 ± 1.7	46.7 ± 1.9		0.64			
N(%) <5%ile	14/86 (16%)	20/97 (21%)	0.79 (0.43–1.47)	0.57	0.84 (0.48–1.47)	0.55	0.99 (0.47–2.08) 0.97
Weight (kg)	10.6 ± 1.4	10.6 ± 1.7		0.72			
N(%) <5%ile	31/86 (36%)	41/98 (42%)	0.86 (0.60–1.24)	0.51	0.93 (0.65–1.32)	0.68	0.97 (0.60–1.57) 0.92

* Adjusted RR - MODEL #1: adjusted for birth weight, center, OI entry criterion strata, gender; MODEL #2: adjusted for birth weight, center, OI entry criterion strata, gender, BPD, IVH 3 or 4 or PVL, length of iNO exposure, postnatal steroids

[†] NDI: any of the following: moderate-severe CP, blind, deaf, MDI<70 or PDI<70

[‡] Isolated delay: MDI<70 or PDI<70 in the absence of moderate-severe CP, deafness or blindness

[§] Unimpaired: all of the following: MDI and PDI>=85, no moderate-severe CP, and not blind or deaf

Table 4

Post-hoc analyses of primary and major secondary outcomes according to birth weight and mode of ventilation at randomization.

	BW<1000 g				BW>1000 g			
	INO	Placebo	RR (95%CI) [†]	P	INO	Placebo	RR (95%CI) [†]	P
N	152	152			48	48		
Death	98 (64%)	79 (52%)	1.22 (1.01–1.46)	0.04	11 (23%)	19 (40%)	0.58 (0.31–1.07)	0.08
Death or NDI*	131/151 (87%)	120 (79%)	1.08 (0.98–1.20)	0.12	23/47 (49%)	26 (54%)	0.91 (0.63–1.33)	0.63
Death or mod-severe CP	111/151 (74%)	89 (59%)	1.22 (1.05–1.43)	0.01	16 (33%)	20 (42%)	0.80 (0.48–1.33)	0.39
Follow-up cohort	54	73			37	29		
NDI	33/53 (62%)	41 (56%)	0.95 (0.71–1.27)	0.73	12/36 (33%)	7 (24%)	1.33 (0.60–2.91)	0.48
Mod-severe CP	13/53 (25%)	10 (14%)	1.75 (0.85–3.58)	0.13	5 (14%)	1 (3%)	4.40 (0.51–37.65)	0.18
			HFV				Conventional	
N	117	119			83	81		
Death	56 (48%)	62 (52%)	0.94 (0.74–1.20)	0.61	53 (64%)	36 (44%)	1.37 (1.05–1.79)	0.02
Death or NDI*	90/115 (78%)	93 (78%)	1.01 (0.88–1.15)	0.91	64 (77%)	53 (65%)	1.15 (0.97–1.36)	0.12
Death or mod-severe CP	68/116 (59%)	66 (55%)	1.06 (0.86–1.32)	0.58	59 (71%)	43 (53%)	1.29 (1.03–1.60)	0.02
Follow-up cohort	61	57			30	45		
NDI	34/59 (58%)	31 (54%)	0.97 (0.70–1.35)	0.88	11 (37%)	17 (38%)	1.07 (0.64–1.80)	0.80
Mod-severe CP	12/60 (20%)	4 (7%)	3.03 (0.98–9.42)	0.055	6 (20%)	7 (16%)	1.49 (0.62–3.59)	0.38

* Data were not available for all infants

[†] RR = relative risk adjusted for birth weight, center, gender and OI criterion strata

Table 5

Post-hoc analysis of primary and secondary outcomes of iNO and placebo groups stratified by birth weight category

	401–750 grams			751–1000 grams			1001–1500 grams		
	iNO	Placebo	P value [†]	iNO	Placebo	P value [†]	iNO	Placebo	P value [†]
N (for analysis) cohort= 400	94	99		58	53		48	48	
Death	69 (73%)	55 (56%)	0.01	29 (50%)	24 (45%)	0.63	11 (23%)	19 (40%)	0.07
Death or NDI	86 (91%)	81 (82%)	0.051	45/57 (79%)	39 (74%)	0.51	23/47 (49%)	26 (54%)	0.54
Death or moderate to severe CP	75/93 (81%)	61 (62%)	0.0039	36 (62%)	28 (53%)	0.34	16 (33%)	20 (42%)	0.35
N (for follow-up group)=210	25	44		29	29		37	29	
NDI [‡]	17 (68%)	26 (59%)	0.47	16/28 (57%)	15 (52%)	0.60	12/36 (33%)	7 (24%)	0.52
Moderate-severe CP	6/24 (25%)	6 (14%)	0.25	7 (24%)	4 (14%)	0.33	5 (14%)	1 (3%)	0.20
MDI<70	13/22 (59%)	22/42 (52%)	0.61	15 (52%)	8/27 (30%)	0.12	9/35 (26%)	5 (17%)	0.56
PDI<70	10/22 (45%)	17/43 (40%)	0.67	12/28 (43%)	11/27 (41%)	0.91	7/35 (20%)	4 (14%)	0.61
Blind	1/24 (4%)	1 (2%)	0.67	0	0	N/A	1 (3%)	0	0.45
Deaf	1/24 (4%)	3 (7%)	0.67	1 (3%)	1 (3%)	0.99	3 (8%)	1 (3%)	0.45
Isolated delay	9/24 (38%)	19 (43%)	0.66	9/28 (32%)	10 (34%)	0.93	6/36 (17%)	6 (21%)	0.59
Unimpaired [*]	3 (12%)	7 (16%)	0.67	5 (17%)	7 (24%)	0.42	13/36 (36%)	12 (41%)	0.72

* Total analysis cohort includes 400 patients due to 10 patients in each treatment group lost to follow-up

[†] Data were not available for all infants

[‡] Statistical comparisons using Cochran-Mantel-Haenszel test controlling for OI strata