A Randomized Trial of Early Versus Standard Inhaled Nitric Oxide Therapy in Term and Near-Term Newborn Infants With Hypoxic Respiratory Failure

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ABSTRACT. *Objective.* **Inhaled nitric oxide (iNO) reduces the use of extracorporeal membrane oxygenation (ECMO)/incidence of death in term and near-term neonates with severe hypoxic respiratory failure. We conducted a randomized, double masked, multicenter trial to determine whether administration of iNO earlier in respiratory failure results in additional reduction in the incidence of these outcomes.**

Methods. **Neonates who were born at ≥34 weeks' gestation were enrolled when they required assisted ventilation and had an oxygenation index (OI) ≥15 and <25 on any 2 measurements in a 12-hour interval. Infants were randomized to early iNO or to simulated initiation of iNO (control). Infants who had an increase in OI to 25 or more were given iNO as standard therapy.**

Results. **The trial enrollment was halted after 75% of target sample size was reached because of decreasing availability of eligible patients. The 150 infants who were given early iNO and 149 control infants had similar baseline characteristics. Arterial oxygen tension increased by >20 mm Hg in 73% of early iNO and 37% of control infants after study gas initiation. Control infants received standard iNO and deteriorated to OI >40 more often than infants who were given early iNO. The incidence of death (early iNO, 6.7% vs control, 9.4%), ECMO (10.7% vs 12.1%), and their combined incidence (16.7% vs 19.5%) were similar in both groups.**

Conclusion. **iNO improves oxygenation but does not reduce the incidence of ECMO/mortality when initiated at an OI of 15 to 25 compared with initiation at >25 in term and near-term neonates with respiratory failure.** *Pediatrics* **2004;113:559–564;** ***persistent fetal circulation syndrome, respiratory insufficiency, randomized controlled trials, inhalation therapy, newborn infant.***

ABBREVIATIONS. iNO, inhaled nitric oxide; ECMO, extracorporeal membrane oxygenation; OI, oxygenation index; FIO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen.

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Respiratory failure in term and near-term newborn infants is often associated with persistence of pulmonary hypertension, which contributes to hypoxemia in these infants.[1–3] Inhaled nitric oxide (iNO) is currently used as a pulmonary vasodilator to improve oxygenation in neonates with severe respiratory failure.[4–7] Infants who fail to respond to iNO may require extracorporeal membrane oxygenation (ECMO), a life-saving rescue therapy[8] associated with significant morbidity and mortality. The current recommended threshold for initiation of iNO in neonatal respiratory failure is an oxygenation index (OI) ≥25, based on previous clinical trials.[4–7] Although iNO decreased the use of ECMO/mortality in these trials, nearly 40% of the infants who were treated with iNO still required ECMO or died. However, a subgroup analysis of the data from our previous trial of iNO[4] in infants with severe hypoxic respiratory failure suggested a greater reduction in incidence of ECMO/death with iNO for infants who were enrolled at the lowest severity of illness (OI 25–30). Severe respiratory failure in neonates is often associated with alveolar atelectasis from progression of underlying disease and from iatrogenic lung damage caused by aggressive ventilation.[9] Strategies that improve alveolar ventilation in neonates with respiratory failure enhance the response to iNO.[10] Therefore, introduction of iNO early in respiratory failure, before alveolar atelectasis supervenes, may improve the response to iNO. In addition, the optimum initial dose of iNO for management of neonatal respiratory failure remains unclear from the previous trials. Although iNO is effective in improving oxygenation at doses <20 ppm,[11] iNO therapy is often initiated at 20 ppm based on previous study protocols.[4–6] However, the long-term safety of using iNO in the neonate during a period of critical lung development remains unknown, making it desirable to use the lowest effective dose in this population. Therefore, initiation of iNO at doses <20 ppm in the management of neonatal respiratory failure requires additional investigation.

We conducted a prospective, randomized, double-masked, multicenter trial to test the hypothesis that early initiation of iNO in neonatal respiratory failure results in additional reduction in the use of ECMO therapy and mortality compared with standard iNO

therapy. We also tested the hypothesis that initiation of iNO therapy at low dose (5 ppm) will improve the oxygenation significantly compared with standard (20 ppm) doses of iNO in these infants.

METHODS

Study Hypotheses

The primary hypothesis was that the use of iNO in term and near-term infants in respiratory failure with an OI ≥15 and <25 would decrease the probability of ECMO and/or mortality from 35% to 20%. The incidence of the primary outcome for the control group was estimated from data collected prospectively in 70 term/near-term neonates who required assisted ventilation for >6 hours at 2 study sites. OI was calculated as mean airway pressure times the fraction of inspired oxygen (F_{IO_2}) divided by the partial pressure of arterial oxygen (P_{aO_2}) times 100. Study infants in either group who deteriorate to OI >25 will receive iNO as standard therapy, consistent with current practice based on previous randomized trials.[4–6] The secondary hypotheses were that early iNO therapy would 1) reduce the probability of using standard iNO therapy; 2) decrease progression to severe respiratory failure, defined as OI ≥40; and 3) would not increase neurodevelopmental impairment among surviving infants at 18 to 24 months of age.

Study Patients

Inclusion criteria were birth at ≥34 weeks of gestation, respiratory failure caused by primary pulmonary hypertension, respiratory distress syndrome, perinatal aspiration syndrome, pneumonia/sepsis or suspected pulmonary hypoplasia, and need for assisted ventilation with an OI ≥15 and <25 on F_{IO_2} ≥0.80 on any 2 arterial blood gases at least 15 minutes and no >12 hours apart. High-frequency oscillatory ventilation was permitted when it was initiated before randomization. Echocardiographic evidence of pulmonary hypertension was not required because iNO improves oxygenation in the absence of elevated pulmonary artery pressure.[4,6]

Exclusion criteria were >14 days of postnatal age, life-threatening congenital malformations, structural heart disease other than patent ductus arteriosus or patent foramen ovale, congenital diaphragmatic hernia, or previous exposure to iNO therapy. Use of high-frequency jet ventilation was not permitted in conjunction with study gas administration. Informed consent was obtained from parents/guardians before randomization, and all participating centers obtained approval for the study from institutional review boards before enrollment began.

Guidelines for Management

Each center developed management guidelines to optimize the care of infants before enrollment. Administration of surfactant during study gas administration was permitted only when it was initiated before randomization. The mode of ventilation was not changed during study gas administration except as part of a weaning strategy from high-frequency oscillatory to conventional ventilation. Initiation of surfactant therapy and high-frequency oscillation were permitted after an infant exited to standard iNO therapy.

Randomization

Infants were stratified by the study center and randomized to early iNO or to simulated initiation of early iNO by a central computer accessed by telephone according to a permuted block design developed and implemented by the data coordinating center.

Administration and Monitoring of Study Gas

Study gas was administered through an approved device (INOVent; INO Therapeutics, Clinton, NJ), modified to mask the display of gas concentrations and tank pressure. NO was supplied in a concentration of 800 ppm in balance nitrogen (INO Therapeutics). Each delivery device had a tank of NO and nitrogen. The study gas was set up and administered by an unmasked respiratory therapist who did not participate in the infant's care. Adjustments to study gas dose were also made by these unmasked respiratory therapists. Nitrogen was used to pressurize the INOVent in control infants but was not injected into the breathing circuit of these infants. All care providers and parents/guardians were masked to study gas assignment. Mock adjustments to study gas were made in control infants, and data that might reveal treatment assignment were recorded on data collection forms kept in sealed envelopes.

Response to study gas was evaluated by the change in P_{aO_2} from baseline to 30 minutes after initiation of study gas. Study gas was initiated at a concentration of 5 ppm, and the dose was increased to 20 ppm when the infant had ≤20 mm Hg increase in P_{aO_2} (less than full response). The dose was kept at 20 ppm when the infant had ≥10 mm Hg increase in P_{aO_2} after 30 minutes at this dose (partial response). When the infant had <10 mm Hg increase in P_{aO_2} at 20 ppm, the dose was returned to 5 ppm (no response).

All infants were continued on the assigned study gas regardless of initial response until they weaned off, exited to standard iNO, or completed 14 days of study gas administration. Weaning of study gas was done at 12-hour intervals according to an algorithm specified by the protocol. The dose was weaned to 0.5 ppm before discontinuation of study gas. The decision to initiate ECMO was made by the masked clinical team based on center-specific criteria.

Monitoring of Safety

Blood methemoglobin concentrations and inspired nitrogen dioxide levels were monitored during study gas administration. The methemoglobin results were reported to the unmasked respiratory therapist. Study gas dose was weaned for methemoglobin levels of 5% to 10% or nitrogen dioxide levels of 3 to 5 ppm and discontinued for methemoglobin levels >10% or nitrogen dioxide levels >5 ppm. Cranial ultrasounds were done within 3 days of study enrollment and before discharge.

Statistical Analysis

A target enrollment of 400 infants was established to demonstrate a reduction in risk of primary outcome from 35% to 20% with a power of 0.90 and a 2-tailed α of .05.[12] Primary data analysis was done using an intention-to-treat model. Continuous variables were compared by t tests or Wilcoxon tests, and categorical variables were compared by χ^2 tests.

The trial was monitored by an independent data safety and monitoring committee (listed in the appendix), with planned evaluations after approximately one third and two thirds of study patients were enrolled. For reducing the probability of a type 1 error, significance was tested at each interim analysis by the group-sequential method of O'Brien-Fleming.[13]

RESULTS

The trial was halted by the investigators after a 3-year recruitment period from July 1998 to May 2001, because of persistent decline in enrollment. The decision to end recruitment was made without previous knowledge of the outcome data and was reviewed by the Data Monitoring Committee and accepted by National Institute of Child Health and Human Development. Trial enrollment ceased on May 2, 2001.

Baseline Characteristics

A total of 302 infants were enrolled in the trial; 3 were excluded after major cardiac malformations were identified. The baseline clinical characteristics were similar for both groups (Table 1). Forty-two percent of all randomized infants had perinatal aspiration syndrome. Among the 187 (63%) study infants who had echocardiography before randomization, pulmonary hypertension was demonstrated in 68% of control and 74% of early iNO infants. There were no clinically important differences between the 2 groups in prerandomization therapies and complications (Table 2). Age and OI at randomization were similar in both groups (Table 2).

TABLE 1. Baseline Characteristics of the Patients*

Characteristics	Early iNO Group (N = 150)	Control Group (N = 149)
Birth weight, g (mean ± SD)	3313 ± 670	3318 ± 562
Gestational age, wk (mean ± SD)	38.5 ± 2	38.7 ± 1.9
Male sex, *n* (%)	80 (53)	90 (60)
Race, *n* (%)		
Asian/Pacific Islander	6 (4)	3 (2)
Black	45 (30)	39 (26)
Hispanic	29 (19)	29 (20)
White	64 (43)	72 (48)
Other	6 (4)	6 (4)
C-section delivery, *n* (%)	85 (57)	76 (51)
1-min Apgar score <3*	36 (24)	42 (28)
5-min Apgar score <3*	5 (3)	7 (5)
Primary cause of respiratory failure, *n* (%)		
Idiopathic PPHN	35 (23)	44 (30)
Respiratory distress syndrome	27 (18)	25 (17)
Perinatal aspiration syndrome	66 (44)	60 (40)
Pneumonia with sepsis	21 (14)	20 (13)
Suspected pulmonary hypoplasia	1 (1)	0

SD indicates standard deviation; PPHN, persistent pulmonary hypertension of newborn.
* Data are based on 148 infants each in early iNO and control groups.

Primary Outcome

The incidence of primary outcome (ECMO therapy and/or death before hospital discharge or 120 days of postnatal age, whichever was sooner) was similar in both groups (Table 3). Twenty-four (8%) study infants died before discharge home or 120 days of age. The causes of death were similarly distributed between the 2 groups. Two in each group died after receiving ECMO as a result of severe intracranial hemorrhage or alveolar-capillary dysplasia. Of the 20 infants who died without ECMO, 13 (6 early iNO and 7 control group) were considered ineligible for ECMO for the following reasons: severe hypoxic ischemic encephalopathy in 7 infants, intraventricular hemorrhage more than grade 2 in 4 infants, and multi-organ dysfunction with disseminated intravascular coagulation in 2 infants. Four infants (2 in each group) on study gas or standard iNO had rapid deterioration and died before ECMO could be initiated. Three infants died unexpectedly after successfully weaning off study gas or standard iNO. Three infants in each group died after 120 days of postnatal age (176–448 days) and were not part of primary outcome analysis. Inclusion of these infants in the study did not change the results of the primary outcome. The number of infants who received ECMO did not differ between the 2 groups (Table 3). Among infants who received ECMO, the median OI (40.5 in early iNO vs 45.2 in control; $P = .23$) and median Pao_2 (50.5 in early iNO and 44.5 in control; $P = .39$) preceding ECMO did not differ between the 2 groups. Similarly, the interval between initiation of study gas and initiation of ECMO did not differ between the 2 groups (3.64 ± 4.33 days in early iNO and 3.24 ± 3.44 days in control group; $P = .36$).

A post hoc subgroup analysis did not demonstrate a difference in the primary outcome with iNO treatment for infants who were enrolled at OI ≥15 and <20 (early iNO: 9 of 88 [10.2%]; control: 16 of 88 [18.2%]; $P = .13$) compared with infants who were enrolled at OI 20 to 25 (early iNO: 16 of 62 [25.8%]; control: 13 of 61 [21.3%]; $P = .56$).

Outcome at Discharge

Infants in the 2 groups did not differ in length of hospital stay, duration of ventilation, days on oxygen at FIO_2 >0.60 (median: 5 days for each group) or 0.21 to 0.60 (median: 7 days for each group), and incidence of chronic lung disease (Table 3). Postnatal steroids were given to 44% of early iNO and 35% of control infants during hospital stay ($P = .12$). The overall use of high-frequency ventilation (early iNO: 83.3%; control: 80.5%) and surfactant therapy (early iNO: 82%; control: 82.5%) at the time of randomization and during study gas administration was similar in both groups.

Response to Study Gas

More infants in the early iNO group had >20 mm Hg increase in Pao_2 in response to study gas initiation (Table 4) compared with control group. Overall, 73% of early iNO infants and 37% of control infants had >20 mm Hg increase in Pao_2 at study gas initiation ($P < .001$). Infants who were given early iNO also had a larger increase in Pao_2 and a larger decrease in OI in response to study gas initiation (Table 4).

Secondary Outcomes

More infants in the early iNO group weaned off study gas compared with control group (early iNO 57% vs control 44%; $P < .03$). Infants in the control group progressed to standard iNO and to OI ≥40 more often than infants who were given early iNO (Table 5).

Safety and Toxicity Data

None of the study infants had study gas weaned or discontinued because of elevated methemoglobin or nitrogen dioxide levels. None of the cranial sonograms performed within 3 days of study gas initiation showed severe (grade 3–4)[14] intraventricular hemorrhage, infarct, or periventricular leukomalacia. One early iNO and 2 control infants had severe (grade 3–4)[14] intraventricular hemorrhage and periventricular leukomalacia diagnosed before discharge home. The cumulative incidence of abnormal cranial sonograms was 5.4% in study infants. Seizures occurred in 14 early iNO (9.4%) and 11 control (7.4%; $P = .68$) infants during hospital stay.

Protocol Deviations

There were 18 incidents of protocol deviation (6% of study infants). Seven infants received their first dose of surfactant during study gas administration. Two infants who were given early iNO and 1 control infant had errors made during study gas initiation. Two infants in each group had unmasking of study gas assignment. Four study infants received standard iNO for >14 days permitted by the protocol.

DISCUSSION

We demonstrated that early initiation of iNO in respiratory failure improves oxygenation without in-

TABLE 2. Treatment Variables and Status of the Infants at Randomization

Variable	Early iNO (N = 150)	Control (N = 149)
Treatment, *n* (%)		
Volume expanders	125 (83)	119 (80)
Vasopressor support	124 (83)	118 (79)
Sedation/analgesia	146 (97)	142 (95)
Paralytic agents	86 (57)	84 (56)
Tolazoline	9 (6)	5 (3)
Alkalosis (pH ≥ 7.45)	91 (61)	87 (58)
Surfactant use	95 (63)	97 (65)
High-frequency ventilation	62 (41)	68 (46)
Postnatal steroids	12 (8)	13 (9)
Air leaks, *n* (%)	21 (14)	30 (20)
Pulmonary hemorrhage, *n* (%)	7 (5)	7 (5)
Seizures, *n* (%)	8 (5)	11 (7)
Any IVH*	3/40 (8%)	3/39 (8%)
Oxygenation index at randomization†, mean ± SD	19.7 ± 4.9	19.2 ± 3.6
Age at randomization in hours, median (1st–3rd quartile range)	28.5 (14–46)	24.8 (12–47)
Time from randomization to study gas initiation in min, median (1st–3rd quartile range)	15 (6–36)	15 (6–42)

IVH indicates intraventricular hemorrhage; SD, standard deviation.
* All were of grade 1.[14]
† OI calculated from the second qualifying arterial blood gas. OI = [FIO_2 × mean airway pressure × 100]/PaO_2.

TABLE 3. Outcome of the Early Administration of Study Gas by Group

Event	Early iNO Group (N = 150)	Control Group (N = 149)	P Value
Death by day 120 or ECMO, *n* (%)	25 (16.7)	29 (19.5)	.530
Death, *n* (%)	10 (6.7)	14 (9.4)	.385
ECMO, *n* (%)*	16 (10.7)	18 (12.1)	.700
Outcomes in surviving infants			
Length of hospitalization, d*	17 (12–27)	18 (12–30)	.51
Duration of assisted ventilation, d*	8 (6–12)	8 (6–13)	.76
Duration of oxygen therapy, d*	13 (9–19)	13 (9–19)	.58
Chronic lung disease, *n* (%)	16 (10.7)	13 (8.7)	.58

* Data are medians with first to third quartile ranges shown in parentheses.

creasing the short-term toxicity of iNO. However, this early improvement in oxygenation did not influence the primary study outcome of ECMO/mortality.

We planned to enroll 400 infants in the study to demonstrate a 43% relative reduction in primary outcome with 90% power. The trial enrollment declined over time from an average of 15 infants per month during the midpoint of the trial to only 6 infants per month during the final quarter of the trial, despite efforts to increase enrollment (including addition of new centers). The decrease in enrollment resulted from decreased availability of study infants and not from failure to enroll eligible infants. Therefore, reaching a sample target of 400 infants did not seem to be feasible. The study sample size of 299 patients has 80% power to detect the hypothesized 43% relative reduction in primary outcome incidence. The primary outcome incidence observed in the control group (19.5%) is approximately half of the projected incidence on the basis of our 1997 pilot data. The difference in primary outcome between the groups (2.8% with 95% confidence intervals of −5.9% to 11.5%) is small and suggests a lack of treatment effect. We did not observe a secular trend in the overall incidence of primary outcome or difference in its incidence between the 2 study groups, suggesting a consistent lack of treatment effect over time.

Before our study, 4 randomized trials[4–7] demonstrated that iNO decreases the incidence of ECMO/mortality in neonates with severe hypoxic respiratory failure and OI ≥25. Because initiation of iNO at an OI ≥25 has become standard practice in the management of hypoxic respiratory failure, we offered iNO therapy to study infants at this OI. The mean OI at enrollment in study infants was nearly 20, and a lack of a clear separation between early and standard iNO groups may have contributed to the lack of treatment effect in our study.

Antunes et al[15] compared early iNO (OI 15–25) and late iNO (OI >25) in 86 term newborn infants with respiratory failure. The incidence of ECMO/death did not differ between early and late iNO groups; however, the incidence of ECMO/death in their trial (46% in early iNO and 53% in late iNO) was nearly 3-fold higher than in our study, suggesting differences in severity of illness or management strategies in the 2 studies. The overall incidence of ECMO/death in our trial (18.1%) is lower than the observed incidence in all previous randomized trials of iNO in term/near-term neonates.[4–7,15] The reasons for this difference are not clear. Although the previ-

TABLE 4. Oxygenation Responses to Initial Administration of Study Gas

Variable	Early iNO Group	Control Group	*P* Value
Response to 5 ppm, *n* (%)			
No. of infants	145	147	
Complete	84 (58)	36 (24)	.001*
Partial	12 (8)	13 (9)	
None	49 (34)	98 (67)	
Change in Pao_2 (mm Hg)†	44 (6 to 111)	8.5 (−8 to 54)	<.0001
Change in OI†	−6.1 (−12 to −1)	−2.2 (−8 to 3)	.0001
Response to 20 ppm, *n* (%)‡			
No. of infants	50	105	
Complete	18 (36)	19 (18)	.002*
Partial	12 (24)	15 (14)	
None	20 (40)	71 (68)	
Change in Pao_2 (mm Hg)†	11 (−3 to 39)	4 (−16 to 28)	.17
Change in OI†	−2.7 (−7 to 1)	−1.6 (−5 to 7)	.17

* Composite *P* value for each dose by Cochrane-Armitage test for categorical factors with ordered variables.
† Data are medians with first to third quartile ranges shown in parentheses.
‡ Infants who had ≤20 mm Hg increase in Pao_2 in response to 5 ppm of study gas (61 early iNO/111 control infants) were eligible to receive the 20-ppm dose. However, 50 early iNO and 105 control infants actually received the 20-ppm dose. Eight of 11 infants in the early iNO group and 5 of 6 infants in the control group who did not receive a trial of 20 ppm of study gas were exited from study gas to standard iNO therapy for rapid deterioration in clinical status. Three of 11 infants in the early iNO and 1 of 6 infants in the control group had discontinuation of study gas for a period of time because of acute deterioration and were later treated with standard iNO.

TABLE 5. Secondary Outcomes of the Study

Variable	Early iNO Group (*N* = 150)	Control Group (*N* = 149)	*P* Value
Duration of study gas administration, h*	57 ± 48	39 ± 38	<.003
Initiation of standard iNO therapy, *n* (%)*	61 (41)	81 (54)	<.02
Duration of standard iNO therapy, h†	121 (41–175)	100 (56–158)	.52
Progression to OI >40, *n* (%)	11 (7)	21 (14)	.056

* Data are mean ± standard deviation.
† Data shown as medians with first to third quartile ranges in parentheses.

ous trials of iNO attempted to enroll infants at an OI ≥25, the average OI at enrollment was nearly 40, compared with 19.5 in our study. OI was closely followed in our study infants, and standard iNO was initiated when the threshold of 25 was reached. Therefore, careful monitoring of infants in respiratory failure may allow us to institute standard iNO expeditiously when the threshold of 25 is reached, decreasing the probability of ECMO/mortality. In addition, wider application of surfactant therapy and high-frequency ventilation (≥80% before or in conjunction with standard iNO) may have contributed to decreased use of ECMO in our study infants, as previously reported.[10,16]

Previous studies demonstrated that iNO improves oxygenation in neonates with severe hypoxic respiratory failure at doses of 5 to 80 ppm,[11,17,18] whereas an initial dose of 2 ppm of iNO was ineffective.[19] However, these studies were done in infants who had an OI >25 at the time of study enrollment. We found that iNO at a dose of 5 ppm improves oxygenation in neonatal respiratory failure at an OI of 15 to 25. We also found that a significant proportion of infants who did not respond to 5 ppm had >20 mm Hg increase in Pao_2 at 20 ppm of iNO. Our results are consistent with the dose-dependent effect at 5 to 20 ppm iNO reported previously.[18] Cornfield et al[19] reported that an initial dose of 2 ppm of iNO had an adverse effect on progression of respiratory failure and attenuated the subsequent response to 20 ppm of iNO. However, we observed that among the 84 infants who had a complete response to the 5-ppm dose of iNO, only 27 (32.1%) progressed to a need for standard iNO therapy. Among the 50 infants who were given 20 ppm of iNO in the initial dose-response assessment, 20 (40%) infants progressed to standard iNO. We therefore did not observe an adverse effect from treatment of infants in respiratory failure with an initial dose of 5 ppm of iNO. Early initiation of iNO also decreased progression of respiratory failure to an OI >25 and >40 in the study infants. Whether this will result in a significant improvement in long-term neurodevelopmental outcome[20] will be determined by the follow-up of survivors at 18 to 24 months of age. Because the use of iNO therapy may result in additional cost to the care of these infants, earlier application of this therapy cannot be recommended unless follow-up data demonstrate a benefit to such use.

In conclusion, although we were unable to demonstrate a significant decrease in the incidence of ECMO/death with our study design, providing low-dose (5–20 ppm) iNO to neonates earlier in their disease process was apparently safe and effective in improving oxygenation. The potential long-term effect of early initiation of this therapy in respiratory failure on the neurodevelopmental outcome of these infants remains to be determined.

APPENDIX

The Neonatal Inhaled Nitric Oxide Study was a collaboration of the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network and the Canadian Inhaled Nitric Oxide Study Group. The following institutions and investigators participated in the trial (members of the Executive Committee are indicated by asterisks). NICHD Neonatal Research Network: Case Western Reserve University, Cleveland: *E. Stork, A.A. Fanaroff, E. Gorjanc; University of Texas, Dallas: A.R. Laptook, S. Madison; Wayne State University, Detroit: S. Shankaran, R. Bara, G. Muran; University of Tennessee, Memphis: S.B. Korones, T. Hudson; University of Miami, Miami: S. Duara, C.R. Bauer, R. Everett; University of New Mexico, Albuquerque: M. Crowley, L.-A. Papile, C. Backstrom; University of Cincinnati, Cincinnati: J. Fridriksson, E.F. Donovan, M. Mersman; Indiana University, Indianapolis: *G.M. Sokol, J.A. Lemons, D. Appel; Yale University, New Haven, CT: *R.A. Ehrenkranz, P. Gettner; Women and Infants' Hospital, Providence, RI: W. Oh, A. Hensman; Stanford University, Palo Alto, CA: *K.P. Van Meurs, D.K. Stevenson, M.B. Ball; University of Alabama, Birmingham: W.A. Carlo, S. Cosby; Harvard University, Boston: E. Eichenwald, A.R. Stark, K. Fournier; University of Texas, Houston: K. Kennedy, J.E. Tyson, G. McDavid; Medical College of Wisconsin, Milwaukee: *G. Konduri, P. Hamm. Canadian Inhaled Nitric Oxide Study Group: University of Alberta, Edmonton: *A. Peliowski, B. Young; University of Calgary, Calgary: *N. Singhal, L. Bourcier; University of British Columbia, Vancouver: *A. Solimano, F. Germain, A.J. Singh; Baylor College of Medicine, Houston: M. Wearden, C. Fernandes, S. Hegemier; University of Manitoba, Winnipeg: R. Alvaro, N. Johnston; McGill University, Montreal: R. Gosselin, K. Mullahoo; McMaster University, Hamilton: *H. Kirpalani, S. Monkman; University of Ottawa, Ottawa: *R. Walker, L. Ramnarine; University of Toronto, Toronto: A. James, M. Finelli; St Joseph's Hospital, Phoenix, AZ: C. Fajardo, E. Ramthun; Children's Hospital and Health Center, San Diego, CA: G. Knight; University of Washington, Seattle: D. Mayock, S. Jacques; Phoenix Children's Hospital, Phoenix, AZ: D. Sprague, J. Andrews. Data Safety and Monitoring Committee: Children's Hospital National Medical Center, Washington, DC: G. Avery (Chairman); New England Medical Center, Boston: M. D'Alton; University of Washington, Seattle: C.A. Gleason; University of Pennsylvania, Philadelphia: M. Maguire; University of Pittsburgh, Pittsburgh: C. Redmond; McMaster University, Department of Clinical Epidemiology and Biostatistics: R.S. Roberts; Research Triangle Institute: W.K. Poole; McMaster University: J. Sinclair. Data Coordination Center: University of British Columbia, Vancouver: *J. Singer, D. Stromberg.

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