

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

JULY 7, 2005

VOL. 353 NO. 1

Inhaled Nitric Oxide for Premature Infants with Severe Respiratory Failure

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ABSTRACT

BACKGROUND

Inhaled nitric oxide is a controversial treatment for premature infants with severe respiratory failure. We conducted a multicenter, randomized, blinded, controlled trial to determine whether inhaled nitric oxide reduced the rate of death or bronchopulmonary dysplasia in such infants.

METHODS

We randomly assigned 420 neonates, born at less than 34 weeks of gestation, with a birth weight of 401 to 1500 g, and with respiratory failure more than four hours after treatment with surfactant to receive placebo (simulated flow) or inhaled nitric oxide (5 to 10 ppm). Infants with a response (an increase in the partial pressure of arterial oxygen of more than 10 mm Hg) were weaned according to protocol. Treatment with study gas was discontinued in infants who did not have a response.

RESULTS

The rate of death or bronchopulmonary dysplasia was 80 percent in the nitric oxide group, as compared with 82 percent in the placebo group (relative risk, 0.97; 95 percent confidence interval, 0.86 to 1.06; $P=0.52$), and the rate of bronchopulmonary dysplasia was 60 percent versus 68 percent (relative risk, 0.90; 95 percent confidence interval, 0.75 to 1.08; $P=0.26$). There were no significant differences in the rates of severe intracranial hemorrhage or periventricular leukomalacia. Post hoc analyses suggest that rates of death and bronchopulmonary dysplasia are reduced for infants with a birth weight greater than 1000 g, whereas infants weighing 1000 g or less who are treated with inhaled nitric oxide have higher mortality and increased rates of severe intracranial hemorrhage.

CONCLUSIONS

The use of inhaled nitric oxide in critically ill premature infants weighing less than 1500 g does not decrease the rates of death or bronchopulmonary dysplasia. Further trials are required to determine whether inhaled nitric oxide benefits infants with a birth weight of 1000 g or more.

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N Engl J Med 2005;353:13-22.

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PREMATURE INFANTS IN RESPIRATORY failure can have dramatic improvements after treatment with exogenous surfactant. However, a subset of premature infants have suboptimal responses to surfactant¹ and may have pulmonary hypertension in association with severe respiratory failure.²⁻⁶ Inhaled nitric oxide may benefit such infants by selectively dilating pulmonary vasculature, improving ventilation-perfusion matching, and decreasing the pulmonary inflammatory response.⁷⁻⁹

Inhaled nitric oxide had been shown to provide only short-term improvement in oxygenation in premature infants¹⁰⁻¹⁴ until a recent single-center study reported an association between the administration of inhaled nitric oxide and a decrease in the incidence of bronchopulmonary dysplasia or death in a cohort of moderately ill infants.¹⁵ We hypothesized that inhaled nitric oxide administered to premature infants with severe respiratory failure would reduce the incidence of death or bronchopulmonary dysplasia.

METHODS

HYPOTHESES AND OUTCOMES

The primary hypothesis was that administration of inhaled nitric oxide to neonates at less than 34 weeks of gestation, with a birth weight of 401 to 1500 g, and with severe respiratory failure would reduce the incidence of bronchopulmonary dysplasia or death (defined as death before discharge to home or within 365 days among hospitalized infants). Severe respiratory failure was defined as an oxygenation index of 10 or more on two consecutive measurements of arterial blood gases between 30 minutes and 12 hours apart. We used the conventional definition of bronchopulmonary dysplasia — treatment with oxygen at 36 weeks of gestation.¹⁶ The oxygenation index was calculated as $100 \times \text{the fraction of inspired oxygen} \times \text{the mean airway pressure (in centimeters of water)} \div \text{the partial pressure of arterial oxygen (PaO}_2\text{) (in millimeters of mercury)}$.

The secondary hypotheses were that inhaled nitric oxide would not increase the incidence of grade 3 or 4 intraventricular hemorrhage or periventricular leukomalacia, and that it would decrease the number of days of assisted ventilation and oxygen use, the length of hospitalization, and the incidence of threshold retinopathy of prematurity.¹⁷ In addition to the conventional definition of bronchopul-

monary dysplasia, we assessed the “physiological requirement” for oxygen at 36 weeks of gestation in infants not on mechanical ventilation and receiving less than 30 percent oxygen by performing a stepwise reduction in oxygen delivery to the lowest oxygen concentration at which the oxygen saturation measured by pulse oximetry remained at least 90 percent.¹⁸ Infants who were unable to maintain a saturation of 90 percent or more while breathing room air were classified as requiring supplemental oxygen and therefore having “physiological bronchopulmonary dysplasia.”

CRITERIA FOR ELIGIBILITY

Neonates who had been born at less than 34 weeks of gestation, according to the best obstetric estimate, had a birth weight of 401 to 1500 g, required assisted ventilation, and had a diagnosis of respiratory distress syndrome, sepsis or pneumonia, aspiration syndrome, idiopathic persistent pulmonary hypertension, or suspected pulmonary hypoplasia were eligible. Eligible infants had received one dose of surfactant at least 4 hours before meeting the respiratory criteria for entry and had an oxygenation index of at least 10 on two consecutive measurements of arterial blood gas between 30 minutes and 12 hours apart.

On the basis of pilot data collected in National Institute of Child Health and Human Development (NICHD) Neonatal Research Network centers, we estimated that the rate of mortality or bronchopulmonary dysplasia in infants identified by the oxygenation-index criterion would be 75 percent. At the first interim analysis of the data safety and monitoring committee, the mortality rate was significantly higher than expected in both treatment groups. The committee requested that the entry criteria be modified to select a cohort whose severity of illness as measured by the oxygenation index was more similar to that of the targeted cohort. Data from the NICHD Neonatal Research Network were analyzed and used to revise the respiratory criteria for entry to an oxygenation index of at least 5 followed by an oxygenation index of at least 7.5, with the second determination made 30 minutes to 24 hours after the first. Hence, for purposes of analysis, the design was considered to have two strata based on the oxygenation-index entry criterion. Infants who required an indwelling arterial line were eligible from 4 to 120 hours after birth.

Infants were ineligible if they had congenital heart disease other than ventricular septal defect,

atrial-level shunt, or patent ductus arteriosus; any major congenital abnormality involving the respiratory system; thrombocytopenia (a platelet count $\leq 50,000$ per cubic millimeter); or bleeding diathesis or if a decision had been made not to provide full treatment. The study was approved by the institutional review board of each study center, and written informed consent was obtained from the parents or guardians of all infants.

Clinical care was not mandated by the protocol, but each center agreed to its own management guidelines to define its approach to mean arterial pressure, partial pressure of carbon dioxide, pH, surfactant replacement therapy, high-frequency ventilation, targets for lung inflation, paralysis, and the use of indomethacin, corticosteroids, bronchodilators, sedation, anesthesia, and analgesia for the duration of the trial.

STUDY DESIGN AND RANDOMIZATION

A dedicated telephone system developed by the data center stratified infants according to center and birth weight (401 to 750 g, 751 to 1000 g, and 1001 to 1500 g). Infants were randomly assigned within each stratum, according to a permuted-block design, to receive inhaled nitric oxide or placebo. Randomization, administration of the study gas, and safety monitoring were performed by designated, nonblinded persons not involved in clinical care. To maintain blinding, they made mock adjustments in the control infants, used a proprietary delivery and monitoring unit (INOvent, Datex-Ohmeda) with a specially designed gauge cover secured with a numbered tether (to keep track of when and by whom the unit had been opened), used an oxygen analyzer upstream of the site of administration of the study gas, and covered the downstream oxygen analyzer. A shroud secured with tamper-resistant tape was used to cover the tank label, and a screen was used to ensure blinding when the gauge cover was opened. All other research and clinical personnel were blinded to the treatment assignment.

ADMINISTRATION OF STUDY GAS

The study protocol was based on previous trials of inhaled nitric oxide performed by the Neonatal Research Network.^{19,20} When a study candidate had an initial measurement of arterial blood gas with a qualifying oxygenation index, parental consent was obtained, and an unblinded respiratory therapist set up the delivery system and analyzer (INOvent, Datex-Ohmeda) according to the manufacturer's

guidelines. When a second qualifying measurement of arterial blood gas was obtained, infants were randomly assigned to either 5 ppm inhaled nitric oxide (INOmax, INO Therapeutics) or simulated flow. Primary-grade nitric oxide was supplied in a concentration of 800 ppm in nitrogen certified to be within ± 1 percent of the stated nitric oxide content and to contain less than 5 ppm of nitrogen dioxide. If the study gas could not be initiated within 15 minutes, an additional sample of arterial blood gas was drawn as a baseline measurement and used to calculate the response to the study gas.

Response to the study gas was defined by the change in the PaO_2 between the baseline measurement and the measurement at 30 minutes without any alterations in ventilator or oxygen settings. A complete response was an increase of more than 20 mm Hg, a partial response an increase of 10 to 20 mm Hg, and no response an increase of less than 10 mm Hg. When a complete response occurred, administration of the same concentration of study gas was continued. For infants with less than a complete response, the study gas was increased to 10 ppm of inhaled nitric oxide or simulated flow, and arterial blood gas was measured again 30 minutes later. Infants who had a complete or partial response to 10 ppm of inhaled nitric oxide continued to be given that concentration; the study gas was discontinued in infants with no response at this flow level. If the condition of the infant deteriorated during administration of the initiation dose of the study gas, administration was discontinued and stabilization of the patient was attempted by such means as adjustment of the ventilator settings or inotropic infusions. If the patient was successfully stabilized, initiation of the study gas was tried again. If treatment with the study gas at the initiation dose was again accompanied by complications, the patient was classified as not having a response, and the study gas was withdrawn.

Weaning of the infants from the study gas followed a defined protocol and occurred 10 to 14 hours after the treatment had been initiated. Weaning was attempted only when the PaO_2 was more than 50 mm Hg and the oxygen saturation measured by pulse oximetry was greater than 90 percent. For weaning, the concentration of nitric oxide in the inhaled gas (or the simulated flow) was reduced as follows: 10.0, 5.0, 4.0, 3.0, 2.0, 1.0, 0.5, 0.0 ppm. If the oxygenation index was 5 or less, weaning was attempted every four to eight hours. Successful weaning was defined as a decrease in

the PaO₂ of less than 20 mm Hg and to a value no lower than 50 mm Hg and oxygen saturation greater than 90 percent in the 30 minutes after the weaning attempt.

The dose of the study gas could be increased if two consecutive oxygenation indexes measured 30 minutes apart were at least 7.5. The study gas could be reinitiated if the original entry criteria were met and if no more than 72 hours had passed since the study gas was discontinued. The maximal duration of the administration of the study gas was 336 hours, and the dose could not exceed 1 ppm after 240 hours.

SAFETY MONITORING

Blood methemoglobin concentrations were measured within the first 3 hours after administration of the study gas, and then after 12 and 24 hours. While the infants were receiving nitric oxide at a concentration of more than 5 ppm, the sampling interval was every 24 hours, and while they were receiving a concentration of less than 5 ppm, the interval was every 48 hours. Methemoglobin levels of 4 percent or more were managed by reducing the concentration of study gas by half until the level fell below 4 percent. The study gas was discontinued if the methemoglobin concentration exceeded 10 percent.

Continuous inhaled nitrogen dioxide concentrations were monitored, and if they exceeded 3 ppm, the delivery system was immediately checked and infants were weaned from the study gas in 50 percent increments until the concentration was below 3 ppm. If the concentration exceeded 5 ppm, the nitric oxide cylinder was changed; the study gas was discontinued if nitrogen dioxide concentrations remained greater than 5 ppm. Cranial ultrasound scans were performed on all infants at 28±3 days.

STATISTICAL ANALYSIS

Assuming an incidence of death or bronchopulmonary dysplasia of 75 percent, we determined that 220 infants would be required in each group to provide the study with 90 percent power to detect a reduction in death or bronchopulmonary dysplasia of 20 percent in the group given inhaled nitric oxide. All tests were two-tailed, with an alpha level of 0.05. We conducted the primary analysis according to the intention-to-treat principle.

Differences between the treatment groups in baseline characteristics, status at randomization, and response to study gas were tested with the use

of t-tests for continuous variables and chi-square tests for categorical variables. Differences in the primary and secondary outcomes were tested with the use of Poisson regression models for categorical variables and linear regression models for continuous variables. The models included birth-weight category, oxygenation-index stratum, center, and treatment group and were used to calculate the adjusted relative risks and 95 percent confidence intervals.²¹ The post hoc analysis used the same model (when appropriate) as the primary analysis, and the interactions were tested by adding the relevant variables to the model.

The interim analyses of the data safety and monitoring committee were performed after one third and two thirds of the study patients had reached an end point of the study. The efficacy stopping rule for the study was based on the O'Brien–Fleming boundary, with three analyses of the data for the primary outcome one third of the way through the study, two thirds of the way through, and at the conclusion of the trial. The nominal significance level was 0.05, and corresponding P values for the looks were 0.005, 0.01, and 0.04, respectively.²²

INO Therapeutics provided the study gas, gas delivery systems, and site monitoring for all hospitals and capitation funding for the hospitals outside the NICHD Neonatal Research Network. The company was otherwise not involved in the study design, data analysis and interpretation, or preparation of the manuscript.

RESULTS

RECRUITMENT

At the recommendation of the data safety and monitoring committee, the trial was terminated after the second planned interim analysis, with 294 (67 percent) of the enrolled infants having reached a study end point (death, discharge to home, or 365 days of age). At that time, the incidence of grade 3 or 4 intraventricular hemorrhage or periventricular leukomalacia was significantly higher in the group being given inhaled nitric oxide than in the control group, and there was no apparent beneficial effect of treatment on the primary outcome. Recruitment ceased with enrollment of 420 patients instead of the planned enrollment of 440.

BASELINE CHARACTERISTICS AND STATUS AT RANDOMIZATION

From January 4, 2001, to September 26, 2003, 420 infants were enrolled in the trial. There were no sig-

nificant differences between treatment groups in the baseline characteristics (Table 1) or status at the time of randomization (Table 2). The distribution by birth weight did not differ significantly between the two treatment groups, with an overall distribution of 47 percent in the infants who weighed 401 to 750 g, 28 percent in those who weighed 751 to 1000 g, and 25 percent in those who weighed 1001 to 1500 g. The mean (\pm SD) oxygenation index at randomization was 24.6 ± 16.3 for the first oxygenation-index stratum, and 20.4 ± 17.4 for the second stratum.

The baseline characteristics for eligible infants who did not undergo randomization were similar to those for enrolled infants. The reasons for not enrolling were refusal of the parent (31 percent); unavailability of the parent (5 percent); or consent not being sought because of the recommendation of the attending physician (17 percent), unavailability of equipment (9 percent), use of high-frequency jet ventilation (8 percent), or other reasons (30 percent).

PRIMARY OUTCOME

There was no difference between the incidence of the primary outcome (bronchopulmonary dysplasia or death) between the group given inhaled nitric oxide and the placebo group (80 percent vs. 82 percent; relative risk, 0.97; 95 percent confidence interval, 0.86 to 1.06; $P=0.52$) (Table 3). The rate of bronchopulmonary dysplasia was 60 percent in the group given inhaled nitric oxide and 68 percent in the placebo group (relative risk, 0.90; 95 percent confidence interval, 0.75 to 1.08; $P=0.26$), and the rate of death was 52 percent in the group given inhaled nitric oxide and 44 percent in the placebo group (relative risk, 1.16; 95 percent confidence interval, 0.96 to 1.39; $P=0.11$). There were no discernible differences between the group given inhaled nitric oxide and the placebo group for the following variables: age at death (20 vs. 24 days, $P=0.54$) or cause of death (respiratory failure, 49 percent vs. 42 percent; neurologic insult, 4 percent vs. 1 percent; infection, 5 percent vs. 10 percent; necrotizing enterocolitis, 8 percent vs. 2 percent; support withdrawn, 19 percent vs. 26 percent; or other, 16 percent vs. 19 percent; $P=0.13$ for the equality of the distribution between the two treatment groups).

SECONDARY OUTCOMES

The frequency of severe intraventricular hemorrhage or periventricular leukomalacia was not sig-

Table 1. Baseline Characteristics of the Infants.*

Characteristic	Inhaled Nitric Oxide (N=210)	Placebo (N=210)
Birth weight — g	840 \pm 264	837 \pm 260
Gestational age — wk	26 \pm 2	26 \pm 2
Male sex — no. (%)	133 (63)	127 (60)
Mother's race or ethnic group — no. (%) [†]		
White	95 (45)	96 (46)
Black	69 (33)	78 (37)
Hispanic	36 (17)	32 (15)
Other	10 (5)	4 (2)
Born at study hospital — no. (%)	165 (79)	159 (76)
Prenatal corticosteroids — no. (%) [‡]	119 (70)	114 (67)
Delivery by cesarean section — no. (%)	144 (69)	139 (66)
Apgar scores <4 at 1 min — no. (%) [‡]	92 (55)	87 (52)
Apgar scores <4 at 5 min — no. (%) [‡]	27 (16)	22 (13)
Cause of respiratory failure — no. (%)		
Respiratory distress syndrome	192 (91)	190 (90)
Sepsis or pneumonia	6 (3)	10 (5)
Aspiration syndromes	1 (<1)	0
Idiopathic persistent pulmonary hypertension of the newborn	6 (3)	5 (2)
Suspected pulmonary hypoplasia	5 (2)	5 (2)

* Plus-minus values are means \pm SD.
[†] Race or ethnic group was self-reported.
[‡] Data were not available for all infants.

Table 2. Status of Infants at Randomization.*

Status	Inhaled Nitric Oxide (N=210)	Placebo (N=210)
Age — hr	26 \pm 23	28 \pm 22
Oxygenation index [†]	23 \pm 17	22 \pm 17
Surfactant — no. of doses given	2 \pm 1	2 \pm 1
Type of ventilation — no. (%)		
High-frequency oscillatory ventilation	116 (55)	116 (55)
High-frequency flow interruption	9 (4)	8 (4)
Conventional mechanical ventilation	85 (40)	86 (41)
Inotropic support — no. (%)	127 (60)	126 (60)
Sedation or analgesia — no. (%)	155 (74)	150 (71)
Paralytic agents — no. (%)	31 (15)	25 (12)
Postnatal corticosteroids — no. (%)	20 (10)	22 (10)
Pulmonary air leaks — no. (%)	26 (12)	31 (15)
Pulmonary hemorrhage — no. (%)	22 (10)	15 (7)
Seizures — no. (%)	8 (4)	6 (3)

* Plus-minus values are means \pm SD.
[†] The oxygenation index was calculated as $100 \times$ the fraction of inspired oxygen \times mean airway pressure (in centimeters of water) \div the partial pressure of arterial oxygen (in millimeters of mercury).

Table 3. Primary and Secondary Outcomes.*

Outcome	Inhaled Nitric Oxide (N=210)	Placebo (N=210)	Relative Risk (95% CI) [†]	P Value
Primary — no. (%)				
Death or bronchopulmonary dysplasia [‡]	167 (80)	170 (82)	0.97 (0.86–1.06)	0.52
Death	109 (52)	93 (44)	1.16 (0.96–1.39)	0.11
Bronchopulmonary dysplasia [§]	65 (60)	86 (68)	0.90 (0.75–1.08)	0.26
Secondary				
Grade 3 or 4 IVH or PVL — no. (%) [¶]	69 (39)	50 (32)	1.25 (0.95–1.66)	0.11
Oxygen use — days	84±63	91±61		0.91
Physiological bronchopulmonary dysplasia — no. (%) ^{**}	50 (50)	69 (60)	0.87 (0.68–1.10)	0.17
Length of hospitalization — days	101±47	111±48		0.65
Duration of ventilation — days	39±45	47±53		0.56
Incidence of air leak — no. (%)	35 (35)	37 (32)	1.12 (0.78–1.61)	0.55
Threshold retinopathy of prematurity — no. (%) ^{††}	29 (30)	36 (32)	1.16 (0.81–1.64)	0.42

* Plus-minus values are means ±SD. CI denotes confidence interval, IVH intraventricular hemorrhage, and PVL periventricular leukomalacia.

[†] Values were adjusted for center, birth-weight group, and oxygenation-index entry stratum.

[‡] The outcome of death or bronchopulmonary dysplasia is for 208 infants in the placebo group.

[§] This outcome is for infants who were alive at 36 weeks (109 in the group receiving inhaled nitric oxide and 127 in the placebo group).

[¶] Results of ultrasound examinations of the head were available for 179 infants in the group receiving inhaled nitric oxide and for 155 in the placebo group.

^{||} This outcome is for infants who survived (101 in the group receiving inhaled nitric oxide and 117 in the placebo group).

^{**} This outcome was defined according to the protocol of Walsh et al.,¹⁸ for 100 infants in the group receiving inhaled nitric oxide and for 115 infants in the placebo group.

^{††} Examination for retinopathy of prematurity was performed in 98 infants in the group receiving inhaled nitric oxide and 112 infants in the placebo group.

nificantly different between the group given inhaled nitric oxide and the placebo group according to concurrent local radiology readings (39 percent vs. 32 percent, respectively; relative risk, 1.25; 95 percent confidence interval, 0.95 to 1.66; $P=0.11$) (Table 3) or by central reading performed after the trial was terminated (37 percent vs. 38 percent; relative risk, 0.97; 95 percent confidence interval, 0.74 to 1.27; $P=0.81$). The local reading was based on the worst results of evaluation among ultrasound examinations of the head performed during the administration of the study gas, at 28 ± 3 days, and after 28 days of age. Ultrasound examinations of the head were not available for 86 infants, 93 percent of whom had died. Death occurred by 14 days in 91 percent and before 28 days in 98 percent. The central reading was based on the worst results of evaluation among all ultrasound examinations of the head performed during hospitalization. There were no significant differences in the two treatment groups with respect to the days on oxygen, the

length of assisted ventilation, the length of hospitalization, the incidence of air leak, threshold retinopathy of prematurity, or “physiological bronchopulmonary dysplasia” for survivors (Table 3).

Thirty minutes after administration of the study gas, at a concentration of 5 ppm, the group given inhaled nitric oxide had a significant increase in the PaO_2 and a significant decrease in the oxygenation index as compared with the placebo group (Table 4). The PaO_2 and the oxygenation index showed no significant change in either group when the concentration of the study gas was increased to 10 ppm. More than 70 percent of the infants in the placebo group did not have a response to the study gas; these infants had a significantly shorter length of time on the study gas (39 vs. 76 hours).

There were 26 deviations from the protocol. Five ineligible infants were randomly assigned to a study group. One infant received the wrong study gas. Four incidents of unblinding occurred. Sixteen infants received open-label inhaled nitric oxide: sev-

en after undergoing randomization to inhaled nitric oxide and nine after undergoing randomization to placebo.

SAFETY AND TOXICITY

In the group given inhaled nitric oxide, two infants had a methemoglobin level of at least 4 percent, and one had a level of at least 8 percent. In the placebo group, two infants had a methemoglobin level of at least 4 percent; neither received open-label inhaled nitric oxide. In the group given inhaled nitric oxide, nitrogen dioxide concentrations were at least 3 ppm in four infants and at least 5 ppm in two infants. No infants in the placebo group had elevated nitrogen dioxide concentrations (Table 4).

POST HOC ANALYSES

Post hoc analyses evaluated the relationship among birth weight (≤ 1000 g or > 1000 g), mode of ventilation (high-frequency ventilation or conventional mechanical ventilation), severity of illness (as measured by a median oxygenation index > 17 vs. ≤ 17) in terms of the primary outcomes, and the incidence of grade 3 or 4 intraventricular hemorrhage or periventricular leukomalacia (Table 5). The interaction between treatment assignment and birth weight had a significant effect on death ($P=0.02$) as well as on death or bronchopulmonary dysplasia ($P=0.02$).

Infants with a birth weight above 1000 g who were treated with inhaled nitric oxide had a significantly lower rate of death or bronchopulmonary dysplasia than infants in the placebo group (50 percent vs. 69 percent; relative risk, 0.72; 95 percent confidence interval, 0.54 to 0.96; $P=0.03$). Infants with a weight of 1000 g or less who were treated with inhaled nitric oxide, as compared with those in the placebo group, had higher mortality (62 percent vs. 48 percent; relative risk, 1.28; 95 percent confidence interval, 1.06 to 1.54; $P=0.01$) and a higher rate of severe intraventricular hemorrhage (43 percent vs. 33 percent; relative risk, 1.40; 95 percent confidence interval, 1.03 to 1.88; $P=0.03$).

The interaction between treatment group and type of ventilation had a significant effect on mortality ($P=0.03$). Infants receiving inhaled nitric oxide by means of conventional mechanical ventilation had a significantly increased rate of death as compared with infants receiving placebo by means of conventional mechanical ventilation (62 percent vs. 40 percent; relative risk, 1.46; 95 percent confidence interval, 1.10 to 1.92; $P=0.01$). Infants giv-

Table 4. Response to Study Gas.*

Variable	Inhaled Nitric Oxide (N=210)	Placebo (N=210)	P Value
Response to concentrations of 5 ppm — no.	208	204	
Increase in PaO ₂ — no. (%)			<0.001
<10 mm Hg	60 (29)	151 (74)	
10–20 mm Hg	30 (14)	18 (9)	
>20 mm Hg	118 (57)	35 (17)	
Change in PaO ₂ — mm Hg	57±88	8±53	<0.001
Change in oxygenation index	-8±13	1±17	<0.001
Response to concentrations of 10 ppm — no.	86	152	
Increase in PaO ₂ — no. (%)			0.24
<10 mm Hg	53 (62)	109 (72)	
10–20 mm Hg	18 (21)	26 (17)	
>20 mm Hg	15 (17)	17 (11)	
Change in PaO ₂ — mm Hg	8±35	10±37	0.68
Change in oxygenation index	-3±15	-1±11	0.29
Duration of administration of study gas — hr†	76±73	39±65	<0.001
Methemoglobin level $\geq 4\%$ — no. (%)	2 (1)	2 (1)	0.99
Methemoglobin level $\geq 8\%$ — no. (%)	1 (<1)	0	0.99
Nitrogen dioxide concentration ≥ 3.0 ppm — no. (%)	4 (2)	0	0.13
Nitrogen dioxide concentration ≥ 5.0 ppm — no. (%)	2 (1)	0	0.50

* Plus-minus values are means \pm SD. PaO₂ denotes the partial pressure of arterial oxygen.

† The duration was calculated only in infants with a response.

en inhaled nitric oxide as compared with those given placebo by means of conventional mechanical ventilation had similar oxygenation indexes at randomization (22.6 ± 19.2 vs. 17.6 ± 14.1 , $P=0.06$) and similar birth weights (814 ± 255 g vs. 853 ± 267 g, $P=0.33$). The interaction between the treatment group and the oxygenation index was not significant.

DISCUSSION

We found that the administration of inhaled nitric oxide as used in this trial for premature infants with severe respiratory failure did not reduce the combined incidence of death or bronchopulmonary dysplasia. There were no significant differences in the secondary outcomes.

Previous randomized trials of the use of inhaled

Table 5. Post Hoc Analysis According to Birth Weight, Type of Ventilation, and Oxygenation Index.*

Variable	Inhaled Nitric Oxide no. (%)	Placebo	Relative Risk (95% CI)†	P Value
Birth weight				
≤1000 g	158	158		
Death or bronchopulmonary dysplasia	141 (89)	133 (85)	1.04 (0.96–1.13)	0.29
Death	98 (62)	76 (48)	1.28 (1.06–1.54)	0.01
Bronchopulmonary dysplasia	49 (73)	65 (73)	1.02 (0.85–1.23)	0.84
Grade 3 or 4 IVH or PVL	55 (43)	39 (33)	1.40 (1.03–1.88)	0.03
>1000 g	52	52		
Death or bronchopulmonary dysplasia	26 (50)	35 (69)	0.72 (0.54–0.96)	0.03
Death	11 (21)	17 (33)	0.65 (0.36–1.18)	0.16
Bronchopulmonary dysplasia	16 (38)	21 (57)	0.68 (0.45–1.05)	0.08
Grade 3 or 4 IVH or PVL	14 (27)	11 (30)	0.95 (0.53–1.69)	0.86
Type of ventilation				
Conventional mechanical ventilation	85	86		
Death or bronchopulmonary dysplasia	69 (81)	63 (74)	1.04 (0.91–1.19)	0.55
Death	53 (62)	34 (40)	1.46 (1.10–1.92)	0.01
Bronchopulmonary dysplasia	17 (52)	33 (60)	0.90 (0.65–1.24)	0.53
Grade 3 or 4 IVH or PVL	29 (43)	24 (36)	1.20 (0.80–1.78)	0.37
High-frequency ventilation	125	124		
Death or bronchopulmonary dysplasia	98 (78)	105 (85)	0.93 (0.84–1.04)	0.21
Death	56 (45)	59 (48)	0.96 (0.75–1.24)	0.75
Bronchopulmonary dysplasia	48 (63)	53 (75)	0.89 (0.72–1.10)	0.29
Grade 3 or 4 IVH or PVL	40 (36)	26 (30)	1.41 (0.96–2.08)	0.08
Oxygenation index				
≤17	100	110		
Death or bronchopulmonary dysplasia	71 (71)	83 (75)	0.93 (0.81–1.08)	0.37
Death	45 (45)	40 (36)	1.27 (0.96–1.68)	0.09
Bronchopulmonary dysplasia	30 (51)	50 (66)	0.80 (0.61–1.06)	0.12
Grade 3 or 4 IVH or PVL	30 (33)	27 (30)	1.18 (0.79–1.76)	0.42
>17	110	100		
Death or bronchopulmonary dysplasia	96 (87)	85 (86)	1.02 (0.92–1.12)	0.75
Death	64 (58)	53 (53)	1.11 (0.88–1.40)	0.39
Bronchopulmonary dysplasia	35 (70)	36 (72)	0.98 (0.77–1.24)	0.85
Grade 3 or 4 IVH or PVL	39 (45)	23 (35)	1.38 (0.97–1.96)	0.07

* Data were not available for all infants in the categories of bronchopulmonary dysplasia and grade 3 or 4 intraventricular hemorrhage (IVH) or periventricular leukomalacia (PVL). Some infants had bronchopulmonary dysplasia and died. CI denotes confidence interval.

† Values were adjusted for center, birth-weight group, and oxygenation-index stratum.

nitric oxide in premature infants have shown varied results. In a trial of 80 premature infants with severe hypoxemic respiratory failure, Kinsella et al. reported a decrease in the number of days on a ventilator and a trend toward a decreased incidence of bronchopulmonary dysplasia.¹⁰ The Franco–

Belgian randomized trial of inhaled nitric oxide showed no significant decrease in bronchopulmonary dysplasia or death in a cohort of premature infants with a median oxygenation index of approximately 20.^{11,12} A recent trial by Schreiber et al. studied a less critically ill cohort with a median oxy-

generation index of 6.94 on mechanical ventilation after the use of surfactant.¹⁵ A significant decrease in bronchopulmonary dysplasia or death and severe intracranial hemorrhage was reported, but the benefit was confined to the cohort with an oxygenation index below 6.94.

The results of our trial may seem to be inconsistent with those of the trial of Schreiber et al. However, the infants enrolled in our trial were smaller and sicker than those in the trial of Schreiber et al. Benefit in the Schreiber trial was limited to infants with an oxygenation index below 6.94, but only 17 infants in our trial had an oxygenation index in this range. Benefit (i.e., decreased bronchopulmonary dysplasia or death) in our trial was evident only in infants with a birth weight above 1000 g (Table 5), and the patients in the trial of Schreiber et al. had significantly higher birth weights than those in our trial. Their trial also had a larger proportion of black infants, but our analysis did not reveal a significant effect of race on responses to inhaled nitric oxide.

The rate of intraventricular hemorrhage has been a concern in trials of preterm infants given inhaled nitric oxide, because nitric oxide is known to inhibit platelet aggregation and increase bleeding time.²³⁻²⁸ Two small pilot studies of the use of inhaled nitric oxide showed high rates of intraventricular hemorrhage,^{29,30} but larger randomized controlled trials have not confirmed those findings.¹⁰⁻¹⁵ Review of our data on intraventricular hemorrhage at the second planned interim analysis showed an increased rate of severe intraventricular hemorrhage or periventricular leukomalacia in the group given inhaled nitric oxide as compared with the placebo group (39 percent vs. 27 percent, $P=0.02$), but this difference was not significant at the conclusion of the trial. Severe intraventricular hemorrhage or periventricular leukomalacia as the cause of death was not significantly higher in the group given inhaled nitric oxide, although our

trial was not adequately powered to address this question.

Post hoc analyses suggested hypotheses that deserve further study. Infants with a birth weight above 1000 g seemed to benefit from inhaled nitric oxide therapy, with a decrease in the incidence of death or bronchopulmonary dysplasia without any increase in the rate of intraventricular hemorrhage. In contrast, infants with a birth weight of 1000 g or less who were treated with inhaled nitric oxide had an apparent increase in mortality and a higher rate of intraventricular hemorrhage. Infants receiving inhaled nitric oxide by means of conventional mechanical ventilation also seemed to have higher rates of death than those receiving inhaled nitric oxide by means of high-frequency ventilation. The article by Mestan et al. in this issue of the *Journal*³¹ documents improved neurodevelopmental outcome at 2 years of age in infants who received inhaled nitric oxide; neurodevelopmental follow-up at 18 to 22 months of age for the infants enrolled in our trial is in progress.

In conclusion, the use of inhaled nitric oxide in premature infants who had a birth weight of less than 1500 g and severe respiratory failure did not result in a decrease in the rate of death or bronchopulmonary dysplasia. The use of inhaled nitric oxide in premature infants born at less than 34 weeks of gestation should be confined to clinical trials until those who benefit can be identified.³²

Supported by grants from the National Institute of Child Health and Human Development (U10 HD34216, U10 HD27853, U10 HD27871, U10 HD40461, U10 HD40689, U10 HD27856, U10 HD27904, U10 HD40498, U10 HD40521, U01 HD36790, U10 HD21385, U10 HD27880, U10 HD27851, and U10 HD 21373) and from the General Clinical Research Centers Program (M01 RR08084, M01 RR06022, M01 RR00750, M01 RR00070, M01 RR00039, and M01 RR00044).

Drs. Steinhorn and Ehrenkranz report having served as consultants to INO Therapeutics. Dr. Konduri reports having received grant support, and Drs. Finer and Van Meurs lecture fees, from INO Therapeutics.

We are indebted to Drs. William Benitz, Susan Hintz, and William Rhine for their advice and review of the manuscript.

APPENDIX

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