

The New England Journal of Medicine

© Copyright, 1997, by the Massachusetts Medical Society

VOLUME 336

FEBRUARY 27, 1997

NUMBER 9



INHALED NITRIC OXIDE IN FULL-TERM AND NEARLY FULL-TERM INFANTS WITH HYPOXIC RESPIRATORY FAILURE

THE NEONATAL INHALED NITRIC OXIDE STUDY GROUP*

ABSTRACT

Background Neonates with pulmonary hypertension have been treated with inhaled nitric oxide because of studies suggesting that it is a selective pulmonary vasodilator. We conducted a randomized, multicenter, controlled trial to determine whether inhaled nitric oxide would reduce mortality or the initiation of extracorporeal membrane oxygenation in infants with hypoxic respiratory failure.

Methods Infants born after a gestation of ≥ 34 weeks who were 14 days old or less, had no structural heart disease, and required assisted ventilation and whose oxygenation index was 25 or higher on two measurements were eligible for the study. The infants were randomly assigned to receive nitric oxide at a concentration of 20 ppm or 100 percent oxygen (as a control). Infants whose partial pressure of arterial oxygen (PaO_2) increased by 20 mm Hg or less after 30 minutes were studied for a response to 80-ppm nitric oxide or control gas.

Results The 121 infants in the control group and the 114 in the nitric oxide group had similar base-line clinical characteristics. Sixty-four percent of the control group and 46 percent of the nitric oxide group died within 120 days or were treated with extracorporeal membrane oxygenation ($P=0.006$). Seventeen percent of the control group and 14 percent of the nitric oxide group died (P not significant), but significantly fewer in the nitric oxide group received extracorporeal membrane oxygenation (39 percent vs. 54 percent, $P=0.014$). The nitric oxide group had significantly greater improvement in PaO_2 (mean [\pm SD] increase, 58.2 ± 85.2 mm Hg, vs. 9.7 ± 51.7 mm Hg in the controls; $P<0.001$) and in the oxygenation index (a decrease of 14.1 ± 21.1 , vs. an increase of 0.8 ± 21.1 in the controls; $P<0.001$). The study gas was not discontinued in any infant because of toxicity.

Conclusions Nitric oxide therapy reduced the use of extracorporeal membrane oxygenation, but had no apparent effect on mortality, in critically ill infants with hypoxic respiratory failure. (N Engl J Med 1997; 336:597-604.)

©1997, Massachusetts Medical Society.

HYPOXIC respiratory failure in neonates born at or near term (at ≥ 34 weeks' gestation) may be caused by conditions such as primary persistent pulmonary hypertension, respiratory distress syndrome, aspiration of meconium, pneumonia or sepsis, and congenital diaphragmatic hernia.^{1,2} Conventional therapy, short of extracorporeal membrane oxygenation, involves support with oxygen, mechanical ventilation, and the induction of alkalosis, neuromuscular blockade, and sedation.³⁻⁶ None of these therapies have been found to reduce mortality or the need for extracorporeal membrane oxygenation. To date, selective pulmonary vasodilators free of systemic side effects have not been studied in large trials of neonates.⁷

Nitric oxide, or endothelium-derived relaxing factor, is important in regulating vascular muscle tone.⁸⁻¹³ In newborn lambs with pulmonary hypertension induced by hypoxia, the inhalation of 40 to 80 parts per million (ppm) of nitric oxide reversed pulmonary vasoconstriction without affecting the systemic circulation.¹⁴⁻¹⁶ Two recent studies of neonates with severe persistent pulmonary hypertension have shown that inhaled nitric oxide rapidly improved preductal oxygen saturation, without detectable toxic effects.^{17,18} A prospective study of multiple randomized doses of inhaled nitric oxide in infants referred for extracorporeal membrane oxygenation did not find a correlation between the dose of nitric oxide and the degree of improvement in oxygenation.¹⁹ We conducted a prospective, multicenter, randomized, controlled, double-blind trial to evaluate whether inhaled

Address reprint requests to Dr. Richard A. Ehrenkranz at the Department of Pediatrics, Yale University School of Medicine, P.O. Box 208064, 333 Cedar St., New Haven, CT 06520-8064.

Dr. Ehrenkranz, as co-principal investigator of the study, assumes responsibility for the overall content and integrity of the article.

*The members of the Neonatal Inhaled Nitric Oxide Study Group are listed in the Appendix.

nitric oxide would reduce mortality or the need for extracorporeal membrane oxygenation in infants born at or near term who had hypoxic respiratory failure that was unresponsive to aggressive conventional therapy.

METHODS

Study Hypotheses

The primary hypothesis in the study was that administering inhaled nitric oxide to infants born at 34 or more weeks of gestation who had hypoxic respiratory failure and an oxygenation index of 25 or higher would reduce the risk of death by day 120 or the initiation of extracorporeal membrane oxygenation from 50 percent in control infants to 30 percent in infants given nitric oxide, a relative reduction of 40 percent. The oxygenation index was calculated as the mean airway pressure times the fraction of inspired oxygen (FiO_2) divided by the partial pressure of arterial oxygen (PaO_2) times 100.

The secondary hypothesis was that 30 minutes after the start of treatment, inhaled nitric oxide would increase PaO_2 and decrease the oxygenation index and the alveolar-arterial oxygen gradient. We hypothesized that among the surviving infants, treatment with inhaled nitric oxide would shorten hospitalization without increasing the duration of assisted ventilation or the incidence of air leakage, bronchopulmonary dysplasia, or neurodevelopmental disability at 18 to 24 months.

Study Patients

Infants born at 34 or more weeks of gestation who required assisted ventilation for hypoxic respiratory failure and had an oxygenation index of at least 25 on two measurements made at least 15 minutes apart were eligible for the trial. Hypoxic respiratory failure was caused by persistent pulmonary hypertension, meconium aspiration, pneumonia or sepsis, respiratory distress syndrome, or suspected pulmonary hypoplasia associated with oligohydramnios and premature rupture of the membranes. All the infants were required to have an indwelling catheter and to undergo echocardiography before randomization. Echocardiographic evidence of pulmonary hypertension was not required, because studies have shown that inhaled nitric oxide improves the matching of ventilation with perfusion and may reduce intrapulmonary shunting in the absence of a direct intracardiac shunt.^{20,21}

Infants were considered ineligible for the study if they were more than 14 days old, had a congenital diaphragmatic hernia, or were known to have congenital heart disease, or if it had been decided not to provide full treatment. The study centers attempted to obtain a cranial ultrasonogram before enrolling an infant in the study. Consent was obtained from the parents or guardians before the infants underwent randomization, and each study center obtained approval from the institutional review board before enrollment began. Copies of the study protocol are available from the authors on request.

Guidelines for Management

The approach to care before enrollment was not specified by the study protocol. Each participating center developed general management guidelines to be used throughout the study and agreed to use the most aggressive forms of conventional therapy before randomization. These guidelines included the maintenance of a mean arterial blood pressure above 45 mm Hg, the induction of alkalosis (range of target pH, 7.45 to 7.6), and treatment with bovine surfactant (BLES, BLES Biochemicals, London, Ont., Canada; or Survanta, Abbott Laboratories, Columbus, Ohio) before the start of treatment with the study gas. The protocol specified that the mode of ventilation (conventional or high frequency) could not be changed after randomization, except as part of weaning from assisted ventilation.

Randomization

The infants were stratified according to study center and randomly assigned by telephone to receive either 100 percent oxygen (the control treatment) or nitric oxide according to a permuted-block design developed and implemented by the coordinating center.

Administration and Monitoring of Study Gas

If treatment with the study gas could be started within 15 minutes after the second qualifying oxygenation-index score was obtained, the arterial-blood gas values from that measurement served as the base-line values in assessing the response to the study treatment. If the treatment could not be started within the 15-minute period, a third measurement of arterial-blood gas, obtained before the administration of the study gas, was used to determine the base-line value. Primary-grade nitric oxide was supplied in a concentration of 800 ppm in balanced nitrogen (Canadian Liquid Air, Montreal; and Ohmeda, Liberty Corner, N.J.); the gas was certified to be within ± 1 percent of the stated nitric oxide content and to contain less than 5 ppm of nitrogen dioxide. The gas mixture was sampled after it entered the injection site of the inspiratory circuit and before it reached the infant's endotracheal tube and was analyzed continuously for nitric oxide and nitrogen dioxide with chemiluminescence (model 42H, Thermo Environmental Instruments, Franklin, Mass.; and model CLD 700AL, ECO Physics, Durten, Switzerland) or with electrochemical analyzers (Pulmonox II, Pulmonox, Tolfeld, Alta., Canada; and Dräger Prac II, Dräger, Chantilly, Va.). Quality-control procedures ensured accurate calibration and prevented the supply tank of nitric oxide gas from being contaminated.

Except when the treatment was initiated and when the concentration of the study gas was changed, the infants were cared for by clinical teams unaware of each infant's treatment assignment; the randomization was performed, the gas administered, and safety monitored by designated persons who were not involved in the clinical care. Levels of inspired oxygen, nitric oxide, and nitrogen dioxide were recorded every two hours and after the settings of the ventilator were changed. We kept the clinical teams unaware of the treatment assignments by making mock adjustments in the case of the control infants, covering the analyzer readings and the gas tanks, and sampling the supply of oxygen before the injection site of the study gas.

A response to treatment was defined according to the change from base line in the PaO_2 30 minutes after the initial exposure to the study gas (a complete response was defined as an increase of more than 20 mm Hg; a partial response, as an increase of 10 to 20 mm Hg; and no response, as an increase of less than 10 mm Hg) when the two measurements were made at comparable sampling sites. When an infant had a complete response, treatment with the study gas (either nitric oxide at a concentration of 20 ppm or 100 percent oxygen) was continued. When an infant had less than a complete response, the treatment was stopped for 15 minutes if the stoppage was tolerated, the arterial-blood gases were measured again, and then the study gas was administered at a maximal concentration of 80 ppm. Arterial-blood gases were measured again 30 minutes later. Infants who had complete responses to the maximal concentration continued to be treated at that concentration; in infants with partial responses, treatment was continued at the lowest concentration of gas that produced at least a partial response. If an infant had no response with either the 20-ppm or the 80-ppm concentration of gas, treatment was discontinued. Gas was also discontinued in any infant whose condition deteriorated (absolute decrease in oxygen saturation, >10 percent) before the end of the initial phase of administration at either the high or the low concentration, and such infants were classified as having no response. When an infant did not respond to the initial administration of the study gas, the treatment could be attempted again as many as three times at six-hour intervals. No crossover between study groups was allowed.

If an infant continued to receive the study gas after the initial

dosing algorithm, the gas was monitored in an unmasked fashion by designated persons who were not involved with the infant's clinical care. The protocol suggested algorithms for weaning infants from the study gas, escalating the dose of gas after the occurrence of clinical deterioration, and starting treatment again after successful weaning. The study protocol permitted treatment with the study gas for a cumulative maximum of 336 hours (14 days). Decisions about initiating extracorporeal membrane oxygenation were made by the blinded clinical team on the basis of center-specific criteria.

Monitoring of Safety

Blood methemoglobin concentrations were measured 1, 3, 6, and 12 hours after the start of treatment with the study gas and every 12 hours thereafter until 24 hours after the treatment ended. Methemoglobin levels of 5 to 10 percent were managed by reducing the concentration of study gas by half until the level fell below 5 percent. The study gas was discontinued if the methemoglobin level exceeded 10 percent. If the concentration of nitrogen dioxide exceeded 7 ppm, the study gas was discontinued; the gas was decreased by half if the concentration was 5 to 7 ppm.

The infants were monitored for signs of bleeding. Cranial ultrasonography was performed before randomization and 24 hours after the final discontinuation of the study gas. All the readings were done by local ultrasonographers.²²

Statistical Analysis

According to the data from the participating centers, we estimated that mortality or the use of extracorporeal membrane oxygenation in infants with an oxygenation-index score between 25 and 40 would be 50 percent. To demonstrate a 40 percent reduction in the primary outcome with a power of 0.90 and a two-tailed alpha of 0.05, 125 patients were required in each group. The primary analysis was an intention-to-treat analysis.

Continuous variables were compared by t-tests or Wilcoxon tests, and discrete variables were compared by chi-square tests. The Gart test was used to evaluate the homogeneity of relative risks.²³

The trial was monitored by an independent Data Safety and Monitoring Committee, which planned evaluations after approximately one third and two thirds of the study patients were enrolled. To reduce the overall probability of a type I error as much as possible, significance was tested at each interim analysis by the group-sequential method of Lan and DeMets with the O'Brien-Fleming spending function.²⁴ Results are presented as means ±SD.

RESULTS

The trial was terminated at the recommendation of the Data Safety and Monitoring Committee after the second planned review of data, which showed that the z value had crossed the predetermined boundary of statistical significance. After the recommendation was reviewed and accepted by the National Institute of Child Health and Human Development and the investigators, recruitment ceased on May 2, 1996.

Base-Line Characteristics

Two hundred thirty-five infants were enrolled in the trial. There were no significant differences between the study groups in the characteristics of the patients (Table 1), treatment methods, or status at the time of randomization (Table 2). Seventy-two percent of the controls and 71 percent of the treated infants received surfactant before randomization, and

TABLE 1. CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	CONTROL GROUP (N=121)	NITRIC OXIDE GROUP (N=114)
Birth weight — g	3359±597	3460±578
Gestational age — wk	38.9±2.2	39.3±1.8
Male sex — no. (%)	76 (62.8)	63 (55.3)
Race — no. (%)†		
Black	19 (16.0)	19 (17.1)
White	72 (60.5)	70 (63.1)
Hispanic	17 (14.3)	13 (11.7)
Other	11 (9.2)	9 (8.1)
Not born in treating facility — no. (%)	93 (76.9)	92 (80.7)
Age at admission‡		
<12 hr	47 (50.5)	41 (45.1)
12–24 hr	20 (21.5)	20 (22.0)
>24 hr	26 (28.0)	30 (33.0)
1-Minute Apgar score <3 — no. (%)§	25 (20.8)	28 (24.8)
Primary diagnosis — no. (%)		
Persistent pulmonary hypertension of the newborn	22 (18.2)	19 (16.7)
Respiratory distress syndrome	15 (12.4)	10 (8.8)
Meconium aspiration syndrome	58 (47.9)	58 (50.9)
Pneumonia or sepsis	24 (19.8)	26 (22.8)
Other	2 (1.7)	1 (0.9)

*Plus-minus values are means ±SD.

†Data on race are based on 119 infants in the control group and 111 infants in the nitric oxide group.

‡Data for this variable are based on 93 infants in the control group and 91 infants in the nitric oxide group.

§Data for this variable are based on 120 infants in the control group and 113 infants in the nitric oxide group.

50 percent and 49 percent, respectively, received it within six hours before randomization. High-frequency ventilation, primarily oscillatory, was used in 55 percent of both groups; 37 percent of the controls and 32 percent of the treated infants received such treatment at randomization. Over 90 percent of all the infants received volume support, vasopressor support, neuromuscular blockade, and sedation before randomization (Table 2).

The causes of hypoxic respiratory failure are shown in Table 1. Forty-nine percent of all randomized infants had meconium aspiration syndrome; 17 percent had persistent pulmonary hypertension. Echocardiography was performed before randomization in 228 infants (97 percent); of the 226 infants for whom complete data were available, 78 percent had evidence of pulmonary hypertension (right-to-left or bidirectional shunting, tricuspid-valve regurgitation, or both). There was no difference in the prevalence of pulmonary hypertension between the study groups.

Randomization occurred 1.7±2.3 days after birth for the controls and 1.7±1.8 days after birth for the treated infants (Table 2). Data from the first qualifying arterial-blood gas measurement are also shown in Table 2; on the second qualifying measurement, the oxygenation index was 46.3±19.9 in the control

TABLE 2. TREATMENT VARIABLES AND STATUS OF THE PATIENTS AT RANDOMIZATION.*

VARIABLE	CONTROL GROUP (N = 121)	NITRIC OXIDE GROUP (N = 114)
Treatment — no. of patients (%)		
Volume support	116 (96.7)†	108 (94.7)
Vasopressor support	121 (100.0)	108 (94.7)
Tolazoline	16 (13.3)†	23 (20.2)
Sedation or analgesia	120 (99.2)	113 (99.1)
Neuromuscular blockade	115 (95.0)	107 (93.9)
Alkalosis	106 (87.6)	88 (77.2)
Surfactant	87 (71.9)	81 (71.1)
High-frequency ventilation	67 (55.4)	63 (55.3)
Air leaks — no. of patients (%)	25 (20.7)	20 (17.5)
Pulmonary hemorrhage — no. of patients (%)	22 (18.2)	18 (15.8)
First qualifying arterial-blood gas value		
Oxygenation index	45.1±22.4	43.0±17.6
Mean airway pressure (cm of water)	18.3±4.4	18.3±4.3
FiO ₂ (mm Hg)	1.0±0.0	1.0±0.0
PaO ₂ (mm Hg)	45.5±13.9	46.8±15.5
Alveolar-arterial oxygen gradient (mm Hg)	613.7±40.3	616.1±33.5
Age at randomization (days)	1.7±2.3	1.7±1.8
Median time, randomization to study-gas initiation (min)‡	10.0	15.0

*Plus-minus values are means ±SD. FiO₂ denotes fraction of inspired oxygen, and PaO₂ partial pressure of arterial oxygen.

†A total of 120 patients were studied for this variable.

‡Data for this variable are based on 117 infants in the control group and 113 in the nitric oxide group.

group and 47.3±31.3 in the nitric oxide group. Sixty-two percent of the control group and 64 percent of the nitric oxide group had a third arterial-blood gas measurement before treatment with the study gas was begun. The median time from randomization to the administration of the study gas was 10 minutes in the control group and 15 minutes in the nitric oxide group (Table 2). Five randomized infants (four in the control group and one in the nitric oxide group) did not receive study gas.

Primary Outcome

The incidence of the primary outcome (death by 120 days of age or the initiation of extracorporeal membrane oxygenation) was significantly lower in the nitric oxide group than in the control group (46 percent vs. 64 percent; relative risk, 0.72; 95 percent confidence interval, 0.57 to 0.91; P = 0.006, a significant difference given the Lan-DeMets cutoff of 0.044) (Table 3). Thirty-six infants died, among whom 17 (9 in the control group and 8 in the nitric oxide group) received extracorporeal membrane oxygenation. Among the other 19 infants who died, 10 (5 in each group) had contraindications to extracorporeal membrane oxygenation; 5 (3 in the control group and 2 in the nitric oxide group) had their life support withdrawn; and 4 (3 and 1 in the respective groups) did not meet center-specific criteria for

TABLE 3. OUTCOMES OF ADMINISTRATION OF THE STUDY GAS, ACCORDING TO GROUP.*

OUTCOME	CONTROL GROUP (N = 121)	NITRIC OXIDE GROUP (N = 114)	P VALUE
Death by day 120 or ECMO — no. (%)	77 (63.6)	52 (45.6)	0.006
Death — no. (%)	20 (16.5)	16 (14.0)	0.60
ECMO — no. (%)	66 (54.5)	44 (38.6)	0.014
Change in PaO ₂ — mm Hg	9.7±51.7	58.2±85.2	<0.001
Change in oxygenation index	0.8±21.1	-14.1±21.1	<0.001
Change in alveolar-arterial oxygen gradient — mm Hg	-6.7±57.5	-60.0±85.1	<0.001
Outcomes in surviving infants			
Length of hospitalization — days	29.5±22.6	36.4±44.8	0.17
Duration of assisted ventilation — days	11.7±13.0	11.6±7.0	0.97
Air leak after randomization — no. (%)	5 (5.1)	5 (5.2)	0.96
Bronchopulmonary dysplasia — no. (%)†	12 (11.9)	15 (15.3)	0.48

*Plus-minus values are means ±SD. ECMO denotes extracorporeal membrane oxygenation, and PaO₂ partial pressure of arterial oxygen.

†This condition was considered to be present when there was dependence on oxygen at the age of 28 days accompanied by abnormal results on chest radiography.

extracorporeal membrane oxygenation. There were no differences between the groups in the causes of death. The infants in the nitric oxide group received extracorporeal membrane oxygenation less often (39 percent) than the controls (55 percent, $P=0.014$) (Table 3). The median time from randomization to the initiation of extracorporeal membrane oxygenation was 4.4 hours in the control group and 6.7 hours in the nitric oxide group ($P=0.04$).

Secondary Outcomes

Among the surviving infants, there were no differences between the groups with respect to the length of hospitalization, the number of days of respiratory support (assisted ventilation, continuous positive airway pressure, or oxygen), or the incidence of air leakage or bronchopulmonary dysplasia (Table 3).

Thirty minutes after the administration of the study gas began, the infants in the nitric oxide group had a significantly greater mean increase in PaO₂ than the controls (58.2 ± 85.2 vs. 9.7 ± 51.7 mm Hg), a significantly greater change in the oxygenation index (a decrease of 14.1 ± 21.1 as compared with an increase of 0.8 ± 21.1), and a significantly greater decrease in the alveolar-arterial oxygen gradient (60.0 ± 85.1 vs. 6.7 ± 57.5 mm Hg; $P<0.001$ for all three comparisons) (Table 3).

More infants in the nitric oxide group than in the

control group had at least a partial response to the initial administration of the study gas (66 percent vs. 26 percent, $P<0.001$) (Table 4). Of the 125 infants who had no response to 20-ppm nitric oxide or control gas, similar proportions of the nitric oxide group (18 percent [7 of 38]) and the control group (20 percent [17 of 87]) had at least partial responses to 80-ppm nitric oxide or control gas ($P=0.30$). Of the 30 infants who had partial responses to the study gas at 20 ppm, 29 percent of the nitric oxide group (5 of 17) and 8 percent of the control group (1 of 13) had at least a partial response at 80 ppm ($P=0.34$). Therefore, a majority of the infants who did not have complete responses at the 20-ppm concentration and who were evaluated at the 80-ppm concentration had no response to the study gas at the higher concentration (nitric oxide group, 77 percent [41 of 53]; control group, 81 percent [75 of 93]).

According to the study protocol, three additional trials were permitted, but only 10 infants (6 in the control group and 4 in the nitric oxide group) underwent such trials. Twenty-eight infants assigned to the control group (23 percent) received the study gas for more than 24 hours, as compared with 64 infants assigned to the nitric oxide group (56 percent) (median duration of gas administration, 2 hours vs. 40 hours; $P<0.001$). Among the infants who had responses to either the 20-ppm or the 80-ppm concentration of

TABLE 4. RESPONSES TO THE INITIAL ADMINISTRATION OF 20-PPM NITRIC OXIDE OR OXYGEN, AND SUBSEQUENT RESPONSES TO 80-PPM CONCENTRATIONS OF STUDY GAS BY INFANTS WHOSE RESPONSES TO THE INITIAL TREATMENT WERE LESS THAN COMPLETE.*

VARIABLE	CONTROL GROUP	NITRIC OXIDE GROUP	P VALUE†
	no. of patients (%)		
Response to treatment at 20 ppm			
No. of infants	117	112	
None	87 (74.4)	38 (33.9)	<0.001
Partial	13 (11.1)	17 (15.2)	
Complete	17 (14.5)	57 (50.9)	
Subsequent response to treatment at 80 ppm			
Infants with no response at 20 ppm			
None	64 (73.6)	29 (76.3)	0.30
Partial	5 (5.7)	5 (13.2)	
Complete	12 (13.8)	2 (5.3)	
80 ppm not tried	6 (6.9)	2 (5.3)	
Infants with partial responses at 20 ppm			
None	11 (84.6)	12 (70.6)	0.34
Partial	1 (7.7)	4 (23.5)	
Complete	0	1 (5.9)	
80 ppm not tried	1 (7.7)	0	

*Data on 229 infants are shown because 4 infants in the control group and 1 in the nitric oxide group did not receive study gas and data on 1 infant treated with nitric oxide were unavailable because of mechanical problems with gas delivery. Seven infants (six in the nitric oxide group and one in the control group) who received the wrong study gas are included in the table under their assigned treatments.

†P values are for the comparison between groups with respect to the number of infants with either a partial or a complete response to the study gas.

TABLE 5. RESULTS OF THE SUBGROUP ANALYSIS.

VARIABLE	NO. OF PATIENTS*	PERCENT WITH IMPROVED OXYGENATION†		PERCENT WITH PRIMARY OUTCOME‡		RELATIVE RISK (95% CI)§
		CONTROL	NITRIC OXIDE	CONTROL	NITRIC OXIDE	
		Primary diagnosis				
Persistent pulmonary hypertension	41	14	61	73	32	0.43 (0.23–0.81)
Respiratory distress syndrome	25	8	60	47	50	1.07 (0.46–2.49)
Meconium aspiration	116	16	47	62	52	0.83 (0.61–1.15)
Pneumonia or sepsis	50	17	52	67	39	0.58 (0.33–1.00)
Pulmonary hypertension found by echocardiography						
Yes	176	15	54	65	47	0.72 (0.55–0.94)
No	50	14	44	50	39	0.79 (0.42–1.48)
Surfactant						
Yes	168	14	51	54	38	0.71 (0.51–0.99)
No	67	15	50	88	64	0.72 (0.55–0.95)
High-frequency ventilation						
Yes	130	14	57	66	46	0.70 (0.51–0.96)
No	105	16	43	61	45	0.74 (0.51–1.06)
Surfactant and high-frequency ventilation						
Both	88	13	59	57	37	0.64 (0.40–1.00)
Neither	25	14	40	93	64	0.69 (0.45–1.04)
Oxygenation index						
25.0–29.9	53	7	76	61	28	0.46 (0.24–0.88)
30.0–39.9	72	27	42	42	47	1.13 (0.67–1.91)
40.0–59.9	74	11	51	76	47	0.62 (0.43–0.89)
≥60.0	35	11	27	84	69	0.82 (0.56–1.18)

*Data on primary diagnosis are based on 232 patients; on pulmonary hypertension found by echocardiography, 226; and on oxygenation index, 234.

†Improved oxygenation was defined as a complete response (an increase of more than 20 mm Hg in the partial pressure of arterial oxygen) to the administration of 20-ppm nitric oxide or control gas at 30 minutes.

‡The primary study outcome was death by 120 days of age or the initiation of extracorporeal membrane oxygenation.

§Relative risks shown are for the occurrence of the primary study outcome in the nitric oxide group as compared with the control group. CI denotes confidence interval.

study gas when it was first administered, 62 percent of those in the nitric oxide group (50 of 81) were successfully weaned, as compared with 40 percent of those in the control group (19 of 47). Among the infants successfully weaned, three of those in the control group and two of those in the nitric oxide group had the study gas administered again.

Post hoc subgroup analyses were performed to evaluate the relations between each of several variables — the primary diagnosis, the presence or absence of echocardiographic evidence of pulmonary hypertension, the first qualifying oxygenation-index score, and treatment with surfactant before randomization, the use of high-frequency ventilation at the time of randomization or earlier, or the use of both surfactant and ventilation — and the incidence of the primary outcome and a complete response to the study gas (Table 5). Tests of homogeneity did not show significant differences between the relative risks. Therefore, there was no conclusive evidence, when the nitric oxide group was compared with the control group, that the relative risk either of the primary outcome or of a complete response to nitric

oxide was related to any of the variables studied in the subgroup analysis.

Safety and Toxicity

The study gas was not discontinued in any infant because of toxic effects. In the nitric oxide group, the mean peak level of nitrogen dioxide was 0.8 ± 1.2 ppm, and the mean peak methemoglobin level was 2.4 ± 1.8 percent. The concentration of inhaled nitric oxide was reduced in 11 infants in the nitric oxide group because of elevated methemoglobin levels (5 to 10 percent).

There were no significant differences between the groups after randomization in the overall incidence or severity of intracranial hemorrhage (total number, 19 in the control group and 18 in the nitric oxide group; grade IV, 8 and 5, respectively). There were also no significant differences between the control group and the nitric oxide group in the occurrence of periventricular leukomalacia (6 vs. 3), brain infarction (7 vs. 7), seizures requiring anticonvulsive therapy (16 vs. 24), and either pulmonary (4 vs. 6) or gastrointestinal (1 vs. 1) hemorrhage.

There were 21 deviations from the protocol. Two infants who were ineligible for the study were randomized: one had a cystic adenomatoid malformation, and the other had a qualifying oxygenation-index score of 24.4. One infant randomly assigned to nitric oxide received oxygen, and six controls received nitric oxide. Two infants received doses of nitric oxide in excess of 80 ppm: 100 ppm for 36 minutes in one, and 101 ppm for 60 minutes in the other. The methemoglobin level in the latter was 6 percent, and the nitrogen dioxide concentration 5.1 ppm; these levels decreased when the dose of nitric oxide was lowered. Two infants received 80-ppm nitric oxide in error, after having complete responses to the 20-ppm concentration. There were eight episodes in which the patient's study assignment became apparent because of equipment leaks or elevated methemoglobin values.

DISCUSSION

This trial demonstrated that nitric oxide therapy reduced the incidence of death or extracorporeal membrane oxygenation in a cohort of full-term and nearly full-term infants with hypoxic respiratory failure who did not respond to aggressive conventional therapy. Furthermore, besides testing clinically important outcomes, the study was designed as a management trial whose findings could serve as the basis of recommendations for practice. Although inhaled nitric oxide reduced the combined outcome of death or the initiation of extracorporeal membrane oxygenation, it did not significantly reduce mortality, which was 17 percent in the control group and 14 percent in the nitric oxide group. The causes of death in the two groups did not differ. Among infants who received extracorporeal membrane oxygenation, overall mortality was 16 percent (14 percent in the control group and 18 percent in the nitric oxide group).

Several open-label studies preceding this trial reported improved oxygenation in infants with severe persistent pulmonary hypertension who were treated with initial doses of nitric oxide ranging from 5 to 80 ppm.¹⁷⁻¹⁹ In the current trial, 47 percent of the infants treated with nitric oxide (53 of 112) received the 80-ppm concentration after having less than a complete response at 20 ppm. Only 15 percent of those infants (8 of 53) had improved responses (3 complete and 5 partial) at 80 ppm, suggesting that limited numbers of infants will benefit from higher doses of nitric oxide.

Nitric oxide treatment appears safe at the concentrations and durations used in this trial. However, the protocol was designed to reduce the likelihood of dose-related toxic effects by encouraging the use of the lowest effective dose. There was no evidence of toxic effects as determined on the basis of elevated levels of nitrogen dioxide, persistently elevated methemoglobin levels, systemic hypotension, or evi-

dence of increased bleeding. The effect of inhaled nitric oxide on coagulation, platelet aggregation, and adhesion is unclear.²⁵⁻²⁷ The study was not designed to evaluate the formation of peroxynitrites or evidence of other tissue damage that could potentially accompany the administration of nitric oxide.^{28,29} Nor was it designed to determine the lowest effective dose of nitric oxide. Further research will be required to address these issues. All the infants in the current trial will receive a blinded neurodevelopmental evaluation at the age of 18 to 24 months.

We intended to treat infants who had an oxygenation index of 25 or above (50 percent risk of requiring extracorporeal membrane oxygenation or dying), but the majority had three oxygenation-index determinations exceeding 40 within a two-hour period, thereby meeting the most common criterion for extracorporeal membrane oxygenation before they were randomized.³⁰ Before extracorporeal membrane oxygenation was widely available, oxygenation indexes in this range predicted a risk of mortality of approximately 80 percent.³⁰ Although post hoc subgroup analyses did not show a significant difference in the relative risks, infants with the lowest oxygenation indexes appeared more likely to have complete responses to the initial administration of nitric oxide and to survive without extracorporeal membrane oxygenation, suggesting that the earlier use of nitric oxide may be beneficial. This question should be tested in a prospective trial. In the interim, nitric oxide therapy should not be delayed until the infant's condition is so unstable that transfer for extracorporeal membrane oxygenation would be difficult or impossible. We believe that appropriate support by conventional means, including the use of surfactant and high-frequency ventilation by experienced practitioners, should precede the administration of inhaled nitric oxide. If such management does not lead to improvement, however, treatment with nitric oxide, whether there is echocardiographic evidence of pulmonary hypertension or not, will substantially reduce the number of infants who receive extracorporeal membrane oxygenation.

Inhaled nitric oxide reduced the use of extracorporeal membrane oxygenation in critically ill neonates born at or near term with hypoxic respiratory failure who had received maximal conventional therapy. Nitric oxide therapy was safe, well tolerated, and relatively easy to administer.

Supported in part by the Canadian Medical Research Council and by grants (U10 HD21364, U10 HD21385, U10 HD21415, U10 HD27853, U10 HD27856, U10 HD27871, U10 HD27880, U10 HD27881, U10 HD27904, and U01 HD19897) from the National Institute of Child Health and Human Development (NICHD).

We are indebted to Ohmeda, a member of the BOC Group, for supplying nitric oxide to the NICHD Neonatal Research Network Centers.

APPENDIX

The Neonatal Inhaled Nitric Oxide Study was a collaboration of the 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, E. Gorjanc; *George Washington University, Biostatistics Center, Rockville, Md.* — J. Verter,* N. Younes, B.A. Stenzel, T. Powers; *Indiana University, Indianapolis* — G. Sokol,* D. Appel; *NICHD, Bethesda, Md.* — L.L. Wright,* S.J. Yaffe, C. Catz; *Stanford University, Palo Alto, Calif.* — K. Van Meurs, W. Rhine,* B. Ball; *University of Cincinnati, Cincinnati* — R. Brill, L. Moles; *University of New Mexico, Albuquerque* — M. Crowley, C. Backstrom; *University of Tennessee at Memphis* — D. Crouse, T. Hudson; *Wayne State University, Detroit* — G. Konduri,* R. Bara; *Women and Infants' Hospital, Providence, R.I.* — M. Kleinman, A. Hensman, R.W. Rothstein; *Yale University, New Haven, Conn.* — R.A. Ehrenkrantz* (co-principal investigator). **Canadian Inhaled Nitric Oxide Study Group:** *British Columbia Children's Hospital, Vancouver* — A. Solimano,* F. Germain; *Children's Hospital of Eastern Ontario, Ottawa* — R. Walker, A.M. Ramirez; *Foothills Hospital, Calgary, Alta.* — N. Singhal, L. Bourcier; *Health Sciences Center, Winnipeg, Man.* — C. Fajardo, V. Cook; *McMaster University, Hamilton, Ont.* — H. Kirpalani,* S. Monkman; *Montreal Children's Hospital, Montreal* — A. Johnston,* K. Mullahoo; *Royal Alexandra Hospital, Edmonton, Alta.* — N.N. Finer* (co-principal investigator), A. Peliowski, P. Etches, B. Kamstra; *Royal University Hospital, Saskatoon, Sask.* — K. Sankarhan, A. Riehl; *Université de Sherbrooke, Sherbrooke, Que.* — P. Blanchard, R. Gouin; *Texas Children's Hospital, Houston* — M. Wearden, M. Gomez, Y. Moon. **NICHD Neonatal Research Steering Committee:** *University of Miami, Miami* — C.R. Bauer; *University of Cincinnati, Cincinnati* — E.F. Donovan; *Yale University, New Haven, Conn.* — R.A. Ehrenkrantz; *Case Western Reserve University, Cleveland* — A.A. Fanaroff; *University of Tennessee at Memphis* — S.B. Korones; *Indiana University, Indianapolis* — J.A. Lemons; *Women and Infants' Hospital, Providence, R.I.* — W. Oh; *University of New Mexico, Albuquerque* — L.A. Papile; *Wayne State University, Detroit* — S. Shankaran; *Stanford University, Palo Alto, Calif.* — D.K. Stevenson; *Emory University, Atlanta* — B.J. Stoll; *University of Texas Southwestern Medical Center, Dallas* — J.E. Tyson; *George Washington University, Biostatistics Center, Rockville, Md.* — J. Verter; *NICHD, Bethesda, Md.* — L.L. Wright. **Data Safety and Monitoring Committee:** *Children's Hospital National Medical Center, Washington, D.C.* — G. Avery (chairman); *New England Medical Center, Boston* — M. D'Alton; *Yale University, New Haven, Conn.* — M.B. Bracken; *NICHD, Bethesda, Md.* — C. Catz (executive secretary); *Johns Hopkins Hospital, Baltimore* — C.A. Gleason; *University of Pennsylvania, Philadelphia* — M. Maguire; *University of Pittsburgh, Pittsburgh* — C. Redmond; *Greenbrae, Calif.* — W. Silverman; *McMaster University, Hamilton, Ont.* — J. Sinclair; *George Washington University, Biostatistics Center, Rockville, Md.* — J. Verter (ex officio).

REFERENCES

1. Gersony WM. Neonatal pulmonary hypertension: pathophysiology, classification, and etiology. *Clin Perinatol* 1984;11:517-24.
2. Graves ED III, Redmond CR, Arensman RM. Persistent pulmonary hypertension in the neonate. *Chest* 1988;93:638-41.
3. Fox WW, Duara S. Persistent pulmonary hypertension in the neonate: diagnosis and management. *J Pediatr* 1983;103:505-14.
4. Drummond WH, Gregory GA, Heymann MA, Phibbs RA. The independent effects of hyperventilation, tolazoline, and dopamine on infants with persistent pulmonary hypertension. *J Pediatr* 1981;98:603-11.
5. Walsh-Sukys MC, Cornell DJ, Houston LN, Keszler M, Kanto WP Jr. Treatment of persistent pulmonary hypertension of the newborn without hyperventilation: an assessment of diffusion of innovation. *Pediatrics* 1994;94:303-6.
6. Wung JT, James LS, Kilchevsky E, James E. Management of infants with severe respiratory failure and persistence of the fetal circulation, without hyperventilation. *Pediatrics* 1985;76:488-94.
7. Kulik TJ, Lock JE. Pulmonary vasodilator therapy in persistent pulmonary hypertension of the newborn. *Clin Perinatol* 1984;11:693-701.
8. Ignarro LJ. Biological actions and properties of endothelium-derived nitric oxide formed and released from artery and vein. *Circ Res* 1989;65:1-21.
9. *Idem*. Endothelium-derived nitric oxide: actions and properties. *FASEB J* 1989;3:31-6.
10. Archer SL, Rist K, Nelson DP, DeMaster EG, Cowan N, Weir EK. Comparison of the hemodynamic effects of nitric oxide and endothelium-dependent vasodilators in intact lungs. *J Appl Physiol* 1990;68:735-47.
11. Furchgott RF, Vanhoutte PM. Endothelium-derived relaxing and contracting factors. *FASEB J* 1989;3:2007-18.
12. Palmer RMJ, Ferrige AG, Moncada S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. *Nature* 1987;327:524-6.
13. Ignarro LJ, Buga GM, Wood KS, Byrns RE, Chaudhuri G. Endothelium-derived relaxing factor produced and released from artery and vein is nitric oxide. *Proc Natl Acad Sci U S A* 1987;84:9265-9.
14. Frostell C, Fratacci MD, Wain JC, Jones R, Zapol WM. Inhaled nitric oxide — a selective pulmonary vasodilator reversing hypoxic pulmonary vasoconstriction. *Circulation* 1991;83:2038-47. [Erratum, *Circulation* 1991;84:2212.]
15. Fratacci MD, Frostell CG, Chen TY, Wain JC Jr, Robinson DR, Zapol WM. Inhaled nitric oxide — a selective pulmonary vasodilator of heparin-protamine vasoconstriction in sheep. *Anesthesiology* 1991;75:990-9.
16. Roberts JD Jr, Chen TY, Kawai N, et al. Inhaled nitric oxide reverses pulmonary vasoconstriction in the hypoxic and acidotic newborn lamb. *Circ Res* 1993;72:246-54.
17. Kinsella JP, Neish SR, Shaffer E, Abman SH. Low-dose inhalational nitric oxide in persistent pulmonary hypertension of the newborn. *Lancet* 1992;340:819-20.
18. Roberts JD, Polaner DM, Lang P, Zapol WM. Inhaled nitric oxide in persistent pulmonary hypertension of the newborn. *Lancet* 1992;340:818-9.
19. Finer NN, Etches PC, Kamstra B, Tierney AJ, Peliowski A, Ryan CA. Inhaled nitric oxide in infants referred for extracorporeal membrane oxygenation: dose response. *J Pediatr* 1994;124:302-8.
20. Rossaint R, Falke KJ, López F, Slama K, Pison U, Zapol WM. Inhaled nitric oxide for the adult respiratory distress syndrome. *N Engl J Med* 1993;328:399-405.
21. Pison U, Lopez FA, Heidelmeier CF, Rossaint R, Falke KJ. Inhaled nitric oxide reverses hypoxic pulmonary vasoconstriction without impairing gas exchange. *J Appl Physiol* 1993;74:1287-92.
22. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. *J Pediatr* 1978;92:529-34.
23. Gart JJ. Approximate tests and interval estimation of the common relative risk in the combination of 2x2 tables. *Biometrika* 1985;72:673-7.
24. Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. *Biometrika* 1983;70:659-63.
25. Radomski MW, Moncada S. Regulation of vascular homeostasis by nitric oxide. *Thromb Haemostasis* 1993;70:36-41.
26. Högman M, Frostell C, Arnberg H, Hedenstierna G. Bleeding time prolongation and NO inhalation. *Lancet* 1993;341:1664-5.
27. Högman M, Frostell C, Arnberg H, Sandhagen B, Hedenstierna G. Prolonged bleeding time during nitric oxide inhalation in the rabbit. *Acta Physiol Scand* 1994;151:125-9.
28. Beckman JS, Beckman TW, Chen J, Marshall PA, Freeman BA. Apparent hydroxyl radical production by peroxynitrite: implications for endothelial injury from nitric oxide and superoxides. *Proc Natl Acad Sci U S A* 1990;87:1620-4.
29. Lafon-Cazal M, Culcasi M, Gaven F, Pietri S, Bockaert J. Nitric oxide, superoxide and peroxynitrite: putative mediators of NMDA-induced death in cerebellar granule cells. *Neuropharmacology* 1993;32:1259-66.
30. Bartlett RH, Gazzaniga AB, Toomasian J, et al. Extracorporeal membrane oxygenation (ECMO) in neonatal respiratory failure: 100 cases. *Ann Surg* 1986;204:236-45. [Erratum, *Ann Surg* 1987;205:11A.]

CORRECTION

Inhaled Nitric Oxide in Full-Term and Nearly Full-Term Infants with Hypoxic Respiratory Failure

Inhaled Nitric Oxide in Full-Term and Nearly Full-Term Infants with Hypoxic Respiratory Failure . On page 602, the last paragraph in the right-hand column should have read, "There were no significant differences between the groups after randomization in the overall incidence or severity of intracranial hemorrhage (total number, 19 in the control group and 18 in the nitric oxide group; grade IV, 8 and 7, respectively). There were also no significant differences between the control group and the nitric oxide group in the occurrence of periventricular leukomalacia (3 vs. 6), brain infarction (7 vs. 7), seizures requiring anticonvulsive therapy (24 vs. 16), and either pulmonary (6 vs. 4) or gastrointestinal (1 vs. 1) hemorrhage."