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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 [±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.)

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, Tolfield, 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 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).

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.

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. FiO_2 denotes fraction of inspired oxygen, and PaO_2 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 PaO_2 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 PaO_2 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.

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