LOW-DOSE NITRIC OXIDE THERAPY FOR PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN

REESE H. CLARK, M.D., THOMAS J. KUESER, M.D., MARSHALL W. WALKER, M.D., W. MICHAEL SOUTHGATE, M.D., JERYL L. HUCKABY, R.R.T., JOSE A. PEREZ, M.D., BEVERLY J. ROY, M.D., MARTIN KESZLER, M.D., AND JOHN P. KINSELLA, M.D., FOR THE CLINICAL INHALED NITRIC OXIDE RESEARCH GROUP*

ABSTRACT

Background Inhaled nitric oxide improves gas exchange in neonates, but the efficacy of low-dose inhaled nitric oxide in reducing the need for extracorporeal membrane oxygenation has not been established.

Methods We conducted a clinical trial to determine whether low-dose inhaled nitric oxide would reduce the use of extracorporeal membrane oxygenation in neonates with pulmonary hypertension who were born after 34 weeks' gestation, were 4 days old or younger, required assisted ventilation, and had hypoxemic respiratory failure as defined by an oxygenation index of 25 or higher. The neonates who received nitric oxide were treated with 20 ppm for a maximum of 24 hours, followed by 5 ppm for no more than 96 hours. The primary end point of the study was the use of extracorporeal membrane oxygenation.

Results Of 248 neonates enrolled, 126 were randomly assigned to the nitric oxide group and 122 to the control group. Extracorporeal membrane oxygenation was used in 78 neonates in the control group (64 percent) and in 48 neonates in the nitric oxide group (38 percent) ($P=0.001$). The 30-day mortality rate in the two groups was similar (8 percent in the control group and 7 percent in the nitric oxide group). Chronic lung disease developed less often in neonates treated with nitric oxide than in those in the control group (7 percent vs. 20 percent, $P=0.02$). The efficacy of nitric oxide was independent of the base-line oxygenation index and the primary pulmonary diagnosis.

Conclusions Inhaled nitric oxide reduces the extent to which extracorporeal membrane oxygenation is needed in neonates with hypoxemic respiratory failure and pulmonary hypertension. (N Engl J Med 2000;342:469-74.)

PERSISTENT pulmonary hypertension is common in neonates with respiratory failure.[1,2] It is characterized by pulmonary hypertension and extrapulmonary right-to-left shunting across the foramen ovale and ductus arteriosus. In many cases, the disease progressively worsens, becoming refractory to treatment.[3-5]

When other therapies fail, neonates are treated with extracorporeal membrane oxygenation.[3-5] This therapy improves survival in neonates with respiratory failure,[6-8] but its administration is labor-intensive and costly and necessitates large amounts of blood products. The mortality rate in neonates treated with extracorporeal membrane oxygenation is 15 to 20 percent, and 10 to 20 percent of the neonates who survive have substantial developmental delay.[7-12]

Nitric oxide is produced in vascular endothelial cells and plays an important part in increasing blood flow to the lungs after birth.[13-17] Exogenously administered nitric oxide causes selective pulmonary vasodilatation in newborn lambs,[13] and the administration of low doses of nitric oxide causes sustained improvement in gas exchange in neonates.[18] However, the efficacy of low-dose inhaled nitric oxide in reducing the use of extracorporeal membrane oxygenation has not been established. This study was undertaken to determine whether low-dose inhaled nitric oxide reduces the use of extracorporeal membrane oxygenation in neonates with pulmonary hypertension.

METHODS

Study Subjects

We studied 248 neonates who were born after 34 weeks' gestation, were 4 days old or younger, required assisted ventilation, and had an oxygenation index of 25 or higher. The oxygenation index was calculated as the mean airway pressure times the fraction of inspired oxygen times 100, divided by the partial pressure of arterial oxygen. The neonates had clinical or echocardiographic evidence of pulmonary hypertension without structural heart disease. Clinical evidence of pulmonary hypertension was defined as a difference of 5 percent between preductal and postductal oxygen saturation or recurrent (more than two) decreases in arterial oxygen saturation (to less than 85 percent) in a period of 12 hours despite optimal treatment of lung disease. Echocardiographic evidence of pulmonary hypertension was defined as an estimated peak systolic pulmonary-artery pressure that was higher than 35 mm Hg or more than two thirds of the systemic systolic pressure as indicated by a tricuspid regurgitant jet, a right-to-left ductus arteriosus shunt, or a right-to-left atrial-level shunt. In addition, we considered as study candidates neonates in whom extreme alkalosis (a pH higher than 7.55) was required to maintain a partial pressure of arterial oxygen of more than 60 mm Hg.

From the Department of Pediatrics, Duke University, Durham, N.C. (R.H.C.); the Division of Neonatology, Carolinas Medical Center, Charlotte, N.C. (T.J.K.); the Department of Neonatology, Greenville Hospital System, Greenville, S.C. (M.W.W.); Medical University of South Carolina, Charleston (W.M.S.); Egleston Children's Hospital, Atlanta (J.L.H.); Arnold Palmer Hospital, Orlando, Fla. (J.A.P.); the Department of Pediatrics, Emory University, Atlanta (B.J.R.); the Division of Neonatology, Georgetown University Hospital, Washington, D.C. (M.K.); and the University of Colorado School of Medicine, Denver (J.P.K.). Address reprint requests to Dr. Clark at Pediatrix Medical Group, 1301 Concord Terr., Sunrise, FL 33323, or at reese_clark@mail.pediatrix.com.

*The members of the Clinical Inhaled Nitric Oxide Research Group are listed in the Appendix.

Pre-enrollment treatment with high-frequency ventilation (model 3100A, SensorMedics, Yorba Linda, Calif.) or surfactant was encouraged. Neonates were not eligible for the study if extracorporeal membrane oxygenation was urgently needed for refractory hypotension (a mean blood pressure lower than 35 mm Hg) or profound hypoxemia (a partial pressure of arterial oxygen lower than 30 mm Hg) or if they had a lethal congenital anomaly, a substantial bleeding diathesis, active seizures, or a history of severe asphyxia. The study was approved by the institutional review board at each study site, and written informed consent was obtained from a parent or guardian.

Randomization

To balance the distribution of pulmonary-disease diagnoses in the two treatment groups, each neonate was assigned to one of five diagnostic categories and then randomly assigned to treatment. The diagnostic categories were the meconium aspiration syndrome, which was diagnosed on the basis of a history of meconium-stained amniotic fluid and abnormal results on chest radiography; pneumonia, with two or more risk factors for sepsis and no history that suggested lung immaturity (the risk factors for sepsis were maternal chorioamnionitis, maternal fever, positive vaginal culture for group B streptococcus, a white-cell count of more than 30,000 cells per cubic millimeter or less than 5000 cells per cubic millimeter, a ratio of immature to total neutrophils of more than 0.2, a serum C-reactive protein concentration of more than 2 μg per milliliter, hypotension that required vasopressor support, and coagulopathy); the respiratory distress syndrome, with fewer than two risk factors for sepsis, a history that suggested lung immaturity, and a chest radiograph that had a reticulogranular appearance; lung hypoplasia syndromes, which were diagnosed on the basis of the presence of a congenital diaphragmatic hernia, a history of prolonged oligohydramnios, or hydrops fetalis; and idiopathic persistent pulmonary hypertension, which required a clinical diagnosis of pulmonary hypertension and a chest radiograph showing little or no lung disease.

Cards on which treatment assignments were written were randomly ordered (shuffled by hand three times) at Emory University in Atlanta and placed in sequentially numbered opaque envelopes in blocks of eight for diagnostic-category strata 1, 2, and 3 and in blocks of four for strata 4 and 5; the number in each block reflected the anticipated frequencies of diagnoses. Notebooks in which the numbered envelopes were stored were sent to each study site.

After the attending physician obtained consent, a respiratory therapist was told the neonate's diagnostic stratum and identified the appropriate sequentially ordered envelope. The therapist then set up the system of treatment delivery, completed the basic information on the randomization card, and mailed the card to the center that coordinated the study. The study coordinator at the coordinating center monitored the order in which the treatment cards were used.

Neither the physicians nor the nurses were told the treatment assignments. Respiratory therapists directed treatment and made adjustments to keep the concentration of nitric oxide within the prescribed range (±10 percent of the target dose). In the first 36 neonates enrolled, the delivery systems for the two treatment groups were identical. The neonates assigned to the control group were treated by continuing the flow of oxygen without initiating the administration of nitric oxide. In the remaining 212 neonates, nitrogen (delivered through the INO Delivery System, Ohmeda, Madison, Wis.) was used as the control to improve the masking of the treatment assignment. The gas tank and monitor readouts were covered so that the tank and the monitored values for nitric oxide and nitrogen dioxide could not be seen.

Treatment Guidelines and Delivery of Gas

In the first 18 neonates in the treatment group, nitric oxide gas (Scott Medical Products, Plumstead, Pa.) was delivered from a 450-ppm cylinder. Nitric oxide was introduced into the afferent limb of the ventilator circuit near the endotracheal tube, thus mixing with the fixed flow of gas in the ventilator circuit. The flow was adjusted to yield the assigned concentrations of nitric oxide. Nitric oxide and nitrogen dioxide were measured with electrochemical monitors (Pac II nitric oxide monitor and model 190 nitrogen dioxide monitor, Drager, Chantilly, Va.). For the 108 remaining neonates in the nitric oxide group, nitric oxide gas (INO Therapeutics, Port Allen, La.) was delivered from an 800-ppm cylinder. The control subjects received 100 percent nitrogen (Ohmeda, BOC Gases, Murray Hill, N.J.). The study gas (nitrogen or nitric oxide) was delivered (with the INO Delivery System) into the inspiratory flow of the ventilator circuit. The device measured the flow of gas in the ventilator circuit, and a mass-flow controller added study gas to the ventilator circuit to create the desired concentration. The device continuously sampled gas from the endotracheal side-port adapter and measured oxygen, nitric oxide, and nitrogen dioxide with electrochemical monitors. Inhaled nitric oxide and nitrogen had a similar effect on the fraction of inspired oxygen (reducing the value to 0.98).[19]

The administration of the study gas (nitrogen or nitric oxide) was started at 20 ppm, and this amount was continued for four hours. At four hours, arterial-blood gases and methemoglobin were measured. The dose was decreased to 5 ppm if the neonate's condition was stable, the partial pressure of arterial oxygen was at least 60 mm Hg, and the pH was 7.55 or lower. If these criteria were not met, the administration of study gas was maintained at 20 ppm, and the neonate was evaluated every 4 hours until the criteria were met or the neonate had been treated for 24 hours. During the first 24 hours, the dose of study gas could be returned to 20 ppm if the neonate's partial pressure of arterial oxygen fell below 60 mm Hg when the fraction of inspired oxygen was 1.0. After 24 hours of treatment, the dose was decreased to 5 ppm. Treatment was continued at 5 ppm until the fraction of inspired oxygen was less than 0.7, the neonate had been treated for 96 hours, or the neonate was seven days old, whichever came first.

If the neonate did not tolerate the decreased dose at 24 hours or if at 96 hours the study gas could not be discontinued, the treatment was considered a failure. If a clinical decision was made to proceed with extracorporeal membrane oxygenation, the study gas was continued until it was started.

Methemoglobin was measured at base line and at 4, 24, and 96 hours while the neonate was receiving the study gas. The concentration of study gas was reduced by half if the neonate had a methemoglobin value of more than 4 percent or a nitrogen dioxide concentration of more than 5 ppm, and the administration of the study gas was discontinued if these values did not become normal.

We aimed to achieve the following blood gas values in the neonates: a partial pressure of arterial oxygen of 60 to 100 mm Hg; a partial pressure of arterial carbon dioxide of 25 to 30 mm Hg and a pH of 7.40 to 7.55 in neonates with a response to alkalosis; and a partial pressure of arterial carbon dioxide of 35 to 45 mm Hg and a pH of 7.35 to 7.45 in neonates with no response to alkalosis. The target mean blood pressure was 45 to 60 mm Hg.

Criteria for Discontinuing Treatment in the Study

Treatment was discontinued if the neonate was successfully weaned from the study gas, met the criteria for treatment failure, or met the criteria for extracorporeal membrane oxygenation. Neonates who met the criteria for treatment failure were not automatically treated with extracorporeal membrane oxygenation. The criteria for the use of extracorporeal membrane oxygenation were an oxygenation index of more than 40 on three of five measurements performed at least 30 minutes apart; a partial pressure of arterial oxygen lower than 40 mm Hg for 2 hours; or progressive hemodynamic deterioration (a mean blood pressure below 35 mm Hg). The decision to use extracorporeal membrane oxygenation was made by the attending physician and by the consulting team for extracorporeal membrane oxygenation.

Study End Points

Our primary hypothesis was that the use of extracorporeal membrane oxygenation would be the same in neonates treated with

nitric oxide and those not treated with nitric oxide. Our secondary hypotheses were that the two groups would have the same improvement in the ratio of arterial oxygen to alveolar oxygen, the same incidence of short-term complications (hypotension, methemoglobinemia, and deterioration in gas exchange), the same incidence of long-term complications (chronic lung disease and neurologic handicaps), and the same incidence of death. The results presented here are for follow-up at 30 days; the results of follow-up at 1 year are being collected now.

Statistical Analysis

We evaluated categorical variables using two-tailed chi-square and Fisher's exact tests. Continuous variables were compared with use of a two-tailed t-test or the Kruskal–Wallis test. Ranked data were assessed with the two-tailed Kruskal–Wallis test. We compared changes over time in the two groups of neonates with regard to gas exchange, methemoglobin values, and nitrogen dioxide concentrations, using analysis of variance for repeated measures. We used a multivariate logistic-regression analysis to evaluate the independent effects of the following covariates on the use of extracorporeal membrane oxygenation and the occurrence of chronic lung disease: treatment group, sex, surfactant treatment, support with high-frequency ventilation, air leak (pneumothorax, pulmonary interstitial emphysema, or pneumomediastinum) at study entry, age at study entry, primary pulmonary diagnosis, and oxygenation index.

RESULTS

Base-Line Characteristics

Two hundred forty-eight neonates were enrolled in the study; 126 were assigned to the nitric oxide group, and 122 to the control group. The base-line characteristics of the two treatment groups were similar, with the exception of prenatal care before the third trimester and the presence of an air leak before enrollment (Table 1). However, there were no differences in obstetrical complications, and all air leaks were stabilized before enrollment.

As compared with the nitric oxide group, the control group had a higher mean (±SD) blood pressure (55±12 mm Hg vs. 51±11 mm Hg, P=0.02) and a lower partial pressure of arterial oxygen (58±42 mm Hg vs. 72±64 mm Hg, P=0.05) (Table 2). However, the mean level of pressor support and the severity of hypoxemia, assessed by the oxygenation index, were similar in the two groups (Tables 1 and 2). There were no differences between the two groups in the incidence of echocardiographic evidence of pulmonary hypertension.

TABLE 1. BASE-LINE CHARACTERISTICS OF THE STUDY SUBJECTS.*

CHARACTERISTIC	CONTROL GROUP (N=122)	NITRIC OXIDE GROUP (N=126)	P VALUE
Prenatal care before third trimester — no. (%)	101 (83)	116 (92)	0.02
Birth weight — kg	3.3±0.6	3.3±0.5	0.59
Male sex — no. (%)	73 (60)	60 (48)	0.06
Referred from another hospital — no. (%)	83 (68)	92 (73)	0.38
Race or ethnic group — no. (%)			0.38
Non-Hispanic black	41 (34)	49 (39)	
Hispanic	14 (11)	10 (8)	
Non-Hispanic white	67 (55)	67 (53)	
Primary pulmonary diagnosis — no. (%)			0.80
Meconium aspiration syndrome	42 (34)	43 (34)	
Pneumonia	26 (21)	26 (21)	
Idiopathic pulmonary hypertension	25 (20)	32 (25)	
Respiratory distress syndrome	11 (9)	11 (9)	
Congenital diaphragmatic hernia	18 (15)	13 (10)	
Pulmonary hypoplasia	0	1 (1)	
Lung disease — no. (%)†			0.50
None	10 (8)	16 (13)	
Mild	31 (25)	33 (26)	
Moderate	57 (47)	51 (40)	
Severe	24 (20)	26 (21)	
Air leak before enrollment — no. (%)	29 (24)	16 (13)	0.03
Drugs used before enrollment — no. (%)			
Surfactant	52 (43)	43 (34)	0.19
Sodium bicarbonate	89 (73)	97 (77)	0.47
Vasopressors (dopamine, dobutamine, and epinephrine)	109 (89)	110 (87)	0.86
Age at enrollment — hr	28±17	28±20	0.77

*Plus–minus values are means ±SD.

†The severity of lung disease was determined on the basis of chest radiography. None indicates no radiographic signs of lung disease; mild indicates minimal streaky infiltrates or reticulogranular changes with easily visualized borders of the heart and diaphragm; moderate indicates diffuse infiltrates or reticulogranular changes with obscure but visible borders of the heart and diaphragm; and severe indicates diffuse infiltrates with borders of the heart and diaphragm that were difficult to visualize.

Deviations from the Protocol

Two neonates assigned to the control group were treated with nitric oxide; both were included in the control group in an intention-to-treat analysis. There were 21 deviations from the protocol. In 12 neonates, an oxygenation index higher than 25 at base line was not documented adequately. Three neonates had partial pressures of arterial oxygen that were lower than 30 mm Hg at base line and thus fulfilled the criteria for exclusion because of their urgent need for extracorporeal membrane oxygenation. Two neonates did not have pulmonary hypertension. Four other neonates should not have been enrolled in the study, because they had congenital heart disease, seizures, an estimated gestational age of less than 34 weeks, or a lethal anomaly (an inoperable cystic hygroma).

Primary Outcome

The use of extracorporeal membrane oxygenation was less common in the nitric oxide group than in the control group (38 percent vs. 64 percent, P=0.001) (Table 3). This was true in all pulmonary diagnostic groups except neonates with congenital diaphragmatic hernia (Table 4). In the neonates treated with extracorporeal membrane oxygenation, the median time from the start of treatment to the start of extracorporeal membrane oxygenation was similar in the two groups (5 hours in the control group [range, 1 to 86] and 9 hours in the nitric oxide group [range, 2 to 150]). Eight neonates (three in the control group and

TABLE 2. BASE-LINE VENTILATORY STATUS OF THE STUDY SUBJECTS.*

VARIABLE	CONTROL GROUP (N=122)	NITRIC OXIDE GROUP (N=126)	P VALUE
Receiving high-frequency oscillation — no. (%)	72 (59)	62 (49)	0.10
Receiving conventional mechanical ventilation — no. (%)	46 (38)	59 (47)	0.10
FiO_2			
Neonates assessed — no. (%)	118 (97)	125 (99)	
Mean value	1.0±0.03	1.0±0.03	0.64
Peak pressure†			
Neonates assessed — no. (%)	46 (38)	59 (47)	
Mean value — cm of water	33±7	33±7	0.64
Pressure amplitude‡			
Neonates assessed — no. (%)	69 (57)	62 (49)	
Mean value — cm of water	42±11	42±11	0.94
Rate for high-frequency oscillation			
Neonates assessed — no. (%)	70 (57)	62 (49)	
Mean value — Hz	10±1	10±2	0.27
Rate for conventional mechanical ventilation			
Neonates assessed — no. (%)	46 (38)	59 (47)	
Mean value — breaths/min	57±13	58±14	0.63
Mean airway pressure			
High-frequency oscillation			
Neonates assessed — no. (%)	69 (57)	62 (49)	
Mean value — cm of water	20±4	20±4	0.72
Conventional mechanical ventilation			
Neonates assessed — no. (%)	43 (35)	55 (44)	
Mean value — cm of water	16±3	15±4	0.21
Arterial-blood gas values			
pH			
Neonates assessed — no. (%)	114 (93)	119 (94)	
Mean value	7.44±0.1	7.45±0.1	0.35
PaO_2			
Neonates assessed — no. (%)	113 (93)	119 (94)	
Mean value — mm Hg	58±42	72±64	0.05
$PaCO_2$			
Neonates assessed — no. (%)	113 (93)	119 (94)	
Mean value — mm Hg	36±12	35±13	0.68
Oxygenation index§			
Neonates assessed — no. (%)	107 (88)	111 (88)	
Mean value	41±21	37±24	0.17

*Values are not included for neonates who were receiving manual ventilation at base line or for whom blood gas values were obtained after the start of treatment. FiO_2 denotes fraction of inspired oxygen, PaO_2 partial pressure of arterial oxygen, and $PaCO_2$ partial pressure of arterial carbon dioxide. Plus–minus values are means ±SD.

†These values are for neonates who were receiving conventional ventilation.

‡These values are for neonates who were receiving high-frequency oscillation.

§The oxygenation index was calculated as the mean airway pressure times the fraction of inspired oxygen times 100, divided by the partial pressure of arterial oxygen.

five in the nitric oxide group) met the criteria for extracorporeal membrane oxygenation but did not receive it. All survived to discharge, and chronic lung disease did not develop in any of them. Four neonates who were not treated with extracorporeal membrane oxygenation died. Two died after prolonged assisted ventilation; one of these neonates had adenoviral bronchiolitis obliterans, and the other had severe chronic lung disease. The other two neonates who died had contraindications to treatment with extracorporeal membrane oxygenation: one had uncontrolled bleeding, and the other had an inoperable cystic hygroma.

Secondary Outcomes

Twenty-three neonates died before discharge: 13 in the control group and 10 in the nitric oxide group ($P=0.82$). There were no differences between the two groups in terms of the cause of death.

After one hour of treatment, the ratio of arterial to alveolar oxygen increased more in the nitric oxide group than in the control group (by 0.10 ± 0.14 vs. 0.05 ± 0.13, $P=0.02$). There was no difference between the two groups with regard to ventilator settings, heart rate, mean blood pressure, or level of dopamine support during the first four hours of treatment.

Thirty neonates had chronic lung disease (as determined by the need for supplemental oxygen at 30 days). Nineteen neonates died before 30 days of age. In the group of 224 survivors for whom data were available, the incidence of chronic lung disease was lower in the neonates treated with nitric oxide than in the neonates in the control group (7 percent vs. 20 percent, $P=0.02$).

Among the survivors, there was no difference between the two treatment groups with regard to age at discharge, age at extubation, or duration of extracorporeal membrane oxygenation. Neurologic abnormalities occurred at the same rate in the two groups (Table 3).

The use of nitric oxide independently affected both the use of extracorporeal membrane oxygenation and the occurrence of chronic lung disease. A high oxygenation index, assignment to the control group, and a diagnosis of congenital diaphragmatic hernia were all associated with the use of extracorporeal membrane oxygenation. The most important factor that affected the development of chronic lung disease was the diagnosis of congenital diaphragmatic hernia. The oxygenation index and the presence of an air leak before enrollment in the study were not independent predictors of chronic lung disease.

DISCUSSION

We found that the administration of low doses of nitric oxide reduced the use of extracorporeal membrane oxygenation and decreased the need for supplemental oxygen at 30 days in neonates with hypoxemic respiratory failure and persistent pulmonary hypertension. We stratified the neonates in both groups according to the diagnosis in order to assess the relative efficacy of treatment across diagnostic groups and to minimize the effect of underlying disease as a confounding variable. Our results confirm the findings of the Neonatal Inhaled Nitric Oxide

TABLE 3. OUTCOME ANALYSIS.*

OUTCOME	CONTROL GROUP (N=122)	NITRIC OXIDE GROUP (N=126)	P VALUE
Received extracorporeal membrane oxygenation			
Intention-to-treat analysis — no./total no. (%)	78/122 (64)	48/126 (38)	0.001
Neonates with no protocol violations — no./total no. (%)	74/116 (64)	43/111 (39)	0.001
Died before 30 days of age — no. (%)	10 (8)	9 (7)	0.40
Died before discharge — no. (%)	13 (11)	10 (8)	0.82
Died before discharge or received extracorporeal membrane oxygenation — no. (%)	80 (66)	50 (40)	0.001
Length of stay in the hospital for survivors			
Neonates assessed — no. (%)	104 (85)	113 (90)	0.09
Mean no. of days	29±23	25±15	
Duration of assisted ventilation for survivors			
Neonates assessed — no. (%)	109 (89)	116 (92)	0.40
Mean no. of days	12±10	11±7	
Pulmonary outcome in survivors			
Were receiving supplemental oxygen at 30 days — no./total no. (%)†	22/110 (20)	8/114 (7)	0.02
Received supplemental oxygen after discharge — no./total no. (%)†	12/107 (11)	6/113 (5)	0.14
Intraventricular hemorrhages (more than two) or infarct — no. (%)	8 (7)	4 (3)	0.34
Seizures — no. (%)	1 (1)	1 (1)	0.49

*Plus–minus values are means ±SD.

†Data were missing for five neonates (two in the control group and three in the nitric oxide group); these neonates were transported back to the referring hospitals, so data were not available at 30 days.

TABLE 4. RELATIVE RISK OF EXTRACORPOREAL MEMBRANE OXYGENATION ACCORDING TO DIAGNOSIS.

DIAGNOSIS	EXTRACORPOREAL MEMBRANE OXYGENATION		RELATIVE RISK (95% CI)*
	CONTROL GROUP (N=122)	NITRIC OXIDE GROUP (N=126)	
	no./total no. (%)		
Meconium aspiration syndrome	26/42 (62)	15/43 (35)	0.6 (0.3–0.9)
Pneumonia	18/26 (69)	9/26 (35)	0.5 (0.3–0.9)
Idiopathic pulmonary hypertension	9/25 (36)	9/32 (28)	0.8 (0.3–1.9)
Respiratory distress syndrome	9/11 (82)	3/11 (27)	0.3 (0.1–0.9)
Congenital diaphragmatic hernia	16/18 (89)	12/13 (92)	1.0 (0.8–1.2)
Pulmonary hypoplasia	0	0/1	

*The relative risk is expressed as the risk of a need for extracorporeal membrane oxygenation in the group of neonates treated with nitric oxide as compared with the control group. CI denotes confidence interval.

Study that nitric oxide is effective across a broad range of diagnoses.[20] The only exception was neonates with congenital diaphragmatic hernia, in whom nitric oxide did not reduce the use of extracorporeal membrane oxygenation or improve the outcome.[21]

The most important difference between our trial and previous studies is that we used a low dose of inhaled nitric oxide for a limited amount of time (a maximum of 96 hours). Other trials have used higher doses (80 ppm) for longer periods (as long as two weeks).[19,20,22] By limiting the duration of treatment, we hoped to avoid delaying extracorporeal membrane oxygenation beyond the point at which its efficacy might be reduced. Our data, combined with the results of previous studies, suggest that this approach is effective. In the Neonatal Inhaled Nitric Oxide Study, neonates who did not have a response to 20 ppm of nitric oxide rarely had a response to 80 ppm.[20] The median duration of successful treatment in our study was 44 hours, and all but two neonates were weaned from nitric oxide by 96 hours.

The potentially toxic effects of inhaled nitric oxide at high doses include decreased platelet aggregation,[15] an increased risk of bleeding,[23-25] acute lung injury as a result of oxidant injury,[26-29] and surfactant dysfunction.[30] In our study, none of the neonates had high concentrations of nitrogen dioxide, only two had high methemoglobin values, and nitric oxide was not associated with an increase in the occurrence of intracranial hemorrhages or chronic lung disease. In fact, nitric oxide was associated with a decrease in the occurrence of chronic lung disease.

The strength of the association between treatment with nitric oxide and an improved pulmonary outcome is demonstrated by the fact that the association remained significant in multivariate and subgroup analyses. The reason for this improvement is unclear. One possibility is that inhaled nitric oxide reduces lung inflammation. Studies in animals suggest that inhaled nitric oxide may reduce the accumulation of neutrophils in the lung and the attendant inflammatory cascade that contributes to acute lung injury.[31-33] Another possibility is that nitric oxide reduces ventilator-induced lung injury by improving gas exchange and reducing the intensity of required ventilatory support.

In conclusion, low-dose inhaled nitric oxide reduces the need for extracorporeal membrane oxygenation and reduces the occurrence of chronic lung disease in neonates with hypoxemic respiratory failure that does not result from congenital diaphragmatic hernia.

Supported in part by a grant from INO Therapeutics.

Dr. Clark has acted as a consultant to INO Therapeutics regarding the submission of data to the Food and Drug Administration. He is also the principal investigator for the grant that supported this study. Dr. Kinsella has acted as a consultant to INO Therapeutics regarding the submission of data to the Food and Drug Administration. Mrs. Huckaby has acted as a clinical research associate for INO Therapeutics in monitoring this study.

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