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Inhaled Nitric Oxide for the Early Treatment of Persistent Pulmonary Hypertension of the Term Newborn: A Randomized, Double-Masked, Placebo-Controlled, Dose-Response, Multicenter Study

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ABSTRACT. *Objectives.* **To assess the dose-related effects of inhaled nitric oxide (I-NO) as a specific adjunct to early conventional therapy for term infants with persistent pulmonary hypertension (PPHN), with regard to neonatal outcome, oxygenation, and safety.**

Methods. **Randomized, placebo-controlled, double-masked, dose-response, clinical trial at 25 tertiary centers from April 1994 to June 1996. The primary endpoint was the PPHN Major Sequelae Index ([MSI], including the incidence of death, extracorporeal membrane oxygenation (ECMO), neurologic injury, or bronchopulmonary dysplasia [BPD]). Patients required a fraction of inspired oxygen [F_{IO_2}] of 1.0, a mean airway pressure ≥10 cm H_2O on a conventional ventilator, and echocardiographic evidence of PPHN. Exogenous surfactant, concomitant high-frequency ventilation, and lung hypoplasia were exclusion factors. Control (0 ppm) or nitric oxide (NO) (5, 20, or 80 ppm) treatments were administered until success or failure criteria were met. Due to slowing recruitment, the trial was stopped at N = 155 (320 planned).**

Results. **The baseline oxygenation index (OI) was 24 ± 9 at 25 ± 17 hours old (mean ± SD). Efficacy results were similar among NO doses. By 30 minutes (no ventilator changes) the Pa_{O_2} for only the NO groups increased significantly from 64 ± 39 to 109 ± 78 Torr (pooled) and systemic arterial pressure remained unchanged. The baseline adjusted time-weighted OI was also significantly reduced in the NO groups (-5 ± 8) for the first 24 hours of treatment. The MSI rate was 59% for the control and 50% for the NO doses ($P = .36$). The ECMO rate was 34% for control and 22% for the NO doses ($P = .12$). Elevated methemoglobin (>7%) and nitrogen dioxide (NO_2) (>3 ppm) were observed only in the 80 ppm NO group, otherwise no adverse events could be attributed to I-NO, including BPD.**

Conclusion. **For term infants with PPHN, early I-NO as the sole adjunct to conventional management produced an acute and sustained improvement in oxygenation for 24 hours without short-term side effects (5 and 20 ppm doses), and the suggestion that ECMO use may be reduced.** *Pediatrics* **1998;101:325–334;** ***extracorporeal membrane oxygenation, bronchopulmonary dysplasia, neonatal outcome, methemoglobinemia, nitrogen dioxide.***

ABBREVIATIONS. PPHN, persistent pulmonary hypertension of the newborn; ECMO, extracorporeal membrane oxygenation; I-NO, inhaled nitric oxide; BPD, bronchopulmonary dysplasia; NO_2, nitrogen dioxide; ppm, parts per million; MSI, Major Sequelae Index; RAD, reactive airway disease; F_{IO_2}, fraction of inspired oxygen; NO, nitric oxide; TWOI, time-weighted oxygenation index; OI, oxygenation index.

Persistent pulmonary hypertension of the newborn (PPHN) is a syndrome of acute respiratory failure, characterized by systemic hypoxemia associated with extrapulmonary shunting of venous blood and evidence of elevated levels of pulmonary artery pressure in the absence of congenital heart disease. This syndrome is seen more commonly in term infants who have underlying diseases such as meconium aspiration, respiratory distress syndrome, sepsis, or lung hypoplasia, or it may be idiopathic PPHN.[1,2] In the United States, approximately 10 000 newborns per year suffer from PPHN.[3,4] The diagnosis of PPHN is usually made by 24 hours after birth and most patients are born at hospitals without extracorporeal membrane oxygenation (ECMO).[4]

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The standard therapy for PPHN typically includes conventional mechanical ventilation, oxygen, sedation, paralysis, alkalosis, inotropic support, intravenous vasodilators, and antibiotics.[4,5] In 1994, the efficacy and safety of surfactant and high-frequency ventilation for PPHN were unproven, and the use of these therapies was becoming more widespread, before resorting to ECMO.[4–7] However, previous case series indicated that inhaled nitric oxide (I-NO) improved oxygenation acutely by selective pulmonary vasodilation.[8,9] Therefore, the overall hypothesis for the present study was that early use of I-NO could reduce inspired oxygen and conventional ventilator requirements. This, in turn, might lead to less secondary lung injury due to the inflammatory effects of hyperoxia and barotrauma, a process that begins within 24 hours[10,11] and may be deleterious to outcome. Accordingly, the first objective of this trial was to determine if early I-NO therapy would reduce the overall incidence of death, need for ECMO, neurologic sequelae, and bronchopulmonary dysplasia (BPD).

At the start of this study, data from animal and human studies had not indicated what was the most safe and effective dose of prolonged I-NO for PPHN.[12–15] The secondary objective of this trial was to determine if there was dose-related efficacy, methemoglobinemia, inspired nitrogen dioxide (NO_2) levels, intracranial hemorrhage, or unsuspected adverse effects of I-NO in the neonatal period.[16] Therefore, eligibility requirements were defined narrowly and potentially confounding, and investigational rescue treatments, such as high-frequency ventilation and surfactant, were prohibited.

METHODS

This clinical trial was a randomized, double-masked, placebo-controlled, dose-response study. Twenty-five neonatal intensive care units enrolled patients; fifteen of the sites were ECMO centers. The protocol, protocol amendments and each institution's Informed Consent forms were approved by the local Institutional Review Board before patient enrollment. Written informed consent was obtained for each patient before enrollment. Equipment, treatment gases and funding based on patient recruitment at each site was provided by Ohmeda, PPD (Liberty Corner, NJ).

Hypotheses

The primary hypothesis was that a fixed dose of I-NO at either 5, 20, or 80 parts per million (ppm), delivered to term infants with PPHN, would reduce the PPHN Major Sequelae Index (MSI) by 30%. This composite endpoint included the incidence of death, ECMO, neurologic sequelae in the neonatal period, or bronchopulmonary dysplasia/reactive airway disease (BPD/RAD). Neurologic sequelae in the neonatal period were defined as clinical or electroencephalogram-proven seizures or an abnormal cranial imaging study (demonstrating either hemorrhage, infarct, or other diagnoses) during the neonatal hospitalization. BPD was defined as the need for supplemental oxygen at 28 days after birth with a concurrent abnormal chest x-ray. RAD was defined as the need for bronchodilator therapy at discharge from the nursery.

Secondary hypotheses were that I-NO would: 1) produce a sustained improvement in oxygenation during the first 24 hours of treatment, 2) reduce the incidence of treatment failures due to hypoxemia and/or hypotension leading to institution of other forms of rescue therapy, and 3) reduce days on the ventilator, on supplemental oxygen, and length of hospital stay.

It was also hypothesized that there would be no increase in adverse events experienced by the neonates receiving I-NO as [illegible] ing of primary or secondary efficacy outcome measures, delay in initiating rescue therapy, adverse events described by the investigators, or abnormalities in clinical hematologic and biochemical blood studies. A separate comprehensive 1-year follow-up study was designed to examine the general pediatric, neurodevelopmental, and audiologic outcomes.

Patient Entry Criteria

Term infants (≥37 weeks gestation) with birth weights of ≥2500 g requiring mechanical ventilation having a fraction of inspired oxygen (F_{IO_2}) of 1.0 were eligible within 72 hours of birth. Small for gestational age infants with birth weights of ≥2000 g were included if the gestational age was assessed to be ≥39 weeks. On study entry, an Infant Star conventional ventilator (Infrasonics, Inc, San Diego, CA) was used, with a continuous flow rate between 10 and 15 L/min. Intermittent mandatory ventilator rates >100 breaths/minute and inverse inspiratory to expiratory ratios

For study entry, patients required an arterial blood gas with a Pao_2 of ≥40 and ≤100 Torr drawn from an indwelling postductal arterial catheter when the mean airway pressure was ≥10 cm H_2O and the F_{IO_2} was 1.0. They also required a color Doppler echocardiogram with evidence of PPHN or a preductal versus postductal transcutaneous O_2 saturation gradient of ≥10%. The following were considered echocardiographic evidence of PPHN: 1) a right-to-left or bidirectional ductal shunt, 2) if the ductus was closed, a right-to-left or bidirectional foramen ovale shunt with either a tricuspid insufficiency jet with an estimated systolic pulmonary artery pressure ≥75% of systolic aortic pressure or posterior systolic bowing of the interventricular septum. Before starting the treatment gas, the patient had to have a chest x-ray within 12 hours and a head ultrasound within 24 hours. A standardized history and physical examination were required. Preductal and postductal transcutaneous O_2 saturations were obtained with all arterial blood gas samples.

Exclusion criteria were lung hypoplasia syndromes, congenital heart disease (other than a small, hemodynamically insignificant ventricular septal defect) as determined by echocardiography, intracranial hemorrhage ≥grade 2, uncorrected polycythemia (hematocrit ≥70%), mean systemic arterial pressure <35 Torr, a lethal syndrome, a suspected or confirmed chromosomal abnormality, use of intravenous vasodilators after entry criteria were met at the study site, uncontrollable coagulopathy or serious bleeding, and enrollment in any other investigational drug or interventional study. Patients were excluded if they had received previous or concomitant surfactant therapy. Patients who received a trial of high-frequency ventilation within 6 hours before starting the treatment gas were also ineligible.

Masking Procedures and Randomization

Strict masking procedures and personnel designations were approved by the steering committee before a site enrollment. Clinical investigators remained masked to the group assignment through the 1-year follow-up for all patients in the study. The clinical investigator managed patient care, assured compliance to the protocol, and assigned adverse events.

The site's unmasked laboratory investigator randomized patients to a placebo or nitric oxide (NO) dose group from a scratch off card. The randomization was blocked for each site in a block size of four patients allocated to one of the four treatment gases. The laboratory investigator set up, calibrated, and operated the I-NO delivery device and measured methemoglobin. All sites used Ciba-Corning 270 Co-oximeters (Ciba Corning Diagnostics Corporation, Medford, MA) for methemoglobin levels.

Baseline Procedures

As soon as the patient was randomized, baseline hemodynamic, ventilator, and blood gas analyses were obtained at three time points 15 to 30 minutes apart. A baseline methemoglobin level was also obtained. If the patient met entry criteria at the first two time points, the F_{IO_2} was reduced to 0.95, and the third baseline measurement was obtained. If the Pao_2 remained ≥40 and ≤100 Torr, treatment gas was begun immediately. A patient who failed baseline criteria was allowed one additional opportunity to meet baseline oxygen criteria if deemed stable by the clinical investigator.

[illegible]

starting the treatment gas: a complete blood count, serum creatinine, blood urea nitrogen, total protein, albumin, total bilirubin, alkaline phosphatase, lactic acid dehydrogenase, serum glutamic-oxaloacetic transaminase, total calcium, inorganic phosphorous, uric acid, and glucose.

I-NO Delivery

The I-NO delivery system (Ohmeda, PPD, Madison, WI) was designed expressly to deliver NO mixed with nitrogen, or nitrogen alone (BOC Specialty Gases, Port Allen, LA) into the inspiratory limb of the ventilator circuit using a mass flow controller. A sample gas catheter was attached to the inspiratory limb of the ventilator immediately before the patient connection. Electrochemical detectors attached to the delivery device provided a continuous measurement of NO and NO_2 (model EC90 NO monitor and model EC40 NO_2 monitor, Bedfont Scientific Ltd, Kent, England). The accuracy of NO measurement for values between 0 to 5 ppm was ± 0.5 ppm and for 5 to 80 ppm, was ± 2 ppm, regardless of the F_{IO_2}.[17] Validation was performed by using a known standard, blended by mass flow controllers and verified by chemiluminescence (error of ± 1%). Electrochemical cell analyzers for NO_2 have been shown to over estimate NO_2 levels, due to the formation of NO_2 in the sampling circuit.[18] In the presence of oxygen, the NO_2 monitor overestimates by 1.2 ppm at 80 ppm of NO, 0.3 ppm at 40 ppm of NO, and 0.1 ppm at 20 ppm of NO. Verification was performed using a selective NO_2 ultraviolet absorbance analyzer. The linearity of the NO_2 analyzers was within ± 3%.

On randomization, the laboratory investigator calibrated the delivery device with standard concentrations of NO (112 ppm) in nitrogen and NO_2 (7.2 ppm) in nitrogen. The I-NO delivery device was [illegible] To deliver NO at doses of 0, 5, 20, and 80 ppm, 1600 ppm of NO, balance N_2, were used. Because delivery of any treatment gas diluted the ventilator gas by 5%, the maximal F_{IO_2} delivered to the patient was 0.95. Therefore, patients were placed on an F_{IO_2} setting of 0.95 before starting treatment gas. The ventilator F_{IO_2} setting was increased to 1.0 when the treatment gas was started. As a result, an F_{IO_2} of 0.95 was delivered on initiation of the treatment gas for all groups.

Protocol for Management During Treatment Gas Administration

No F_{IO_2} or ventilator changes were to be made over the first half hour of treatment gas. High-frequency jet and oscillatory ventilation were not permitted. Ventilator settings, heart rate, blood pressure, and postductal arterial blood gases, preductal and postductal transcutaneous oxygen saturations, inspired gas levels, and methemoglobin levels were obtained at 0.5, 1, 2, 3, 4, and then every 4 hours or as needed while on 100% treatment gas. Patients were not permitted to receive treatment gas for >14 days.

Study patients received a fixed dose of either 0, 5, 20, or 80 ppm of NO until one of four events occurred: 1) a treatment success was achieved, based on improved oxygenation (Pa_{O_2} ≥60 Torr, F_{IO_2} <0.6, and mean airway pressure <10 cm H_2O); 2) a treatment failure resulted, based on a decrease of Pa_{O_2} <40 Torr for 30 minutes in the absence of a reversible mechanical problem, a mean systemic arterial pressure <35 Torr, the patient reached the site's ECMO criteria, 14 days of treatment gas had elapsed, or if remaining in the study was not in the best interest due to cardiopulmonary instability or local ECMO criteria that was not covered by the study's failure criteria; 3) inspired NO_2 levels were >3 ppm for 30 minutes[19]; or 4) a methemoglobin level that exceeded 7%. All patients, whether treatment successes or failures, were included in the data analyses.

For treatment successes and failures, the protocol permitted sequential 20% decrements in treatment gas at a minimum of 30 minutes and maximum of 4 hours. Ventilator settings, an arterial blood gas, preductal and postductal transcutaneous saturations, inspiratory gas levels, and vital signs were required immediately before and 30 minutes after a 20% reduction. During this half hour period, it was requested that no ventilator change be made unless the Pa_{O_2} became <40 Torr. If this level of hypoxemia occurred on a reduction, the treatment gas could be increased 20%. The weaning process would begin again when the criteria for success were met or in the case of a treatment failure, the treatment gas would [illegible]. Treatment gas could not be re-instituted and no other investigational drug or intervention was permitted. I-NO for treatment failures was not permitted.

For patients with elevated methemoglobin and inspired NO_2 levels based on the protocol definitions, treatment gas could be continued at a lower level (one of the 20% decrements) if the methemoglobin or NO_2 levels dropped below threshold levels.

Posttreatment Gas Data

A methemoglobin level was obtained 2 hours after the treatment gas was discontinued. The baseline complete blood count and blood chemistries were repeated within 12 hours of discontinuing the treatment gas. A repeat head ultrasound, computerized axial tomography, or magnetic resonance imaging was required before discharge. A bilateral evoked response hearing screen was obtained before discharge. A chest x-ray was performed on day 28 if the patient still required supplemental oxygen.

Safety Monitoring

An independent data safety and monitoring board was composed of statisticians and pediatric specialists. An interim, blinded safety analysis was performed after data from 100 patients were obtained.

Sample Size and Statistics

We estimated the incidence of PPHN major sequelae before the start of this trial by a retrospective survey of seven sites. Data were obtained on 107 patients who would have been eligible for the present study. The incidences of the major sequelae were: death, 8%; ECMO, 36%; neonatal neurologic sequelae 20%; and BPD, 5%. To determine if NO could reduce PPHN major sequelae by 30% (α level = 0.05, β level = 0.2), a total of 320 patients (80 in each of 4 groups) were required. The Cochran-Mantel-Haenszel χ^2 test was used for discrete or categorical data, such as PPHN major sequelae (death, ECMO, neurologic sequelae, BPD, or composite), treatment failures due to cardiopulmonary instability, and adverse events by organ systems. Fisher's exact test was used if the frequencies were small.

The Wilcoxon rank sum test was used to analyze continuous variables (eg, the time-weighted oxygenation index [TWOI], duration of supplemental oxygen, acute change in Pa_{O_2}, or methemoglobin levels). For ventilatory and hemodynamic data, baseline was considered as the third qualifying time point (F_{IO_2} = 0.95) immediately before starting the treatment gas. A two-tailed t test was used only for the change from baseline for the clinical hematologic and biochemical variables. The significance level for all tests was set at 0.05. There was no α level adjustment for pairwise comparisons performed in the study. The incidence of adverse events was tabulated using the COSTART body system classification.[20]

One of the major secondary endpoints of this study was to determine whether I-NO produced a sustained improvement in oxygenation. Therefore, we prospectively defined the TWOI as the change in oxygenation index (OI) from the individual's baseline OI over time, divided by the duration on treatment gas up to 24 hours. This method adjusts for attrition from treatment failure or success. If the patient worsened from his/her own baseline, the TWOI would be a positive number. If the patient improved, the index would be a negative number as shown in Fig 1.

RESULTS

Enrollment began in April 1994. One hundred fifty-five patients were enrolled. The trial was halted in June 1996 because of slow recruitment. The accrual goal was 320 patients.

Patients Screened and Patients Enrolled

A total of 1282 patients were screened. The most common conditions preventing enrollment were: oxygenation outside the eligible range (26%) and lack of echocardiographic evidence of PPHN (19%). Surfactant therapy (12%), high-frequency ventilation (9%), prematurity (8%), lung hypoplasia syndromes

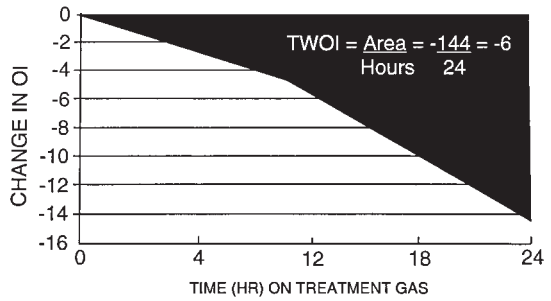

Fig 1. Calculation of the time-weighted oxygenation index (TWOI) as a measure of the change in oxygenation over time by a treatment gas (control or NO) in term infants with PPHN. The black area is the change in the OI from the baseline OI over the duration of the treatment gas or 24 hours, whichever came first. The area is divided (weighted) by time. In this theoretical example, the patient had a negative TWOI indicating an improvement in oxygenation over time.

(8%), and age >72 hours (5%) were the other conditions preventing enrollment.

A total of 8 patients, 2 in the control group and 6 in the NO groups were erroneously enrolled. All patients were included in the efficacy and safety analyses. Of the 155 randomized patients, the number of patients who received treatment in each group (0, 5, 20, and 80 ppm) were 41, 41, 36, and 37 respectively.

Baseline Patient Profile

Baseline variables were similar among treatment groups. Baseline data are presented (Tables 1 and 2) for the control group (N = 41) and the pooled I-NO group (N = 114). The majority of patients were delivered by cesarean section (62%) and at hospitals other than the study site (over 90%). Most infants (77%) received conventional mechanical ventilation and 5% received high-frequency jet or oscillatory ventilation before admission to the study site. Underlying conditions associated with PPHN were also well-balanced among treatment groups with a majority of patients diagnosed with meconium aspiration. Although there were more patients with idiopathic PPHN in the NO groups compared with placebo, this was not statistically significant. Seizures were documented in 17% of the control patients and 20% of the patients who went on to receive NO. Abnormal head ultrasounds, almost all due to low-grade intracranial hemorrhages, were demonstrated in 10% of the control patients and 5% of the pooled NO patients.

TABLE 1. Patient Profile

Trait	Control Group (n = 41)	Nitric Oxide Groups (n = 114)
Birth weight, kg*	3.4 ± 0.5	3.4 ± 0.5
Gestational age, wk*	39.7 ± 1.8	39.8 ± 1.6
5-Min Apgar Score, no. *‡	7 ± 2	7 ± 2
Age, start R_x gas, h*	26 ± 18	25 ± 17
Male sex, no. (%)	27 (66)	58 (51)
Race, no. (%)		
Black	11 (27)	25 (22)
Hispanic	10 (24)	20 (18)
White	20 (49)	59 (52)
Other	0 (0)	10 (9)
Cesarean section, no. (%)†	25 (61)	70 (62)
Inborn, no. (%)	3 (7)	12 (11)
Primary diagnosis, no. (%)		
Meconium aspiration syndrome	26 (63)	60 (53)
Sepsis	13 (32)	30 (26)
Idiopathic PPHN	5 (12)	24 (21)
Respiratory distress syndrome	4 (10)	13 (11)
Other	5 (12)	22 (19)

* Values are mean ± SD.
† One patient has missing information.

TABLE 2. Baseline Ventilatory Status

Variable	Control Group (n = 41)	Nitric Oxide Groups (n = 114)
F_{IO_2}	0.95 ± 0	0.95 ± 0
Mean airway pressure (cm H_2O)	14 ± 4	14 ± 3
Pao_2 (Torr)	59 ± 16	64 ± 39
Oxygenation index (cm H_2O/Torr)	25 ± 10	24 ± 9
Arterial/alveolar Po_2 ratio	0.09 ± 0.02	0.10 ± 0.06
pH	7.48 ± 0.12	7.50 ± 0.11
$Paco_2$ (Torr)	33 ± 10	30 ± 9
Intermittent mandatory ventilation (breaths/min)	59 ± 15	59 ± 15
Peak inspiratory pressure (cm H_2O)	33 ± 6	32 ± 6
Positive end expiratory pressure (cm H_2O)	5 ± 2	5 ± 1

Values are mean ± SD at 25 ± 17 hours after birth.

The baseline ventilatory (Table 2) and hemodynamic conditions were also very similar between control and NO groups. The patients required high levels of conventional ventilatory support. The baseline inspiratory F_{IO_2} for all patients was 0.95 by protocol. Systolic, mean, and diastolic, systemic arterial pressures were 67 ± 13, 53 ± 10, and 44 ± 10 Torr, respectively. Dopamine and/or dobutamine (to a lesser extent) were used in 76% and 74% of the control and the pooled NO group, respectively, at the start of the treatment gas. Most patients had echocardiographic evidence for PPHN; only 9% were diagnosed by preductal versus postductal oxygen saturation difference of >10%. The mean preductal and postductal transcutaneous oxygen saturations were similar for all groups; for the control group the saturations were 93.6 ± 3.0% and 93.2% ± 4.1%, respectively.

Acute Changes in Blood Gases, pH, and Hemodynamics

The acute changes in Pao_2 after the first half hour of treatment gas, on stable ventilator settings are shown in Fig 2. There was a statistically significant increase in Pao_2 from baseline for each NO group compared with control. Although a higher mean Pao_2 was observed for the 80 ppm dose, this was not statistically different from the other NO doses. The corresponding OIs at 30 minutes for each group from lowest to highest NO dose were 24 ± 14, 20 ± 11, 21 ± 13, and 15 ± 10; the pooled NO value was 19 ± 11 (cm H_2O/Torr). There were no appreciable differences between and within groups for pH, $Paco_2$, or

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