Efficacy of Inhaled Nitric Oxide for Hypoxic Respiratory Failure in Term and Late Preterm Infants by Baseline Severity of Illness: A Pooled Analysis of Three Clinical Trials

Sergio G. Golombek, MD, MPH[1,2]; and Joseph N. Young, MS[3]

[1]Regional Neonatal Center–Maria Fareri Children's Hospital at Westchester Medical Center, Valhalla, New York; [2]Division of Neonatology, Department of Pediatrics, New York Medical College, Valhalla, New York; and [3]Ikaria, Clinton, New Jersey

ABSTRACT

Background: The use of inhaled nitric oxide (NO) has been studied for the treatment of hypoxic respiratory failure (HRF) in newborns who require mechanical ventilation. Although inhaled NO is typically used in patients with a greater severity of illness, the treatment response (eg, improvement in oxygenation) and the associated outcomes (eg, time on mechanical ventilation) may be affected by the timing of treatment and baseline severity of illness.

Objectives: This analysis was conducted to assess the effects of inhaled NO on measures of oxygenation, efficacy of inhaled NO across a range of illness severity strata, and duration of mechanical ventilation.

Methods: This was a retrospective pooled analysis of 3 pivotal clinical trials comparing inhaled NO (starting dose, 20 ppm) with control (100% oxygen or nitrogen gas) in term and late preterm (gestational age ≥34 weeks) infants with HRF who required mechanical ventilation. Data on partial pressure of arterial oxygen (PaO_2), inspired oxygen concentration, and mean airway pressure at 0 and 30 minutes after administration of inhaled NO were extracted from the case-report forms from the 3 clinical trials and used to calculate the oxygenation index (OI). The change in PaO_2 was assessed by baseline severity of illness, stratified based on the OI (≤15 = mild, >15 to ≤25 = moderate, >25 to ≤40 = severe, >40 = very severe). The duration of mechanical ventilation was compared between the inhaled NO and control groups.

Results: Five hundred twenty-four patients were analyzed (260 inhaled NO, 264 control). The overall mean (SD) birth weight and gestational age of the patients were 3.4 (0.58) kg and 39.1 (1.96) weeks, respectively. After 30 minutes of treatment, there was a significant increase from baseline in PaO_2 with inhaled NO compared with control (54.91 vs 14.15 mm Hg, respectively; $P < 0.001$). The increases from baseline in PaO_2 at 30 minutes were statistically significant for inhaled NO compared with controls across all severity strata (mild: 62.39 vs –23.03 mm Hg, respectively [$P = 0.003$]; moderate: 52.93 vs 18.28 mm Hg [$P = 0.004$]; severe: 62.07 vs 13.95 mm Hg [$P < 0.001$]; very severe: 45.17 vs 18.66 mm Hg [$P < 0.001$]). On Kaplan-Meier analysis, the median duration of mechanical ventilation was 11 and 14 days in the inhaled NO and control groups, respectively ($P = 0.003$).

Conclusions: This pooled analysis of data from 3 clinical trials in term and late preterm infants with HRF requiring mechanical ventilation found that inhaled NO at a starting dose of 20 ppm was associated with improved oxygenation acutely and a reduced median duration of mechanical ventilation. The improvements were significant across all severity-of-illness strata. (*Clin Ther.* 2010;32:939–948) © 2010 Excerpta Medica Inc.

Key words: hypoxia, hypoxic respiratory failure, newborn, nitric oxide, oxygenation index, arterial oxygen pressure.

INTRODUCTION

The annual number of term and late preterm newborns in the United States requiring mechanical ventilation as a result of hypoxic respiratory failure (HRF) has been estimated at 35,000.[1] Underlying causes of HRF include idiopathic persistent pulmonary hypertension of the newborn (PPHN), aspiration of meconium, respiratory distress syndrome, pneumonia, congenital diaphragmatic hernia, and oligohydramnios.[1] Increased pulmonary

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vascular resistance, ventilation–perfusion mismatch, and right-to-left shunting are frequently associated with HRF and lead to systemic hypoxemia.[1]

Past treatments for HRF have included alkalinization by hyperventilation, neuromuscular blockade, sedation, and use of inotropic support or intravenous nonselective vasodilators.[2] If patients become unresponsive to therapy, extracorporeal membrane oxygenation (ECMO) may be used,[2] although this procedure is highly invasive and is considered a treatment of last resort.[2,3] Nitric oxide (NO) is produced endogenously and plays an important role in the regulation of vascular smooth muscle tone via the guanylate cyclase signaling pathway.[3] Studies in animals and humans have reported that exogenous inhaled NO relaxes the pulmonary vasculature with no appreciable systemic effects and can improve ventilation–perfusion matching and oxygenation.[4–9]

In the United States, inhaled NO is approved for use in conjunction with ventilatory support and other appropriate agents in term and late preterm neonates with HRF associated with PPHN, as confirmed by echocardiographic or clinical evidence.[10] The approved labeling does not limit use of inhaled NO to patients with a specific severity of illness, as determined by either the oxygenation index (OI)—calculated as inspired oxygen concentration · mean airway pressure/partial pressure of arterial oxygen (PaO_2)—or any other physiologic parameter. A study by Konduri et al,[11] however, found that the standard practice was to initiate treatment with inhaled NO in neonates with more severe HRF (ie, OI >25). This was further supported by a recent 2-year analysis of the European inhaled NO registry, which found that the median baseline OI in term and near-term infants receiving inhaled NO therapy ranged from 23 (treatment nonresponders) to 26 (responders).[12]

Three multicenter, prospective, randomized, double-blind, controlled clinical trials have examined the tolerability and efficacy of inhaled NO in the treatment of HRF in newborns.[13–15] In these trials, treatment with inhaled NO at a starting dose of 20 ppm was well tolerated and effective, and was associated with a decreased need for ECMO, with no additional benefit at a dose of 80 ppm. Although the trials did not assess improvement in oxygenation based on severity of illness, it was subsequently hypothesized that earlier treatment (ie, initiation of treatment at a less severe stage of illness) might result in better outcomes. Post hoc analysis of one of the trials found that a complete response to inhaled NO treatment was more likely in infants with a lower OI.[13] Thus, administration of inhaled NO at earlier, less severe stages of disease may be beneficial.

Whereas the 3 clinical trials focused on the primary end points of death and the need for ECMO, the present pooled analysis was designed to more closely examine the effect on oxygenation, measured in terms of PaO_2 across a range of illness severity strata, as well as the required number of days of mechanical ventilation.

PATIENTS AND METHODS

Pivotal Trials

Three pivotal clinical trials formed the basis for the approval of inhaled NO for the treatment of HRF in term and late preterm (gestational age ≥34 weeks) neonates[10]: the Neonatal Inhaled Nitric Oxide Study (NINOS),[13] the Inhaled Nitric Oxide/Persistent Pulmonary Hypertension of the Newborn (I-NO/PPHN) study,[14] and the Clinical Inhaled Nitric Oxide Research Group Initiative (CINRGI).[15] The protocols and protocol amendments for the 3 studies were approved by local institutional review boards before patient enrollment, and written informed consent was obtained from the parents or guardians of each patient before the start of the study.

The study analyses included all patients with data captured at 0, 0.5, 1, or 24 hours after receipt of inhaled NO (starting dose, 20 ppm) or control. Control was 100% oxygen in NINOS,[13] inhaled NO 0 ppm in I-NO/PPHN,[14] and nitrogen gas in CINRGI.[15] Because data were not available for the change from baseline in PaO_2 at 1 and 24 hours in NINOS, these time points were not included in the pooled analysis. Patients who received randomized starting doses other than inhaled NO 20 ppm were excluded from the pooled analysis; this cutoff was chosen to establish as large and heterogeneous an analytic pool as possible. Dose increases were permitted in the NINOS and I-NO/PPHN trials; however, doses >20 ppm were not permitted in the CINRGI study. No exclusion criteria were based on demographic characteristics or underlying diagnoses. The principal characteristics of the 3 trials are summarized in **Table I**.

Pooled Analysis

Deidentified data for the present retrospective analysis were extracted from the case-report forms of the 3 clinical trials. The analysis was approved by the institutional review board of New York Medical College, Valhalla, New York.

Data were pooled to assess the degree and time course of change in PaO_2 across all 3 studies. For inclusion in

Table I. Principal details of the 3 clinical trials of inhaled nitric oxide (NO) included in the pooled analysis.

Study	No. of Patients	Patient Characteristics	Regimens	Major Results
NINOS[13]	235	Inclusion criteria: Gestational age ≥34 wk, requiring assisted ventilation for HRF; OI ≥25 Exclusion criteria: Age >14 d; congenital diaphragmatic hernia; known congenital heart disease	Inhaled NO 20 ppm or control (100% O_2) for up to 14 d; if PaO_2 increased ≤10–20 mm Hg, inhaled NO could be increased up to 80 ppm	Significantly lower incidence of combined primary end point (death by 120 d of age or initiation of ECMO) with inhaled NO vs control (46% vs 64%, respectively; $P = 0.006$); no significant reduction in mortality (14% vs 17%); significant differences in change in PaO_2 (58.2 vs 9.7 mm Hg; $P < 0.001$), OI (–14.1 vs +0.8; $P < 0.001$), and alveolar–arterial O_2 gradient after 30 min (–60.0 vs –6.7 mm Hg; $P < 0.001$); no significant differences in mean length of hospitalization (36.4 and 29.5 d) or duration of mechanical ventilation (11.6 and 11.7 d)
I-NO/ PPHN[14]	155	Inclusion criteria: Gestational age ≥37 wk and birth weight ≥2500 g (≥2000 g if gestational age ≥39 wk) Exclusion criteria: Lung hypoplasia syndromes; congenital heart disease; intracranial hemorrhage ≥grade 2; uncorrected polycythemia; mean systemic arterial pressure ≤35 mm Hg; suspected/confirmed chromosomal abnormality; use of intravenous vasodilators after meeting entry criteria; uncontrollable coagulopathy or serious bleeding; previous or concomitant surfactant therapy; high-frequency ventilation within 6 h of start of study treatment	Inhaled NO 5, 20, or 80 ppm or control (0 ppm)	No significant differences between inhaled NO and control in primary end point (PPHN MSI, including death, neurologic injury, bronchopulmonary dysplasia, and ECMO rescue) (50% and 56%, respectively); significant increases vs baseline in PaO_2 at 30 min for all doses of inhaled NO ($P < 0.05$); significant reductions vs control in baseline-adjusted, time-weighted OI over 24 h ($P = 0.01$)
CINRGI[15]	248	Inclusion criteria: Gestational age ≥34 wk, requiring assisted ventilation with evidence of pulmonary hypertension; OI ≥25 Exclusion criteria: Mean blood pressure <35 mm Hg; PaO_2 <30 mm Hg; lethal congenital anomaly; substantial bleeding diathesis; active seizures; history of severe asphyxia	Inhaled NO 20 ppm or control (nitrogen 20 ppm) for up to 24 h; after 4 h of treatment, dose decreased to 5 ppm if stable, PaO_2 ≤60 mm Hg, and pH ≤7.55	Significantly lower incidence of primary end point (use of ECMO) with inhaled NO vs control (38% vs 64%, respectively; $P = 0.001$); significant increase in arterial:alveolar O_2 ratio with inhaled NO vs control (0.10 vs 0.05; $P = 0.02$); no significant differences in death (8% and 11% of patients), length of hospitalization (25 and 29 d), duration of assisted ventilation (11 and 12 d), supplemental O_2 use after discharge (5% and 11%), intraventricular hemorrhage (3% and 7%), or seizure (1% and 1%)

NINOS = Neonatal Inhaled Nitric Oxide Study; HRF = hypoxic respiratory failure; OI = oxygenation index; PaO_2 = partial pressure of arterial oxygen; ECMO = extracorporeal membrane oxygenation; I-NO/PPHN = Inhaled Nitric Oxide/Persistent Pulmonary Hypertension of the Newborn; MSI = Major Sequelae Index; CINRGI = Clinical Inhaled Nitric Oxide Research Group Initiative.

the evaluation of change from baseline in PaO_2, patients needed to have values from both hour 0 and 30 minutes after administration of inhaled NO or control. Data on PaO_2, inspired oxygen concentration (FiO_2), and mean airway pressure at 0 and 30 minutes after administration of inhaled NO or control were used to calculate the OI. The change in PaO_2 was then examined by severity of illness, stratified by baseline OI as follows: ≤15 = mild, >15 to ≤25 = moderate, >25 to ≤40 = severe, and >40 = very severe. Finally, the duration of mechanical ventilation was assessed.

Statistical Analysis

No censoring was applied in the analyses of PaO_2 or baseline severity of illness; patients who died or received ECMO were censored from the analysis of duration of mechanical ventilation. The Wilcoxon rank sum test was used to calculate *P* values for the difference between the inhaled NO and control groups. Kaplan-Meier analysis was performed to analyze the duration of mechanical ventilation, with significance calculated using the log-rank test.

RESULTS

Five hundred twenty-four patients (260 inhaled NO, 264 control) met the inclusion criteria for the pooled analysis (**Table II**). Baseline demographic characteristics were comparable between groups. The overall mean (SD) birth weight and gestational age of study patients were 3.4 (0.58) kg and 39.1 (1.96) weeks, respectively.

Oxygenation

After 30 minutes of treatment, mean PaO_2 was significantly higher in the inhaled NO groups compared with the control groups in the NINOS[13] (116.20 vs 62.01 mm Hg, respectively; $P < 0.001$) and CINRGI[15] (129.50 vs 72.30 mm Hg; $P < 0.001$) trials, whereas the difference between inhaled NO and control at 30 minutes was not significant in the I-NO/PPHN[14] study (97.94 vs 77.00 mm Hg) (**Table III**). In the pooled analysis of patients who had values at 30 minutes (n = 494), PaO_2 was significantly higher at 30 minutes in the inhaled NO group compared with the control group (118.92 vs 68.28 mm Hg; $P < 0.001$).

In those patients in NINOS who initiated treatment at inhaled NO 20 ppm, the change from baseline in mean PaO_2 at 30 minutes was significant compared with control (60.28 vs 8.85 mm Hg, respectively; $P < 0.001$). The comparison was also significant in I-NO/PPHN[14] (38.63 vs 17.95 mm Hg; $P = 0.046$) and CINRGI[15] (54.64 vs 19.08 mm Hg; $P < 0.001$), as well as in the 3-study pooled data set (54.91 vs 14.15 mm Hg; $P < 0.001$) (**Figure 1**). These changes occurred without any adjustment in FiO_2 during the 30-minute window.

Table II. Pooled demographic characteristics of patients in the Neonatal Inhaled Nitric Oxide Study,[13] Inhaled Nitric Oxide/Persistent Pulmonary Hypertension of the Newborn,[14] and Clinical Inhaled Nitric Oxide Research Group Initiative[15] trials.

Variable	Inhaled Nitric Oxide (n = 260)	Control (n = 264)	All Patients (N = 524)
Birth weight, mean (SD), kg	3.4 (0.56)	3.3 (0.59)	3.4 (0.58)
Gestational age, mean (SD), wk	39.2 (1.79)	39.0 (2.12)	39.1 (1.96)
Sex, no. (%)			
Male	135 (51.9)	166 (62.9)	301 (57.4)
Female	125 (48.1)	98 (37.1)	223 (42.6)
Race, no. (%)			
White	138 (53.1)	145 (54.9)	283 (54.0)
Black	71 (27.3)	65 (24.6)	136 (26.0)
Hispanic	32 (12.3)	39 (14.8)	71 (13.5)
Asian	4 (1.5)	5 (1.9)	9 (1.7)
Other/unknown	15 (5.8)	10 (3.8)	25 (4.8)

Table III. Partial pressure of arterial oxygen (PaO_2) at baseline and after 30 minutes of treatment with inhaled nitric oxide (NO) in the 3 clinical trials included in the pooled analysis.

	NINOS[13]		I-NO/PPHN[14]		CINRGI[15]		All Studies	
Time Point	NO	Control	NO	Control	NO	Control	NO	Control
Baseline								
No. of patients	114	121	36	41	107	102	257	264
PaO_2, mean (SD)								
mm Hg	55.43 (39.77)	52.50 (29.79)	60.06 (15.76)	58.63 (15.80)	75.71 (67.39)	53.14 (33.03)	64.52 (52.00)	53.70 (29.43)
kPa	7.4 (5.3)	7.0 (4.0)	8.0 (2.1)	7.8 (2.1)	10.1 (9.0)	7.1 (4.4)	8.6 (6.9)	7.1 (3.9)
Pairwise *P**	0.610		0.826		0.005		0.029	
30 Minutes								
No. of patients	111	116	35	40	98	94	244	250
PaO_2, mean (SD)								
mm Hg	116.20 (102.12)	62.01 (50.94)	97.94 (74.90)	77.00 (53.83)	129.50 (104.91)	72.30 (64.50)	118.92 (100.05)	68.28 (56.94)
kPa	15.5 (13.6)	8.2 (6.8)	13.0 (10.0)	10.2 (7.2)	17.2 (14.0)	9.6 (8.6)	15.8 (13.3)	9.1 (7.6)
Pairwise *P**	<0.001		0.232		<0.001		<0.001	

NINOS = Neonatal Inhaled Nitric Oxide Study; I-NO/PPHN = Inhaled Nitric Oxide/Persistent Pulmonary Hypertension of the Newborn; CINRGI = Clinical Inhaled Nitric Oxide Research Group Initiative.
*Wilcoxon rank sum test.

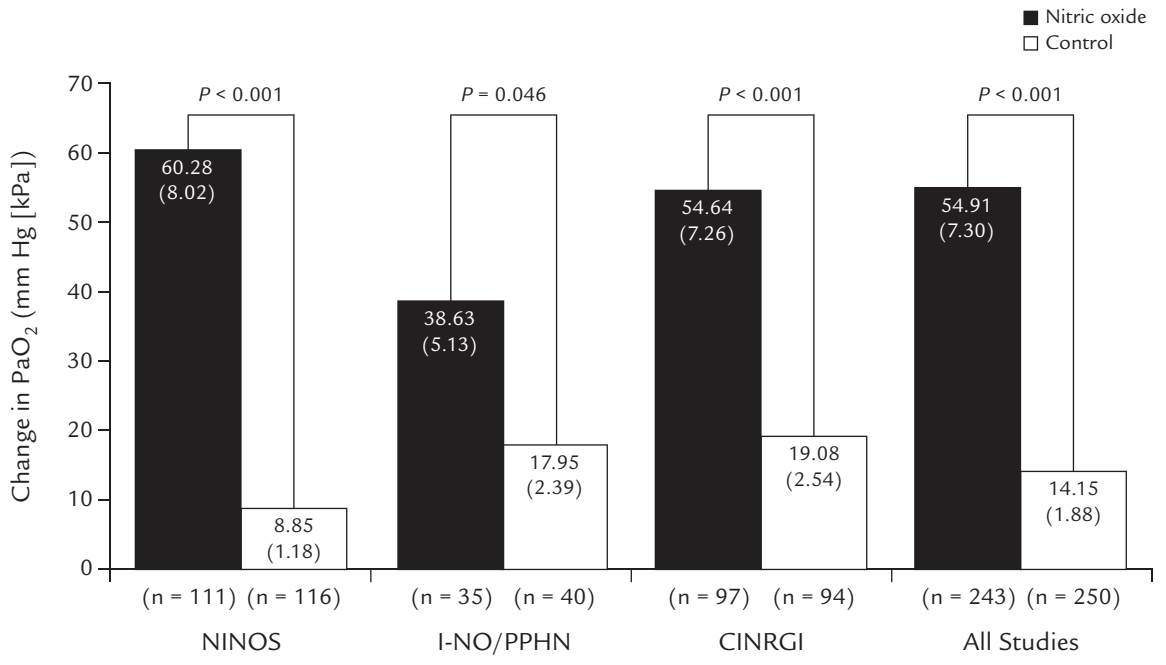

Figure 1. Change from baseline in mean partial pressure of arterial oxygen (PaO_2) after 30 minutes of inhaled nitric oxide treatment. Pairwise *P* values were calculated using the Wilcoxon rank sum test. NINOS = Neonatal Inhaled Nitric Oxide Study[13]; I-NO/PPHN = Inhaled Nitric Oxide/Persistent Pulmonary Hypertension of the Newborn[14]; CINRGI = Clinical Inhaled Nitric Oxide Research Group Initiative.[15]

Severity of Illness

Patients who received inhaled NO had a significantly higher PaO_2 after 30 minutes compared with those who did not receive inhaled NO in all severity strata (mild: 239.96 vs 96.76 mm Hg, respectively [$P < 0.001$]; moderate: 133.49 vs 86.72 mm Hg [$P < 0.001$]; severe: 116.09 vs 68.76 mm Hg [$P = 0.001$]; very severe: 82.24 vs 55.65 mm Hg [$P < 0.001$]) (**Table IV**).

When the change from baseline in PaO_2 after 30 minutes was analyzed by baseline severity of illness, there were significant increases from baseline with inhaled NO compared with control in those with mild illness (62.39 vs –23.03 mm Hg, respectively; $P = 0.003$), moderate illness (52.93 vs 18.28; $P = 0.004$), severe illness (62.07 vs 13.95; $P < 0.001$), and very severe illness (45.17 vs 18.66; $P < 0.001$) (**Figure 2**).

Duration of Mechanical Ventilation

In the Kaplan-Meier analysis of subjects who survived without ECMO, the median duration of mechanical ventilation was 11 days in those receiving inhaled NO and 14 days in the control group. The log-rank test indicated a significant reduction in this end point in the inhaled NO group compared with the control group ($P = 0.003$) (**Figure 3**).

DISCUSSION

This pooled analysis of data from 3 clinical trials in term and late preterm (gestational age ≥34 weeks) infants with HRF found that administration of inhaled NO was associated with significant increases in PaO_2 after 30 minutes of treatment compared with control ($P \leq 0.001$), regardless of baseline OI. Kaplan-Meier analysis found a significant reduction in the median duration of mechanical ventilation with inhaled NO compared with control ($P = 0.003$).

Although each of the original clinical trials found significant improvements in oxygenation after administration of inhaled NO, they used varying criteria and parameters. Using the pooled findings to examine the single parameter of PaO_2 after 30 minutes allowed a sharper focus on the effect of inhaled NO on oxygenation in patients with HRF.

Because of the retrospective design of this study, it was not possible to determine whether earlier treatment

Table IV. Partial pressure of arterial oxygen (PaO_2) at baseline and after 30 minutes of treatment with inhaled nitric oxide (NO), stratified by baseline severity of illness (oxygenation index [OI]).*

	OI ≤15		OI >15 to ≤25		OI >25 to ≤40		OI >40	
Time Point	NO	Control	NO	Control	NO	Control	NO	Control
Baseline								
No. of patients	24	18	52	49	99	83	86	112
PaO_2, mean (SD)								
mm Hg	180.13 (94.13)	119.31 (61.06)	74.75 (31.20)	68.02 (18.39)	53.97 (13.37)	54.44 (13.46)	37.27 (15.35)	36.75 (10.65)
kPa	24.0 (12.5)	15.9 (8.1)	9.9 (4.1)	9.0 (2.4)	7.2 (1.8)	7.2 (1.8)	5.0 (2.0)	4.9 (1.4)
Pairwise P†	0.023		0.301		0.600		0.772	
30 Minutes								
No. of patients	23	17	47	47	96	79	81	105
PaO_2, mean (SD)								
mm Hg	239.96 (116.10)	96.76 (46.84)	133.49 (81.01)	86.72 (58.34)	116.09 (94.00)	68.76 (41.76)	82.24 (84.73)	55.65 (64.39)
kPa	31.9 (15.4)	12.9 (6.2)	17.8 (10.8)	11.5 (7.8)	15.4 (12.5)	9.1 (5.6)	10.9 (11.3)	7.4 (8.6)
Pairwise P†	<0.001		<0.001		0.001		<0.001	

*OI ≤15 = mild, OI >15 to ≤25 = moderate, OI >25 to ≤40 = severe, OI >40 = very severe.
†Wilcoxon rank sum test.

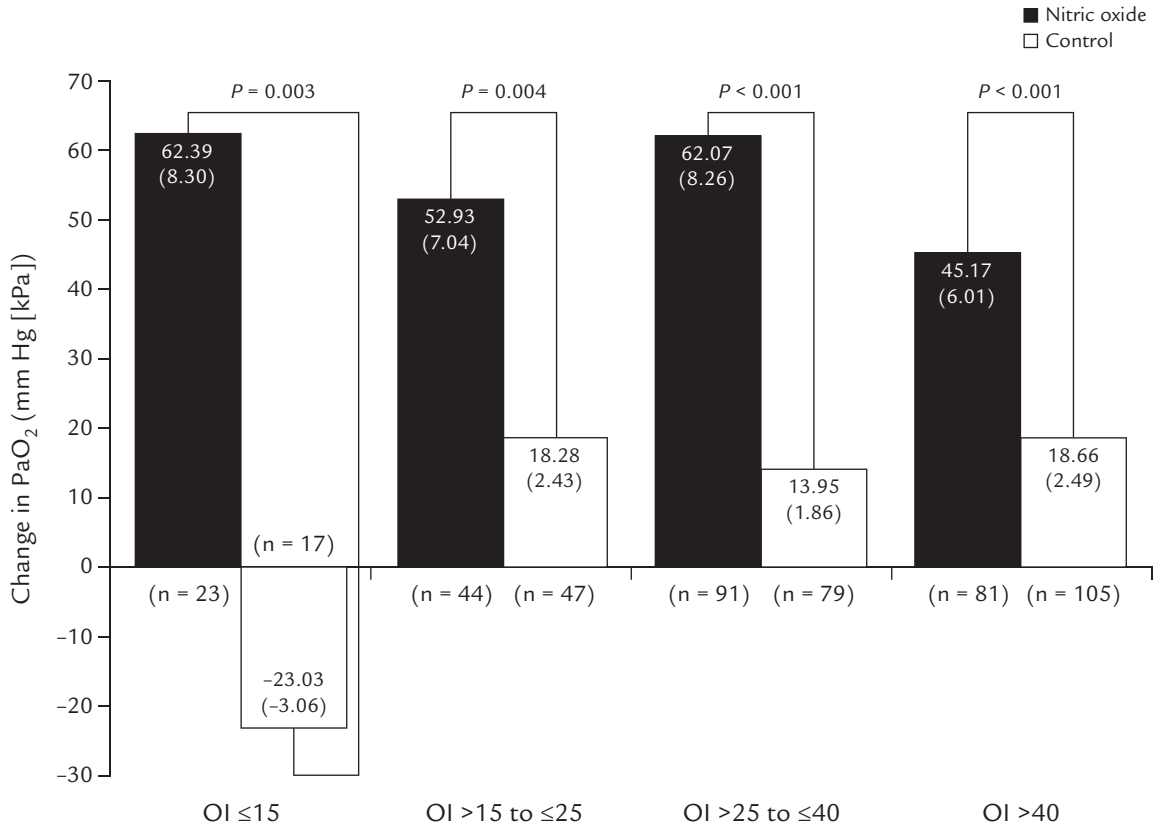

Figure 2. Change from baseline in mean partial pressure of arterial oxygen (PaO_2) after 30 minutes of inhaled nitric oxide treatment, stratified by baseline severity of illness (oxygenation index [OI]). Pairwise *P* values were calculated using the Wilcoxon rank sum test.

(ie, treatment in patients with less severe HRF) with inhaled NO was associated with better outcomes. However, this pooled analysis found that inhaled NO treatment was associated with significant increases in PaO_2 across the entire range of severity-of-illness OI strata ($P \leq 0.001$). This finding is supported by the results of a study in which early initiation of inhaled NO (starting dose, 5 ppm; OI ≥15 to <25) was associated with a significant increase in PaO_2 compared with standard treatment (inhaled NO 20 ppm; OI ≥25) (44.0 vs 8.5 mm Hg, respectively; $P < 0.001$), as well as a significant decrease in OI (–6.1 vs –2.2 mm Hg; $P = 0.001$).[11]

Although the improvement in oxygenation after inhaled NO treatment would be expected to result in a shorter duration of mechanical ventilation, none of the individual studies in this pooled analysis found a significant difference in this variable between the inhaled NO and control groups.[13–15] The studies may not have been sufficiently powered to address this variable.

Although oxygenation and the median duration of mechanical ventilation improved with inhaled NO treatment, the pooled analysis was limited by its retrospective design and the paucity of data. Based on their protocols, the NINOS[13] and CINRGI[15] studies primarily included severely hypoxic patients (OI ≥25), which limited the amount of data on less severely ill patients (OI <25) in the pooled analysis.

Another potential limitation of this analysis involves variations in the gestational age of eligible patients in the 3 studies. Two studies included patients with a gestational age ≥34 weeks,[13,15] whereas the I-NO/PPHN[14] study included term newborns (gestational age ≥37 weeks). Given the physiologic and metabolic immaturity of late preterm infants relative to term infants, there is a pos-

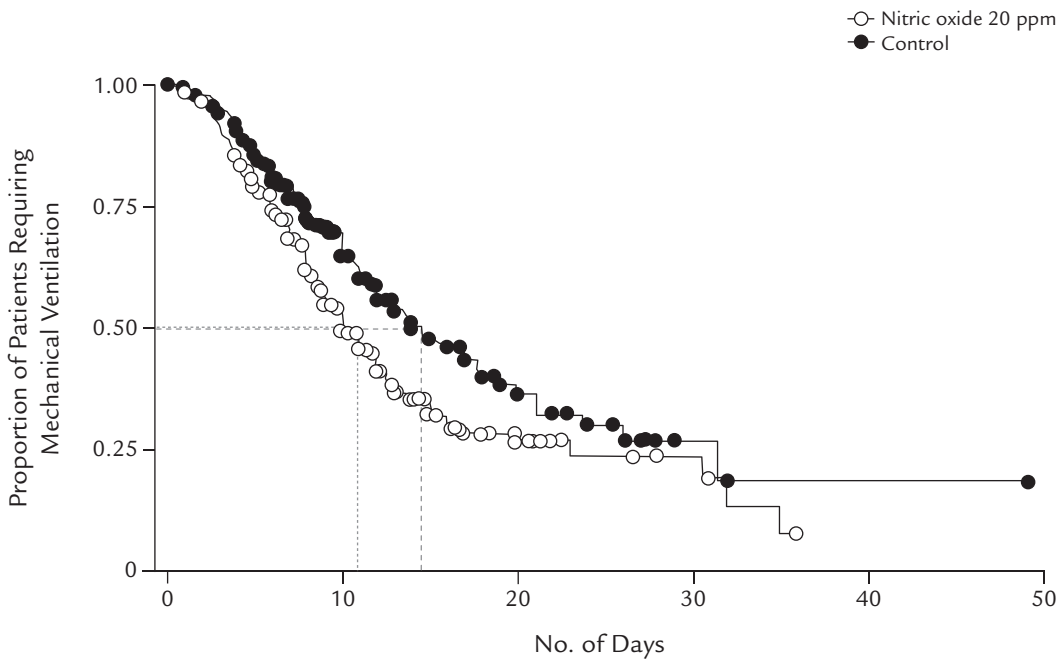

Figure 3. Kaplan-Meier analysis of the time to removal from mechanical ventilation. The broken line at 11 days represents the median duration of mechanical ventilation in the inhaled nitric oxide group, and the broken line at 14 days represents the corresponding value in the control group.

sibility that inclusion of late preterm infants may have influenced the results in the overall population. The 3 clinical trials were conducted before the 2006 National Institute of Child Health and Human Development report defining the subgroup of late preterm infants,[16] and evaluating the effects of inhaled NO in these gestational-age subsets (term and late preterm infants) was not a study objective. Nonetheless, the impact of the inclusion of late preterm infants on the response to treatment is likely to be minimal at most, as the majority of the patients were term newborns, as evidenced by the mean (SD) gestational age of 39.1 (1.96) weeks in the pooled study population.

There are few published clinical data comparing earlier and later initiation of treatment with inhaled NO. This analysis and other studies have found improvements in oxygenation with earlier treatment,[11,17] but data on outcomes such as risk of death and need for ECMO are limited. There is a need for future prospective studies that are adequately powered and designed to compare outcomes in patients with different degrees of illness severity to help determine whether earlier treatment with inhaled NO is associated with improved outcomes compared with later treatment.

CONCLUSIONS

In this pooled analysis of 3 clinical trials in term and late preterm (gestational age ≥34 weeks) infants with HRF, inhaled NO at a starting dose of 20 ppm had a positive impact on PaO_2 within 30 minutes, regardless of the initial severity of illness. Inhaled NO treatment was also associated with a significant reduction in the median duration of mechanical ventilation, which was 11 days with inhaled NO and 14 days in controls.

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Address correspondence to: Sergio G. Golombek, MD, MPH, Professor of Pediatrics and Clinical Public Health, New York Medical College, Attending Neonatologist, Regional Neonatal Center–Maria Fareri Children's Hospital, Westchester Medical Center, 100 Woods Road, Valhalla, NY 10595. E-mail: sergio_golombek@nymc.edu