Inhaled nitric oxide in persistent pulmonary hypertension of the newborn refractory to high-frequency ventilation

Saleh Al-Alaiyan and Edward Neiley

Background: This study was designed to evaluate the effect of nitric oxide (NO) on the management of neonates with severe persistent pulmonary hypertension refractory to high-frequency oscillatory ventilation.

Methods: The birth weight and the gestational age of infants were 3125.5 ± 794 g (mean ± SD) and 39 ± 2.4 weeks, respectively. All neonates were ventilated for an average of 137.5 min (range 90–180 min) prior to NO therapy. The mean oxygenation index (OI) of all neonates prior to NO was 46.3 ± 5 (mean ± SEM). NO was initially administered at 20 parts per million (ppm) for at least 2 h and increased gradually by 2 ppm to a maximum of 80 ppm.

Results: Eighteen infants (75%) responded and six (25%) did not respond to the treatment. Three neonates died in the responding group, while all the non-responders died ($P=0.0001$). The survival rate was 62.5% among all neonates. NO significantly decreased OI ($P<0.0001$) and improved the arterial/alveolar (a/A) oxygen ratio ($P<0.0001$) within the first 2 h of NO therapy in 61.1% of the responders. However, the OI and the a/A oxygen ratio remained almost the same throughout the treatment in the non-responders and the non-survivors.

Conclusion: Inhaled NO at 20 ppm, following adequate ventilation for 2 h without significant response, could be used to identify the majority of the non-responders in order to seek other alternatives.

Address: King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia.

Correspondence: Dr Saleh Al-Alaiyan, King Faisal Specialist Hospital and Research Centre, Department of Pediatrics, P.O. Box 3354, MBC-58, Riyadh 11211, Saudi Arabia.
Tel.: +966 1 442 7761; fax: +966 1 442 7784

Keywords: neonates, pulmonary hypertension, nitric oxide, high-frequency ventilation

Received: 16 March 1998
Revisions requested: 24 July 1998
Revisions received: 31 January 1999
Accepted: 12 February 1999
Published: 15 March 1999

Crit Care 1999, **3**:7–10

The original version of this paper is the electronic version which can be seen on the Internet (http://ccforum.com). The electronic version may contain additional information to that appearing in the paper version.

Introduction

A wide range of life-threatening lung diseases are characterized by compromised capacity of the lung to match ventilation and perfusion. This results in poor oxygenation of arterial blood and significant hypoxemia. Pulmonary hypertension and poor myocardial function often play a role in the pathophysiology of pulmonary disease [1]. Several vasodilator agents have been shown to decrease pulmonary vascular resistance, but their use was limited by concomitant decreases in systemic vascular resistance and worsening of intrapulmonary shunt [2]. Recently, selective pulmonary vasodilation with inhalational nitric oxide (INO) has been demonstrated in both clinical and experimental settings [3–5].

This pilot study was conducted to evaluate the effect of INO in the management of neonates with severe persistent pulmonary hypertension refractory to high-frequency oscillatory ventilation.

Methods

Subjects

Between October 1994 and June 1997, 24 consecutive neonates with persistent pulmonary hypertension of the newborn (PPHN) who failed high-frequency oscillatory ventilation were enrolled in this study. The diagnosis of PPHN was made clinically and confirmed by echocardiogram (either right-to-left or bidirectional flow at the ductal or arterial level, or estimated pulmonary pressures from a tricuspid regurgitation jet, being greater than two-thirds of the systemic arterial pressures). The studied neonates had birthweights of 3125.5 ± 794 g (mean ± SD), and gestational ages of 39 ± 2.4 weeks (mean ± SD). There were 12 females and 12 males, and 22 were born outside the hospital. All neonates were ventilated for an average of 137.5 min (range 90–180 min) prior to INO therapy with 3100A high-frequency oscillatory ventilator (HFOV; Sensor Medics, Yorba Linda, California, USA). Metabolic alkalosis was induced with a bicarbonate infusion. Sedation with morphine and/or midazolam and neuromuscular blockade with pancuronium were used. Synthetic surfactant (Exosurf Neonatal, The Wellcome Foundation Ltd, London, UK) was administered to all neonates with respiratory distress syndrome (RDS) and meconium aspiration syndrome (MAS). Dopamine and dobutamine were used to maintain a mean arterial pressure between 45 and 55 mmHg.

Study protocol

Neonates were enrolled after informed consent was obtained from parents. At enrollment, postductal arterial blood samples were drawn for determination of pH, blood

gas tensions, and methemoglobin saturation (270 Co-oxime, Ciba-Corning, Diagnostics, Medfield, Massachusetts, USA) 10 min prior to the treatment with INO and every 2–4 h thereafter. The mean oxygenation index of all neonates [OI = mean airway pressure × fractional inspired concentration of oxygen (FiO_2)/post-ductal partial pressure of arterial oxygen (PaO_2)] during high-frequency ventilation and before starting INO was 46.3 ± 5 (mean ± SEM). The NO gas (AHG, Jeddah, Saudi Arabia) used in this study was certified at a concentration of 800 ppm NO with < 1% contamination by other oxides of nitrogen. NO gas was introduced into the ventilator circuit via an adaptor positioned on the inspiratory port of the Fisher and Paykel humidification chamber. Thus, NO was mixed with the bias flow gas of the oscillator and subsequently delivered to the neonate via the inspiratory limb of the ventilator circuit. The resulting concentration of the inhaled NO and NO_2 was verified in-line by using an electrochemical sensor (Pulmonox, Tofield, Alberta, Canada). Exhaled gas was scavenged; the oxygen concentration was analyzed continuously before it reached the neonate's endotracheal tube. Nitric oxide was initially administered at 20 ppm for at least 2 h. If there was no response while the neonate was on high ventilatory support and FIO_2 of 1.0, INO was increased gradually by 2 ppm to a maximum of 80 ppm. If there was a response, INO was maintained at 20 ppm and FIO_2 was gradually decreased to 0.6, provided the PaO_2 was 80–120 mmHg. Nitric oxide then was weaned to discontinuation. Ventilatory parameters thereafter were weaned and HFOV was replaced by a conventional ventilator. An arterial/alveolar oxygen (a/A) ratio less than 0.22 was used to define failure of HFOV and INO therapy, if INO reached 80 ppm on high ventilatory support.

Statistical analysis

Statistical analysis was performed with the assistance of the Department of Biostatistics. Normally distributed continuous variables were analyzed with the Student's *t*-test. Variables without a normal distribution were analyzed with the Wilcoxon signed rank test. This study has been approved by the Department of Pediatrics Research Committee and the King Faisal Specialist Hospital and Research Centre's Research Advisory Council.

Results

Of the 24 consecutive neonates treated with both HFOV and INO, 18 (75%) responded and 6 (25%) did not respond to the treatment. Three neonates died in the responding group, while all the non-responders died ($P = 0.0001$). The survival rate was 62.5% among all neonates.

The underlying diseases of the responders and non-responders are depicted in Table 1. In addition to severe PPHN, six neonates had birth asphyxia, 13 had MAS, three had congenital diaphragmatic hernia (CDH) and two had RDS. Of the 13 neonates with MAS, 12 responded to INO, while none of the infants with CDH responded to INO therapy.

Table 1

The underlying diseases of all infants

	Responders ($n = 18$)	Non-responders ($n = 6$)
Birth asphyxia/hypoxia	4	2
Meconium aspiration syndrome	12	1
Respiratory distress syndrome	2	0
Congenital diaphragmatic hernia	0	3

Table 2

Comparison between responders and non-responders

	Responders ($n = 18$)	Non-responders ($n = 6$)	*P*
Birth weight (g)	3180 ± 190.2	2970 ± 329.4	0.59
Gestational age (weeks)	39 ± 0.58	39 ± 1	0.96
OI pre INO	42.9 ± 5.8	56 ± 10	0.25
OI during INO	11.3 ± 3.5	39 ± 6	0.0007*
a/A pre INO	0.09 ± 0.008	0.071 ± 0.014	0.28
a/A during INO	0.315 ± 0.021	0.137 ± 0.063	0.0003*

OI, oxygenation index; a/A, arterial/alveolar oxygen ratio; INO, inhalational nitric oxide. All values shown as mean ± SEM; *$P < 0.05$.

Inhalation of NO significantly decreased OI ($P < 0.0001$) and improved the a/A ratio ($P < 0.0001$) within the first 2 h of INO therapy in 61.1% of the responders, and the remaining responded gradually during the INO treatment. However, OI and a/A ratio remained almost the same throughout the treatment in the non-responders and the non-survivors (Tables 2 and 3). Four of the responders (two with MAS and two with RDS) became INO-dependent and required phosphodiesterase inhibitor (dipyridamole) to wean them from INO. Tolazoline was unsuccessfully attempted in two neonates in the referring hospitals. Methemoglobin and nitrogen dioxide were maintained below 5% during INO therapy. The average age when INO was started was 2.6 days (range 1–11 days). The mean duration of INO used in all neonates was 4.6 days (range 1–10 days). Three neonates responded to INO but died of other causes. The first neonate had severe intracranial hemorrhage, *Klebsiella pneumoniae* sepsis, renal failure and, consequently, brain death. The second neonate had *Escherichia coli* sepsis and interstitial lung disease. The lung biopsy revealed a diffuse alveolar

Table 3

Comparisons between survivors and non-survivors

	Survivors ($n = 15$)	Non-survivors ($n = 9$)	P
Birth weight (g)	3362 ± 193.3	2736 ± 249.5	0.06
Gestational age (weeks)	39.5 ± 0.60	38.2 ± 0.78	0.20
OI pre INO	45.7 ± 6.5	47.3 ± 8.4	0.90
OI during INO	11.9 ± 4.5	28.84 ± 3.8	0.03*
a/A ratio pre INO	0.090 ± 0.009	0.076 ± 0.011	0.36
a/A ratio during INO	0.317 ± 0.026	0.193 ± 0.034	0.009*

OI, oxygenation index; a/A, arterial/alveolar oxygen ratio; INO, inhalational nitric oxide. All values shown as mean ± SEM; *$P < 0.05$.

damage. The third neonate developed multiple pneumatoceles in both lungs and the lung biopsy showed proliferative phase of diffuse alveolar damage. Subsequent lung tissue culture was positive for methicillin-resistant *Staphylococcal aureus*.

Discussion

PPHN is a common endpoint of several very different pathophysiological mechanisms. It is extremely important to understand the underlying etiology of PPHN, as therapeutic interventions must be tailored to specific circumstances; for example, PPHN associated with hyaline membrane disease should first be treated with surfactant therapy.

Maintenance of adequate circulating blood volume, systemic vascular resistance, and optimal lung inflation are essential for the management of PPHN. High-frequency ventilation has been introduced as a mode of therapy in PPHN. There were no randomized studies of HFOV in the management of infants with PPHN, but attention has been focused on the potential of HFOV to reduce the need for extracorporeal membrane oxygenation (ECMO). A number of reports identify a number of infants who, although referred for ECMO, survived without using this type of intervention [6,7].

A comparison between HFOV and INO in reducing the need for ECMO has been studied. Kinsella *et al* [8] combined HFOV and INO in the treatment of infants with hypoxic respiratory failure and PPHN who were ECMO candidates. These authors found no difference in the need for ECMO or death in the INO group compared with the HFOV group, and they suggest that combined treatment with INO and HFOV may improve outcome.

In this study, we found that 75% of infants with PPHN who failed HFOV responded to INO therapy and 62.5% survived to discharge. Recently, the NINOS Study Group has conducted a study to evaluate whether INO would reduce the incidence of death or the need for ECMO in infants with hypoxic respiratory failure [9]. HFOV was used in 55% of the infants. The authors found that treatment with INO resulted in a significant reduction in the combined incidence of death in less than 120 days or the need for ECMO. Moreover, Roberts *et al* [10] studied 58 full-term infants with severe hypoxemia and PPHN who were randomized to receive either INO or nitrogen. They found that INO improved systemic oxygenation in these infants and they suggest that INO may reduce the need for more invasive treatment.

In this study, we found that 61.1% of the responders responded within the first 2 h after the initiation of INO and their response sustained to the end of the treatment and the remaining neonates showed a gradual response throughout the course of INO. Similarly Goldman *et al* [11] evaluated INO in a group of 25 severely hypoxic term neonates and identified four patterns of response. Two neonates did not respond, nine neonates who responded well initially then failed within 24 h, 11 neonates responded and sustained that response, and three neonates responded to INO but required high doses for prolonged periods of time. We also found that 25% failed INO therapy, most likely as a result of severe pulmonary hypoplasia seen in CDH, and severe lung damage due to severe hypoxia as in asphyxia and RDS. A number of studies have noted a general lack of a sustained improvement in oxygenation in response to INO in the management of CDH [12–14]. In this study ECMO was not used as an alternative therapy for the INO non-responders because it was not available in our hospital for neonates.

It has been observed that some infants who showed a dramatic response to INO developed a decrease in oxygenation when INO was discontinued. This response may reflect downregulation of endogenous nitric oxide synthase activity secondary to the administration of exogenous nitric oxide [15]. In addition INO may increase the concentration of phosphodiesterase, which then degrades cyclic GMP when INO is discontinued, resulting in vasoconstriction. In this study, four infants became INO-dependent and successfully weaned from INO following the use of phosphodiesterase inhibitor (dipyridamole) [16]. Study of the mechanism of INO dependency may give insight into new therapies that augment the pulmonary vasodilatory effect of INO and the activity of the endogenous NO system.

In conclusion, the administration of INO at 20 ppm, following adequate ventilation for a maximum of 2 h without significant response could be used to identify the majority of the non-responders. In these situations, other means of therapy, such as ECMO, could be considered.

References

1. Calvin JE, Baer RW, Glantz SA: **Pulmonary artery constriction produces a greater right ventricular afterload than lung microvascular injury in the open chest dog.** *Circ Res* 1985, **56**:40–56.
2. Rondermacher P, Santak P, Becher H, Falke KJ: **Prostaglandin E1 and nitroglycerin reduce pulmonary capillary wedge pressure but worsen V/Q distribution in patients with adult respiratory distress syndrome.** *Anesthesiology* 1989, **70**:601–609.
3. Frostell C, Fratacci MD, Wain JC, Jones R, Zapol WM: **Inhaled nitric oxide: a selective pulmonary vasodilator reversing hypoxic pulmonary vasoconstriction.** *Circulation* 1991, **83**:2038–2047.
4. Kinsella JP, Neish SR, Shaffer E, Abman SH: **Low dose inhalational nitric oxide in persistent pulmonary hypertension of the newborn.** *Lancet* 1992, **340**:819–820.
5. Roberts J, Polaner D, Lang P, Zapol W. **Inhaled nitric oxide in persistent pulmonary hypertension of the newborn.** *Lancet* 1992, **340**: 818–819.
6. Carter JM, Gerstmann DR, Clark EH *et al*: **High-frequency oscillation and extracorporeal membrane oxygenation for the treatment of acute neonatal respiratory failure.** *Pediatrics* 1990, **85**:59–64.
7. Kohelet D, Perlman M, Kirpalani H, *et al*: **High-frequency oscillation in the rescue of infants with persistent pulmonary hypertension.** *Crit Care Med* 1988, **16**:10–16.
8. Kinsella JP, Truog WE, Walsh WF, *et al*: **Randomized, multi-center trial of inhaled nitric oxide and high-frequency ventilation in severe persistent pulmonary hypertension of the newborn.** *Pediatr Res* 1996, **139**:252A.
9. The NINOS Study Group: **Inhaled nitric oxide for near-term infants with respiratory failure.** *N Engl J Med* 1997, **336**:597–604.
10. Roberts JD, Fineman JR, Morin FC, *et al*: **Inhaled nitric oxide and persistent pulmonary hypertension of the newborn.** *N Engl J Med* 1997, **336**: 605–610.
11. Goldman AP, Tasker RC, Haworth SG, *et al*: **Four patterns of response to inhaled nitric oxide for persistent pulmonary hypertension of the newborn.** *Pediatrics* 1996, **98**:706–713.
12. The Neonatal Inhaled Nitric Oxide Study (NINOS) Group: **Inhaled nitric oxide and hypoxic respiratory failure in infants with congenital diaphragmatic hernia.** *Pediatrics* 1997, **99**:838–845.
13. Shah N, Jacob T, Exler R, *et al*: **Inhaled nitric oxide in congenital diaphragmatic hernia.** *J Pediatr Surg* 1994, **29**:101–115.
14. Henneberg SW, Jepsen S, Andersen PK, Pedersen SA: **Inhalation of nitric oxide as a treatment of pulmonary hypertension in congenital diaphragmatic hernia.** *J Pediatr* 1995, **30**:853–855.
15. Bult H, De Meyer GRY, Jordaens FH, Herman AG: **Chronic exposure to exogenous nitric oxide may suppress its endogenous release and efficacy.** *J Cardiovasc Pharmacol* 1991, **17 (suppl)**:S79–S82.
16. Al-Alaiyan S, Al-Omran A, Dyer D: **The use of phosphodiesterase inhibitor (dipyridamole) to wean from inhaled nitric oxide.** *Intensive Care Med* 1996, **22**:1093–1095.